Pulmonary Function Testing
A PRACTICAL APPROACH

Jack Wanger, MSc, RRT, RPFT, FAARC
Senior Clinical Research Scientist
PRA International
Raleigh, North Carolina
Contents

Preface v
Acknowledgments vii
Reviewers ix
Contributing Author xi

Chapter 1 Forced Spirometry and Related Tests 1
Chapter 2 Lung Volumes 69
Chapter 3 Single-Breath Carbon Monoxide Diffusing Capacity 113
Chapter 4 Airway Resistance by Body Plethysmography 143
Chapter 5 Cardiopulmonary Exercise Test 159
Chapter 6 Six-Minute Walk Test 201
Chapter 7 Exercise-Induced Bronchoconstriction Test 211
Chapter 8 Bronchial Challenge Testing with Pharmacological Agents 223
Chapter 9 Maximal Inspiratory and Expiratory Pressures 257
Chapter 10 Pediatric Pulmonary Function Testing 263
Chapter 11 Blood Gases and Associated Technologies 281
Chapter 12 Pulmonary Function Testing Reference (Predicted) Values 333
Appendices

A  Answers to Self-Assessment Questions      343
B  Conversion of Volumes                   347
C  Mathematics of Boyle’s Law             351
D  Pulmonary Terms, Symbols, and Definitions 353
E  Calculation of Mean and Standard Deviation 359

Index                                           361
Preface

Pulmonary function tests are used to evaluate a broad range of lung disorders, including airflow obstruction, restrictive disorders, exercise limitations, and bronchial hyperreactivity. The information obtained from these tests enables the practitioner to recognize impairment, determine patients’ responses to therapy, and follow the progress of disease. Today, these tests are performed by a range of healthcare workers, including respiratory care practitioners, nurses, medical assistants, and industrial (occupational) hygienists. Typically, these workers receive minimal classroom instruction and often learn their skills from others on the job. They may have sought but not found an appropriate practical how-to manual, finding instead books that are too theoretical or books that cover many topics, not all of them relevant.

The third edition of this book maintains the same general philosophy and purpose of the first two editions—to provide a practical entry-level textbook for students and a reference for those performing the tests. This edition contains some necessary and welcome updates, and focuses on the more commonly performed tests and strives to keep the material workable from an instructor's perspective. Hence, less commonly performed and ordered tests (e.g., gas distribution, ventilatory drive, forced oscillation) and certain extensive topics (e.g., bronchoscopy) that require more than a chapter to discuss properly have been deliberately excluded.

The basic organization and presentation of the content has been maintained in most chapters. Each chapter is a self-contained unit that typically has a brief historical perspective as well as any pertinent background material. This is followed by relevant physiology, instrumentation, techniques, calculations, quality control, basic elements of interpretation, and infection control. Each chapter concludes with references, self-assessment questions, and, in most chapters, case presentations.

The first three chapters discuss the most commonly ordered and performed tests: spirometry, lung volumes, and single-breath carbon monoxide diffusing capacity. Chapter 4 discusses airway resistance, and Chapter 9 discusses maximal inspiratory and expiratory pressures, tests commonly performed in many hospital pulmonary function laboratories. Chapters 5 through 7 discuss different exercise tests—cardiopulmonary exercise test, 6-minute walk, and exercise-induced bronchoconstriction test. Chapter 8 discusses bronchial challenge testing, including methacholine challenge and the mannitol challenge test. Chapters 10 and 11 are new additions and present brief and practical descriptions of pediatric pulmonary function testing and blood
Preface

gases, respectively. Chapter 12 presents a discussion of reference or predicted equations to help evaluate observed results. Finally, there are a number of appendices that present more detailed and helpful information on a variety of topics.

Jack Wanger, MSc, RRT, RPFT, FAARC
Acknowledgments

The Third Edition of Pulmonary Function Testing: A Practical Approach evolved from the First and Second Editions. There were many individuals who provided advice and support for those works, and I extend a special thanks to them. The staff at Jones Bartlett & Learning, including Maro Gartside and David Cella, were helpful in the development of this new edition, and I want to offer a special thank you to them.

Some of the special illustrations in this Third Edition were included in previous editions and are the result of the artistic talents of Leigh Landskroner.

My heartfelt thanks to Reuben Cherniack and Charles Irvin for their encouragement, insight, guidance, and knowledge they have given me over the years.

My special thanks to Bruce Toben, RRT-NPS, CPFT, for his contributions to this Third Edition. His knowledge and insight for the chapter on arterial blood gases and associated technologies have made it a stronger text. Also, special thanks to Pam Leisenring, RRT, for her input and contributions on pediatric pulmonary function testing.

Finally, I want to thank my wife, Tammy, for her encouragement, suggestions, patience, and support during the preparation of this new edition.
Reviewers

Tammy Hunt, MS, RRT, RPFT
Respiratory Therapy Program
Clarian Health & Affiliated Universities
Indianapolis, Indiana

Linda M. Lair, MS, RRT, CPFT
Director of Clinical Education
University of Missouri
Columbia, Missouri

Debra Laken, MAEd, RRT, AE-C, CTTS
Associate Professor
University of Alabama at Birmingham
Birmingham, Alabama

Pam Leisenring, AS, RRT, CPFT
Pulmonary Lab Supervisor
Arkansas Children’s Hospital
Little Rock, Arkansas

Mary Martinasek, MPH, RRT
Adjunct Faculty
Respiratory Care Program
Hillsborough Community College
Tampa, Florida

Gina Ricard, BS, RRT-NPS
Director of Clinical Education
Respiratory Care Program
Hillsborough Community College
Tampa, Florida

April Scribner, BS, RRT, CPFT
Pulmonary Lab Therapist
Arkansas Children’s Hospital
Little Rock, Arkansas
Contributing Author

Bruce Toben, RRT-NPS, CPFT
Director, Clinical Affairs
ITC Nexu Dx
Piscataway, New Jersey
Forced Spirometry and Related Tests

Introduction

Forced spirometry, often referred to as spirometry, is an essential component in the medical evaluation of patients complaining of shortness of breath. It is also widely used to evaluate the beneficial effects and adverse reactions of therapeutic interventions and to monitor the effects of environmental and occupational exposures. In addition, forced spirometry is used in disability/impairment evaluations, in preoperative assessments, and to monitor lung function over time.

Spirometry has shown considerable growth in the past 30 years, for several reasons: 
(a) published standards and testing guidelines,1-6 (b) improved spirometers and software, (c) evidence that both patients and physicians have inaccurate perceptions of the severity of airflow obstruction,7-11 (d) evidence that history taking and physical examination by themselves are not
helpful in identifying patterns of lung disease, recommendations that spirometry be included in the assessment of patients suspected of having asthma, and recommendations for objective measurements to reduce the impact of chronic obstructive pulmonary disease (COPD).

This chapter will provide information for both the student and the practitioner by discussing relevant physiology, instrumentation, techniques of performance and calculations, and basic elements of interpretation. Because spirometry is frequently performed before and after administration of a bronchodilator, this chapter will discuss how to administer bronchodilators in the pulmonary function laboratory and how to assess patient response. Also, because they are related and often performed with spirometry, included in this chapter are discussions on maximum voluntary ventilation and peak expiratory flow rate monitoring.

Definitions

VC Vital capacity is the maximum volume of air exhaled after a maximum inspiration.

FVC Forced vital capacity is the maximum volume of air exhaled with maximum force from a maximum inspiration.

FEV₁ Forced expiratory volume in 1 second is the volume of air exhaled in the first second of an FVC maneuver.

FEF₂₅–₇₅% Forced expiratory flow between 25% and 75% is the average flow during the middle half of an FVC maneuver.

PEFR Peak expiratory flow rate is the maximum flow attained during an FVC maneuver.

MVV Maximum voluntary ventilation is the volume of air a patient can breathe rapidly and forcefully over a specified period of time (e.g., 12 seconds).

Physiology

Although the lung is sometimes regarded simply as sort of a bellows system that moves air in and out of the body, it is a complex organ involved in many physiologic processes, such as gas transfer between the environment and blood and defense against harmful agents (e.g., pollutants), and in biochemical processes that produce important substances in the body.

The lower airways, as shown in Figure 1.1, begin with the trachea and divide into a right and left main stem bronchus. These main stem bronchi (referred to as the first generation of airways) divide into small branches, which become narrower and more numerous as they go deeper into the lung, ending 16 generations later in the terminal bronchioles. These are the conducting airways and contain no alveoli. Beyond the terminal bronchioles are the alveoli, of which there are approximately 300 million.

Inspiration is an active process that occurs when the respiratory muscles contract. The major respiratory muscle is the diaphragm, and when it contracts, it pushes down toward the abdomen. Other respiratory muscles, including the external intercostals, scalenes, and sternocleidomastoids, increase the lateral and anteroposterior diameter of the thorax.
During quiet breathing expiration is passive—occurring with relaxation of the respiratory muscles and the return of the lungs and thorax to resting volume. However, during fast, hard breathing, expiration becomes active and the abdominal muscles contract, pushing the diaphragm upward. Additionally, during fast, hard breathing, the internal intercostal muscles pull the ribs down and inward, decreasing the diameter of the thorax.

During spirometry, the forced expiratory maneuver consists of a maximal inspiration and then a rapid, forceful, and complete expiration. A number of physiologic factors influence the gas flow during this maneuver, but they can be broadly divided into two groups: (a) mechanical properties of the lungs and (b) resistive elements.

The mechanical properties of the lung refer to the compliance and elastic recoil. Compliance (Ct) describes stiffness and is the change in volume of air in the lung divided by the pressure change. When we take a deep breath, the respiratory muscles contract, the chest wall moves outward, and the diaphragm moves downward. The result is a negative pressure in the thorax and lungs, allowing air to enter. Lung tissue that is stiff, or less compliant, requires relatively greater negative pressure. Conversely, lung tissue that is not stiff, or more compliant, requires relatively less negative pressure for the same amount of volume. Figure 1.2 shows examples of three different pressure–volume relationships during a maximum inhalation from the tidal volume end-expiratory level, which is also known as functional residual capacity (FRC). FRC is explained in detail in Chapter 2.
In Figure 1.2A, a pressure change of 3 cm H\textsubscript{2}O results in a 0.5 liter volume change above FRC. This means that an additional 3 cm H\textsubscript{2}O pressure was required to produce the 0.5 liter volume change. It took approximately 30 cm H\textsubscript{2}O of additional pressure to reach maximum inhalation volume (i.e., total lung capacity [TLC]), which is approximately 6 liters in this figure. Cl near FRC can be calculated by dividing the volume change (\Delta V) on the vertical axis by the transpulmonary pressure change (\Delta P) on the horizontal axis, which in this example equals 0.17 liter/cm H\textsubscript{2}O. The shape of the pressure–volume relationship in Figure 1.2A, as well as the Cl near FRC, are normal.

In Figure 1.2B, a pressure change of 9 cm H\textsubscript{2}O results in a 0.5 liter volume change above FRC, equaling a Cl of 0.06 liter/cm H\textsubscript{2}O. In other words, it took more pressure to move the lung tissue to allow 0.5 liter of air to enter the lung. This is an example of stiff lungs, found in various forms of pulmonary fibrosis.

In Figure 1.2C a pressure change of 1.5 cm H\textsubscript{2}O results in a 0.5 liter volume change above FRC, equaling a Cl of 0.33 liter/cm H\textsubscript{2}O. It took less pressure to move the lung tissue to allow 0.5 liter of air to enter the lung. This is an example of overly compliant lungs, found in patients with emphysema.

Elastic recoil refers to the lungs’ tendency to return to their resting or relaxed state. The more the lung tissue is stretched, the stronger the elastic recoil and the higher the maximal flow in the airways. Thus, the elastic recoil pressure and maximal flow are greatest when the lungs are fully inflated and the least when the lungs are nearly emptied. Elastic recoil also varies with disease. Patients with emphysema have lower elastic recoil because of tissue loss. Patients with pulmonary fibrosis have increased elastic recoil.

The second major factor that influences gas flow is the resistance to airflow. The caliber of the conducting airways plays the major role. The smaller the diameter of the conducting airway, the more the resistance. Two main factors affect airway caliber: (a) lung volume and (b) bronchial smooth muscles.

During inspiration the airways are pulled open and become wider and longer. Airway caliber is greatest when the lungs are full. As the lungs are emptied and lung volume decreases, the airways become smaller and airway resistance increases. When the bronchial smooth muscles contract, the airway caliber decreases. This process is amplified if there is airway wall thickening or an increase in mucus in the airways.

Airway collapsibility also affects airway caliber and is best explained by the pressure–flow relationship and the single equal-pressure-point model (Figure 1.3). When there is no flow in

**Figure 1.2**

Three pressure–volume curves illustrating the relationship between transpulmonary pressure and volume. A. Normal pressure–volume curve where the change in volume divided by the change in pressure between FRC and 0.5 liter above FRC (i.e., 0.17 liter/cm H\textsubscript{2}O) is in the normal range of 0.12 to 0.25 liter/cm H\textsubscript{2}O. B. Pressure–volume curve where the change in volume divided by the change in pressure between FRC and 0.5 liter above FRC (i.e., 0.06 liter/cm H\textsubscript{2}O) is lower than the normal range, which might be seen in individuals with stiff lungs (e.g., pulmonary fibrosis). C. Pressure–volume curve where the change in volume divided by the change in pressure between FRC and 0.5 liter above FRC (i.e., 0.33 liter/cm H\textsubscript{2}O) is higher than the normal range, which might be seen in individuals with overly compliant lungs (e.g., emphysema).
Transpulmonary pressure (cm H₂O)

Volume (L)

A

FRC

CL = \frac{\Delta V}{\Delta P} = \frac{0.500}{3} = 0.17 \text{ L/cm H₂O}

B

FRC

CL = \frac{\Delta V}{\Delta P} = \frac{0.500}{5} = 0.06 \text{ L/cm H₂O}

C

FRC

CL = \frac{\Delta V}{\Delta P} = \frac{0.500}{1.5} = 0.33 \text{ L/cm H₂O}
the airways, the alveolar pressure and the airway pressure are equal and approximately atmospheric. During an inspiration, alveolar and pleural pressures become subatmospheric and air rushes into the lungs. During expiration, alveolar and pleural pressures become positive and exceed atmospheric pressure. During a forced expiration this pressure change is amplified, as shown in Figure 1.3. The airways are forced to narrow at the point when pressure in the thorax becomes greater than the airway pressure. The point where these two pressures (thorax and airway) are exactly equal is called the equal pressure point (EPP). The airways on the alveolar side of the EPP are referred to as the upstream airways, and those on the mouth side of the EPP are called the downstream airways.

Figure 1.3
The dynamic compression of the airways showing the EPP. During the forced expiration the respiratory muscles compress the thorax. Alveolar pressure ($P_{alv}$) is the sum of the pleural pressure ($P_{pl}$) and the elastic recoil pressure ($P_e$). In this example, $P_{pl}$ is 20 cm H$_2$O, $P_e$ is 10 cm H$_2$O, and thus $P_{alv}$ is 30 cm H$_2$O. The pressure in the airways falls as the mouth is approached. The EPP is reached when $P_{pl}$ equals $P_{alv}$. Downstream from that point (toward the mouth) the airways narrow, limiting airflow.

$P_{alv} = P_{pl} + P_e$
Spirometry Instrumentation

The maximal flow that can be achieved, as explained by the EPP model, can be shown mathematically by the following formula:

\[
\text{Maximal flow} = \frac{\text{Pressure change}}{\text{Resistance}}
\]

The pressure change is the difference between the pressure in the alveolus (\(P_{alv}\)) and the pressure at the EPP (\(P_{EPP}\)). Thus,

\[
\text{Maximal flow} = \frac{P_{alv} - P_{EPP}}{\text{Resistance}}
\]

Because \(P_{alv}\) is the sum of the pressure created by the muscles of the chest wall, which is called pleural pressure (\(P_{pl}\)) and the elastic recoil pressure (\(P_{el}\), or \(P_{alv} = P_{pl} + P_{el}\)), and the EPP equals \(P_{pl}\), then the pressure change is \(P_{el}\).

\[
\text{Maximal flow} = \frac{(P_{pl} + P_{el}) - P_{pl}}{\text{Resistance}} = \frac{P_{el}}{\text{Resistance}}
\]

The resistance to airflow is the resistance of the upstream airways (\(R_{us}\)). Thus,

\[
\text{Maximal flow} = \frac{P_{el}}{R_{us}}
\]

Hence, airflow is determined by the driving pressure (\(P_{el}\)) and the resistance of the airways upstream (\(R_{us}\)) of the EPP.

Patients with obstructive lung disease have reduced airflow (i.e., airflow limitation). Patients with asthma have increased resistance because bronchial smooth muscle contraction reduces maximal flow. In patients with emphysema the primary cause of reduced airflow is a loss of elastic recoil. Some asthmatics may also demonstrate a loss of elastic recoil, which compounds the effect of increased resistance.

**Spirometry Instrumentation**

Available spirometers can be classified as: (a) *volume-displacing* or (b) *flow-sensing*. The usually large and bulky volume-displacement spirometer collects exhaled air or acts as a reservoir for inhaled air. The flow-sensing devices are smaller, more portable, and measure flow, which is then integrated electronically to give volume.

**Volume-Displacing Spirometers**

The volume-displacement spirometer has a very long history and was the type John Hutchinson used in his experiments around 1840. These spirometers were the mainstay for more than a century but have been mostly replaced in clinical practice with smaller and more portable devices. There are four main types of volume-displacement spirometers: (a) water seal, (b) rolling seal, (c) bellows, and (d) diaphragm.
Water Seal

Figures 1.4A and 1.5 show a water-seal spirometer (Stead-Wells spirometer), which is considered to be the gold standard. This spirometer consists of three cylinders: an outer hollow cylinder open on the top, a second cylinder approximately one-half inch smaller in diameter and closed on the top except for one or two large holes, and a third cylinder of lightweight plastic with its open bottom placed into the space between the first and second cylinders. The space between the first and second cylinders is also filled with water. The third cylinder (sometimes called the bell) moves up and down in the water when a patient is connected to it. When the patient exhales and keeps this air from escaping—a water seal. A pen connected to the bell writes on paper affixed to a rotating drum (the kymograph). Volumes used to be measured manually with a pencil and ruler and were corrected for temperature, pressure, and water saturation. The time-consuming manual measurements were eventually replaced by electronic measurements, with the addition of a potentiometer (a device for measuring the potential or voltage in a circuit) to the bell.

The Stead-Wells water-seal spirometer has several potential problems, including leaks, making sure there is an appropriate water level, and infection control concerns. Because of these issues and technology advancement, this type of spirometer was eventually replaced in practice with the dry-seal spirometer, shown in Figure 1.4B.

Rolling Seal

The dry rolling-seal spirometer is another type of volume-displacement spirometer (Figure 1.6). The piston-in-cylinder configuration can be vertical or horizontal. A silicone-based elastic material seals the spirometer contents by rolling with the piston as it moves (thus the name rolling-seal spirometer). Volume is measured by a potentiometer that is mechanically connected to the piston rod with a slide wire. Flow data are obtained by electronic differentiation of the volume signal. Like the bellows spirometer, the rolling-seal spirometer can display results electronically or mechanically with a pen.
Figure 1.5

An illustration of the water-seal Stead-Wells spirometer showing how the air moves in and out of the spirometer bell.

Source: Courtesy of nSpira Health, Inc.
Bellows
The bellows-type spirometer is another example of the volume-displacement spirometer. Exhaled air is collected in a bellows, much like the one used to coax flames from fireplace coals. Bellows spirometers are usually made of plastic, and the material expands as exhaled air enters and contracts as air exits. The vertical bellows or wedge spirometer, shown in Figure 1.7, is large and bulky and was popular in the 1960s and 1970s. The horizontal bellows shown in Figures 1.8 and 1.9 is smaller and more practical. Both of these bellows systems can display results electronically with a computer or microprocessor or mechanically with a pen and kymograph.

Diaphragm
The fourth type of volume-displacement spirometer, one that incorporates a diaphragm, is shown in Figure 1.10. Such spirometers are small, lightweight, and simple to use and come with or without a microprocessor. As shown in Figure 1.10, the patient breathing tube connects
to the bottom of the unit. A rubber diaphragm fits snugly into the lower housing. As the patient’s exhaled air enters the lower housing, it moves the bottom side of the diaphragm upward. As the diaphragm moves upward, it moves a pusher plate upward, and volume is then measured. The exhaled air escapes back out of the patient breathing tube when the patient’s mouth is removed. A volume–time tracing can be obtained, and if the instrument is equipped with a microprocessor, this device will calculate several parameters.
Advantages and Disadvantages

The volume-displacing spirometers are generally designed to measure exhaled volumes and, before testing starts, contain no air. However, certain types (e.g., rolling seal) do allow the user to add air by moving the resting position. This allows the patient to both inhale deeply from and exhale into the spirometer (i.e., closed-circuit breathing). This feature allows the measurement of inspired vital capacity as well as maximal voluntary ventilation.

The major disadvantage with volume-displacing spirometers is they can develop leaks. If they leak, the volume cannot be collected accurately. Therefore, one of the most important quality control activities is to leak test these devices. This can be done when calibration checks are performed on some types of spirometers, but on others it may take a bit more ingenuity.
Summary of Characteristics of Volume-Displacing Spirometers

Desirable
- Directly measures volume
- Low cost
- Ease of operation
- Water-seal spirometer is considered to be the gold standard

Possibly undesirable
- Some are very large and bulky
- Less portable
- Water in water-seal devices needs to be changed and levels need to be checked frequently
- Leaks
- Without microprocessor or computer, manual calculations are necessary
- Infection control issues

Flow-Sensing Spirometers

The shortcomings of volume-displacing spirometers (e.g., large, bulky) as well as improved electronic technology and software led to the development of flow-sensing devices.

Flow-sensing spirometers directly measure flow (volume per unit of time) using various methodologies. Volume is then calculated by multiplying flow by time, which is known as integration. This process requires a computer or microprocessor with appropriate software. The accuracy of the calculated volume measurement requires careful calibration and detection of low flow. Several types of airflow measuring devices are available, including: (a) differential pressure device (pneumotachograph), (b) thermistor or heated-wire anemometer, (c) turbine or impeller device, and (d) ultrasonic.

Pneumotachograph

An example of the differential pressure device (pneumotachograph or pneumotach) is shown in Figure 1.11. The device consists of a tube with fixed resistance. The fixed resistance, which is very small and not sensed by the patient, can be a bundle of capillary tubes running parallel to the flow (Fleisch type) or a fine mesh screen or set of screens. As air flows through the tube in either direction, it meets the fixed resistance. The pressure on the side from which the flow originates becomes greater than the pressure on the other side. The greater the flow, the greater the pressure difference. The pressure difference is measured with a pressure transducer, and the signal is sent electronically to amplifiers and then to a computer or microprocessor.

The relationship among flow, pressure, and resistance can be explained mathematically with the following formula:

\[
\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}
\]
CHAPTER 1 Forced Spirometry and Related Tests

Figure 1.11
An illustration of the pneumotachograph flow-sensing device showing the differential pressure principle. As airflow enters the pneumotachograph it meets the resistive element (capillary tubes). The pressure on the airflow side of the element (P1) is greater than the pressure on the other side of the resistive element (P2). The two pressures are transmitted through the pressure ports to a transducer, which is connected to electronic amplifiers and computers or recorders. The heating coil heats the resistive element to reduce moisture buildup. If heated to 37° C, airflow is measured at body temperature.

The accuracy of a pneumotachograph depends on assuring that the resistance remains constant. One can see from the preceding formula that with constant resistance, pressure is directly proportional to flow. However, if the resistance changes from when the device was calibrated (e.g., increases with secretions or exhaled water vapor that can collect on the screens or in the capillary tubes), this relationship changes and flow can be incorrectly measured.

One unique type of pneumotach, manufactured by Medical Graphics Corporation (St. Paul, Minn.), is a pitot-type sensor that measures impact pressure with proprietary signal processing (Figures 1.12 and 1.13). The lack of a resistive element makes this flow-measuring device impervious to condensed water vapor and secretions. This device combines the mouthpiece and flow-sensing mechanism into one piece, and it is disposable.

Thermistor or Heated-Wire Anemometer
The thermistor or heated-wire anemometer (also referred to as a mass-flow sensor) consists of a fine piece of wire (e.g., platinum) in the center of a tube as shown in Figures 1.14 and 1.15. As air moves through the tube, it cools the heated wire. More electrical current is then needed...
**Figure 1.12**
An illustration of the preVent Pneumotach (Medical Graphics Corporation, St. Paul, Minn.).
A. Side view. B. Front view. The device consists of an open-ended barrel and one pair of integrally molded ribs intersecting to form a cross. The ribs include a series of small apertures and a pair of inner lumens. The impact pressure is measured in the paired lumens of the ribs as respiratory gases pass over the exterior of the ribs during inspiration and expiration.

**Figure 1.13**
Photograph of preVent Pneumotach.
*Source: Courtesy of Medical Graphics Corporation*
to reheat the wire and maintain it at a specific temperature. The current, which rises with the airflow, is measured, electronically linearized, and read as flow through the device. The device is very sensitive to flow, and some devices incorporate two wires to improve accuracy.

Heated-wire devices have some problems. Turbulent flow cannot be measured accurately, and laminar flow must be ensured by providing a long tube between the patient and the heated-wire device.

**Figure 1.14**
The heated-wire anemometer (thermistor) type of flow-sensing device.

**Figure 1.15**
Photograph of the mass-flow sensor (i.e., heated-wire anemometer).
*Source: Courtesy of CareFusion Corporation*
housing. Manufacturers have improved on these problems by employing a second heated wire. Also, the heated wire is fragile and responds to movement when the device is handheld.

**Turbine**

A turbine device is shown in Figure 1.16. It consists of a vane or wheel connected to gears. As air flows into the device, the vane turns at a speed proportional to airflow. An electronic circuit counts the revolutions and calculates flow. The Wright Respirometer, which is a mainstay in respiratory care for measuring volumes at the bedside, is based on this principle. Accuracy is not affected by turbulent flow, water vapor, or gas composition, but turbine inertia introduces inaccuracies with changing airflow. Newer designs have tried to improve on this problem by decreasing the weight of the rotating vanes.

**Ultrasonic**

The ultrasonic flow measurement device shown in Figure 1.17 consists of a flow sensor with a disposable mouthpiece tube (spirette). Transducers are located on opposite sides of the spirette cavity and emit and receive sound in alternating directions. When airflow is present in the tube, an ultrasonic sound pulse that travels against the flow is slowed down and takes a longer time to reach the opposite transducer. Conversely, a sound pulse traveling with the flow is sped up and takes a shorter time to reach the opposite transducer. The transit time of the sound pulses is accurately measured with a digital clock, and gas flow can then be calculated. This calculation is not affected by gas composition, pressure, temperature, or humidity. The disposable mouthpiece acts as a hygienic shield and allows the ultrasonic pulses to travel.
between the measurement transducers. It has no sensor elements, does not actually perform a measurement function, and thus does not require calibration.

**Summary of Characteristics of Flow-Sensing Spirometers**

**Desirable**
- Smaller and usually more portable
- Computerized; thus no manual calculations
- Bidirectional devices provide flow–volume loop capability
- Easier infection control with some models

**Possibly undesirable**
- Frequent and careful calibration checks needed for some models
- Moisture and secretions can cause problems
- Gas composition can affect results
- May not sense low flows

**Spirometer Display**

There are two ways to display the spirogram: *(a)* volume–time and *(b)* flow–volume. Both are considered useful and important for operator and interpreter inspection, as well as quality assurance.

The volume–time display (Figure 1.18) puts volume (in liters) on the *y* (vertical) axis and time (in seconds) on the *x* (horizontal) axis. This display is most useful in assessing the length of and viewing the terminal portion of the spirometry maneuver to assess whether a plateau was achieved and the patient exhales fully.

The flow–volume display (Figure 1.19) puts flow (in liters/sec) on the *y* axis and volume (in liters) on the *x* axis. This display is most useful in assessing the initial portion of the
Figure 1.18

The volume–time curve as might be seen during an FVC maneuver. The advantage of this display is the ability to view small changes in volume as the maneuver ends, thus helping the operator better detect the end of the test.

---

Figure 1.19

The flow–volume curve as might be seen during an FVC maneuver. The advantage of this display is the ability to see peak flow (which provides information on patient effort and technique at the start of the test).
20 CHAPTER 1 Forced Spirometry and Related Tests

spirometry maneuver including peak expiratory flow (PEF). Typically, this plot is scaled so that flow is twice that of volume (i.e., a 2:1 ratio).

The 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations suggest the volume–time display include at least 0.25 to 1 second before exhalation starts. This is helpful in viewing back-extrapolation volume and to evaluate effort during the initial portion of the maneuver. It is also recommended that the last 2 seconds of the maneuver be displayed to assure the patient has exhaled fully.6

**Calibration**

Spirometers, like other monitoring and diagnostic instruments, can generate erroneous information. However, if they have calibration checked and they are leak tested (volume-displacing spirometers) every day of use, the likelihood of error is greatly reduced. Calibration of spirometers is usually done by the manufacturer. It establishes the relationship between the flow or volume sensed by the spirometer and the actual flow or volume. A calibration check or verification is different from calibration in that it ensures the spirometer is within the calibration limits of the known value. If a spirometer does not meet the calibration check limits (e.g., ±3.5%), a calibration is indicated. Calibration checks should be done at least every day the spirometer is used and ideally before any patients are tested. Every laboratory or office should obtain a calibration syringe (Figure 1.20) with a volume of at least 3 liters that has been checked against a standard. The manufacturer should provide recommendations concerning appropriate intervals for having the syringe checked for leaks and accuracy. Typically this interval is 1 year.

Volume-displacing spirometers should have the patient testing tube attached during the calibration check so it too can be included in the calibration and leak testing process. Visual

**Figure 1.20**

Photograph of several calibration (known-volume) syringes. 

*Source:* Printed with permission from: Hans Rudolph, Inc.
inspection alone may not reveal tears resulting from use and cleaning. The procedure for checking calibration and leak testing the volume-displacing spirometer is easy. Inject the entire syringe volume and observe the spirometer or mechanical pen tracing. If the bell falls or the pen line does not travel in a straight line (Figure 1.21), a leak is present. Knowledgeable staff should locate and repair leaks. If no leak is present, the volume shown on the chart paper or on the computer should equal the syringe volume within $\pm 3.5\%$. For example, if a 3-liter syringe is used, the acceptable range would be 2.90 to 3.11 liters.

The calibration syringe is used to make at least three different injections at different flows varying between 0.5 (very slow) and 12 (very fast) liters/sec. This corresponds to injection times of approximately 6 seconds and less than 0.5 second. The process of injecting a known volume (e.g., 3 liters) at different speeds assures the device is linear in the range of flows used. The volume reported by the spirometer at each flow should meet the accuracy requirement (i.e., $\pm 3.5\%$).

*If the spirometer cannot measure the calibration syringe volume within $\pm 3.5\%, do not use it until it is serviced or repaired.*

Establish a calibration log or notebook for each spirometer, and enter the date and time, expected or known volume, measured volume, and technologist’s initials. Many computerized models allow the user to store or print a page with all this information. This log is useful in verifying that the device was checked for accuracy and for noting trends that may indicate equipment problems. The log should also be used to document quality control procedures, repairs, and computer software or hardware updates.
CHAPTER 1 Forced Spirometry and Related Tests

Quality Control
Along with daily calibration checks, several other procedures will help ensure quality.

Biological Controls
Choose two or three healthy nonsmokers to serve as biological controls. Gather spirometry data on each of these biological controls and record the results in a quality control or calibration log. Repeat this procedure on a regular basis (e.g., weekly or monthly). Establish a mean and standard deviation (SD) (see Appendix E) for several parameters (e.g., FVC and FEV₁). Values measured during regularly scheduled biological control testing, or at other times when the spirometer data are suspect, should fall within a range of ±2 SDs of the mean. If the value is outside that range, remedial action for the spirometer should be taken.

The coefficient of variation (CV) can also be obtained for these data. It is calculated as the SD divided by the mean. Ideally the CV is less than 5% for FVC and FEV₁ values.

Recorder Time Sweep
If the spirometer is a volume-displacement device that has a recorder with a time sweep, check the speed against a stopwatch.

Entire Range
Check volume-displacement spirometers over their entire range using the calibration syringe or equivalent volume standard. Use a larger calibration syringe (e.g., 7 liters) for this procedure. Another option is to calibrate this type of spirometer at other starting points besides the zero position, and check it against the chart paper.

Technologist Monitoring and Feedback
The importance of a monitoring and feedback program has been shown. This type of program may involve some sort of scoring system that objectively evaluates test quality and repeatability. Feedback should be provided on a regular basis and should include unacceptable test information as well as recognition for good performance. One example of a scoring system for evaluating technologists who performed spirometry in clinical research trials is shown in Table 1.1. This system can be modified to meet your laboratory's needs. For example, you may want to exclude the use of PEFR.

What Spirometer to Choose for Your Needs
The ATS first published recommendations for spirometer standards in 1979 and updated them in 1987 and 1995. The ERS published similar recommendations in 1983 and 1993. The ATS and ERS appointed a task force to combine these spirometry recommendations, which were published in 2005. Manufacturers are very much aware of these standards and design their instruments to comply with them. However, you should be aware of some specific standards before you select a spirometer.

If the spirometer measures FVC, it should be able to accumulate volume for at least 15 seconds and measure volumes of at least 8 liters, and it should be able to measure flow rates...
between 0 and 14 liters/sec. Although it is rare to find patients with vital capacity greater than 7 liters, they do exist. Also, one rarely sees maximum flow rates greater than 14 liters/sec, but many healthy individuals can achieve flows in the 12 to 14 liters/sec range. The total resistance to airflow at 14 liters/sec must be less than 1.5 cm H₂O/liter/sec. This total resistance must be measured with any tubing, valves, and filters that might be inserted between the patient and the spirometer.

An evaluation of spirometers in 1990 found that 12% of the spirometers did not accurately measure a 3-liter calibration syringe, and 29% of the spirometers performed “unacceptably” when an FVC simulator introduced 24 different waveforms. Additionally, this evaluation found software errors in 25% of the computerized systems. A more recent evaluation of smaller flow-sensing office spirometers reported differences among these smaller devices and the standard (laboratory) devices. Thus, spirometers should be carefully evaluated before purchase.

The companies that make and design the spirometers in use today are continually developing new devices or modifying and upgrading existing ones. Users usually benefit from this process and from the competition among companies. This text will not recommend specific brands or types but will present a method designed to enable the user to decide what is best for a particular application.

### Table 1.1

<table>
<thead>
<tr>
<th>Scoring System for the Objective Evaluation of Technologists Performing Spirometry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td><strong>Acceptability</strong></td>
</tr>
<tr>
<td>3 or B: ≤ 3 acceptable maneuvers with comments</td>
</tr>
<tr>
<td>2 or C: ≤ 3 acceptable maneuvers, no comments</td>
</tr>
<tr>
<td>1 or D: ≤ 2 acceptable maneuvers, with obvious errors or inappropriate comments</td>
</tr>
<tr>
<td><strong>Repeatability (FVC)</strong></td>
</tr>
<tr>
<td>3 or B: 2 highest of acceptable maneuvers agree within 0.110 to 0.150 L</td>
</tr>
<tr>
<td>2 or C: 2 highest of acceptable maneuvers agree within 0.160 to 0.200 L</td>
</tr>
<tr>
<td>1 or D: 2 highest of acceptable maneuvers do not agree within 0.210 L</td>
</tr>
<tr>
<td><strong>Repeatability (FEV₁)</strong></td>
</tr>
<tr>
<td>3 or B: 2 highest of acceptable maneuvers agree within 0.110 to 150 L</td>
</tr>
<tr>
<td>2 or C: 2 highest of acceptable maneuvers agree within 0.160 to 0.200 L</td>
</tr>
<tr>
<td>1 or D: 2 highest of acceptable maneuvers do not agree within 0.210 L</td>
</tr>
<tr>
<td><strong>Repeatability (PEFR)</strong></td>
</tr>
<tr>
<td>3 or B: 2 highest agree within 5.1% to 10%</td>
</tr>
<tr>
<td>2 or C: 2 highest agree within 10.1% to 15%</td>
</tr>
<tr>
<td>1 or D: 2 highest do not agree within 15%</td>
</tr>
</tbody>
</table>
First, be clear about your needs. The answers to some of the following questions should help you narrow the choices:

- Who will conduct the tests, and what is that person’s level of knowledge?
- How many tests per day will be performed?
- What pulmonary function values are needed? Will FVC and FEV\textsubscript{1} be enough, or will other values, such as inspiratory flows, be needed?
- How much money is available?
- Must the system be portable?
- Is a computer necessary to operate the device?

When you have chosen a type of spirometer, you must decide which brand to purchase. Criteria to examine include price, service, ease of cleaning, delivery time, and the user-friendliness of the software.

Request a demonstrator unit to evaluate. The evaluation process should consist of at least the following:

- Check the unit’s specifications against ATS/ERS recommendations.
- Use a known-volume calibration syringe to inject or withdraw known volumes at different speeds. Do this step in the patient testing mode, not the calibration mode. The results from the instrument will be at body temperature and pressure saturated (BTPS), which means that if you use a 3-liter syringe, the reported FVC should be approximately 3.3 liters (BTPS).
- Test yourself or other laboratory staff members and simulate problem patients. For example, perform a poor start of test and an early termination to observe the instrument’s response. Does it warn you about back-extrapolation error? Does it start prematurely from moving the mouthpiece around before actually blowing into the spirometer? Does it end the maneuver prematurely?
- Ask the salesperson for the names of other users who have purchased the instrument. Call or write to them and ask for their opinions and experiences.

**Spirometry Testing Techniques**

Successful spirometry depends on numerous factors, including: *(a)* proper patient preparation, *(b)* explaining and demonstrating the maneuver, and *(c)* proper performance and careful inspection of each maneuver.

**Patient Preparation**

In many hospitals and offices, patient preparation really begins when the patient is scheduled. At that time, the patient is usually instructed about which medications (if any) to stop taking, whether to stop smoking for a specific time, and so on.

When the patient arrives at the laboratory for testing, patient preparation consists of: *(a)* explaining the purpose of the test and completing necessary paperwork, *(b)* determining if there are any contraindications to performing spirometry, *(c)* obtaining the patient’s age, height, and weight, and *(d)* positioning the patient.
Explaining the Purpose of the Test
Whenever a patient visits a physician’s office or hospital laboratory for a new procedure, that individual is usually anxious or fearful of what lies ahead. Is it going to hurt? Are they going to poke a needle in my arm? Is it going to take a long time? These and other questions are going through the patient’s mind, and therefore a brief explanation of the test, how it will be done, and why it should be done is important. Keep the explanation of spirometry simple, and be brief. Do not try to second-guess the ordering physician (e.g., questioning the orders for spirometry or type of bronchodilator) in front of the patient, and do not make statements that might make the patient more uncomfortable. The following explanation works well: “I am going to have you blow into a machine to see how big your lungs are and how fast the air comes out. It doesn’t hurt, but it will require your cooperation and lots of effort.”

Some laboratories include a questionnaire that the patient completes prior to testing. Common questions include: How are you feeling today? What medications have you taken today and when? Has a doctor ever told you that you have lung disease (e.g., asthma)? Have you ever been hospitalized for respiratory problems? Have you ever experienced respiratory symptoms like shortness of breath, wheezing, or chest tightness? Have you experienced any of these symptoms in the last 2 weeks? If you are a smoker, when did you last smoke? Have you had a respiratory infection in the past 3 weeks? Do you have high blood pressure? Are you pregnant?

Determining Contraindications
Spirometry can be significantly influenced by the patient’s condition. Therefore, postponing testing for an hour or two, for a day, or even for several weeks is not out of the question. Several important relative criteria that would contraindicate spirometry include: (a) recent use of a bronchodilator when spirometry is ordered for before and after bronchodilator administration; (b) a current or recent viral infection (within 2 to 3 weeks) or other acute illness, especially when occupational or other screenings are being done for longitudinal studies (comparisons over time); (c) a serious illness, such as recent myocardial infarction, pulmonary emboli, etc.; and (d) smoking or a heavy meal within an hour of testing.

Other conditions that may interfere with obtaining optimal or repeatable results include chest or abdominal pain from any cause, oral or facial pain, stress incontinence, and dementia or confusion.

Age, Height, and Weight
Spirometric results are usually compared to reference or predicted values. To do this correctly, the patient’s age (on the day of the test), height (without shoes), and sometimes weight (wearing indoor clothes) are needed. In patients with spinal deformities, such as kyphoscoliosis, and for patients who cannot stand, the measurement of the arm span from fingertip to fingertip closely approximates the person’s standing height.

Positioning the Patient
Getting the patient comfortable and in the proper position is the next important step. Have the patient loosen any tight clothing, such as neckties, belts, or bras. Dentures should be left in place unless they are loose and interfere with performance of the test.

There is no significant difference in spirometric results between the sitting and standing positions, but the sitting position is preferred for safety reasons (avoid falling due to syncope).
If the patient sits, be sure the patient sits up straight and the patient’s legs are uncrossed. Ideally, the chair should have arms and be without wheels. If the standing position is used, a chair can be placed behind the patient in case the patient needs to be moved into a sitting position if he or she becomes dizzy or lightheaded during the maneuver. Obese patients, especially those with large midsections, are likely to do better in the standing position. The test position should be noted, and the same position should be used each time the patient is tested.

Explaining and Demonstrating the Maneuver

Show the patient the mouthpiece and nose clip. The use of a nose clip or manual occlusion of the nares is recommended by the ATS and ERS, and it is something I always insist on. However, some data shows no clear advantage of wearing nose clips when performing open-circuit spirometry, and some patients express discomfort when wearing nose clips. Explain how the mouthpiece fits into the mouth. In the case of plastic or cardboard disposable mouthpieces, be sure to tell the patient not to bite down because this will obstruct the tubing hole. The patient’s lips should be sealed tightly, and the tongue should not stick out into the mouthpiece.

Show the patient the proper chin and neck position. As shown in Figure 1.22, the chin should be slightly elevated and the neck slightly extended. This position should be maintained.

Figure 1.22

The correct chin and neck position when performing forced spirometry. Note that the chin is not bent excessively toward the chest.
throughout the forced expiratory procedure. Do not let the patient bend the chin to the chest. Some bending at the waist is common and acceptable, but discourage the patient from bending all the way over.

**Oxygen Use**
Many patients require the use of supplemental oxygen. Stop the oxygen supply during the testing maneuver, and restart it during rest periods between maneuvers.

**Placing the Mouthpiece**
There are two techniques for placing the mouthpiece into the patient’s mouth: (a) **open circuit** and (b) **closed circuit**.

The open-circuit technique has the patient perform the maximum inhalation before putting the mouthpiece in his or her mouth. It is preferred because of infection control concerns, and some spirometers are not designed for the closed-circuit technique. However, it requires the patient to place the mouthpiece in his or her mouth correctly and seal the lips well while holding the lungs completely full. Some patients find this difficult.

The closed-circuit technique has the patient rebreathe on the mouthpiece and spirometer. This is easier for the patient and also allows inspiratory flow and volume to be assessed.

**Instructions**
Give specific instructions in simple terms that describe the rapid and maximal inspiration, a strong exhalation (blasting the air out), and continued exhalation until all the air is exhaled. For example, when using the open-circuit technique, you could say, “I want you to take the deepest breath possible, put the mouthpiece in your mouth and seal your lips tightly, and then blast all of your air into the tube as hard and as fast as you can in one long complete breath.”

For spirometers that allow the patient to breathe through the mouthpiece before the test (i.e., closed circuit), the instructions would be simpler. An additional statement that can be used to explain the maneuver further is “it’s like blowing out the candles on a birthday cake and they all don’t go out, so you need to keep blowing in the same breath until they do.”

**Demonstrate the Maneuver**
Many patients will forget some or all of the instructions, so a demonstration reinforces exactly what they are supposed to do. Show the patient the proper chin and neck position, how to get the mouthpiece in at the right time, and how to **blast** (not just blow) the air out and continue to blow.

When the demonstration is done, remind the patient of a few key points: “Be sure to take as deep a breath as possible, blast out hard and fast, and don’t stop blowing until I tell you.” If inspiratory flow–volume curves are desired, remind the patient to inhale deeply and as fast as possible.

**Summary of Important Points for Procedure Explanation**

1. Keep the explanation simple, and be brief.
2. Demonstrate how to place the mouthpiece, the proper chin and neck position, and the maneuver.
3. Remind the patient of key points (e.g., take as deep a breath as possible, **BLAST** the air out, and keep blowing in one long breath until all the air is expired).
Coaching and Encouragement During Testing

Use enthusiastic, active, and forceful coaching to help the patient perform the maneuver (Figure 1.23). You may need to raise your voice with some urgency, using such phrases as “BLAST your air out,” “blow, blow, blow,” “keep blowing, keep blowing,” or “don’t stop blowing.” However, some patients perform better with softer coaching. A good technologist recognizes when to use a raised voice and when not to.

Patient Observation and Feedback

Observe both the patient and the spirogram during the test by having the spirometer and the patient positioned in such a way that both can be watched with minimal head movement. Sometimes the mouthpiece comes out of the patient’s mouth and the operator is watching only the spirometer monitor, encouraging the patient to keep blowing, keep blowing.

After a test maneuver, give the patient feedback on the quality of the test and describe what improvements, if any, could be made. For example, statements like “that was great, Mr. Smith, but on this next maneuver BLAST out harder at the beginning” or “on this next maneuver, keep blowing out longer.” In cases when there is excessive hesitation at the start of the maneuver, which is usually caused by a lack of synchronization between the patient being ready to blast the air out and the operator prompting the patient to blast the air out. It is helpful to tell the patient to BLAST out when he or she has completely filled the lungs, even if the operator has not prompted the patient to blast out.

Allow time for the patient to catch his or her breath between maneuvers. This may take a few seconds to a minute after each maneuver. Some patients may need to take oxygen between
Spirometry Testing Techniques

General Maneuver Evaluation, Acceptability, and Repeatability

General Maneuver Evaluation

There are three main parts to evaluate when a patient performs the FVC maneuver: (a) rapid and maximal inspiration, (b) blowing out hard and fast, and (c) continued and complete expiration.

The FVC maneuver assumes a rapid and maximal inspiration. Ensure that the patient quickly takes as big a breath as possible. Submaximal inspirations will result in reduced FVC, FEV₁, and PEFR values.

When the maximal inspiration is complete, the patient should be prompted to blow the air out as hard and fast as possible with minimal hesitation. Reductions in PEFR and FEV₁ have been shown when inspiration is slow and there is a pause at total lung capacity.26 Any pause at full inspiration should be kept to no more than 1 or 2 seconds. When prompted to blow out hard, the patient should BLAST the air out, not just blow the air out from the lungs.

The third part is continued and complete exhalation. Throughout the maneuver, the patient should be coached to keep blowing and keep blowing, as previously described. Also as mentioned earlier, keep an eye on both the patient and the spirometer display (spirogram) during the test to ensure continued exhalation and to watch for any signs of dizziness. Incomplete expirations will lead to reduced FVC values.

Within Maneuver Acceptability

There are four main within-maneuver acceptability criteria: (a) good start of test, (b) no artifacts including no cough during the first second, (c) no variable flow, and (d) no early termination of exhalation. In addition, there should not be glottis closure, a leak at the mouth, or obstruction of the mouthpiece by the tongue or teeth.

Good Start of Test

There must be a good start of test. The beginning of expiration of the forced expiratory maneuver is extremely important in calculating many parameters. Therefore, the start of the expiration must be quick and forceful. An unsatisfactory start is characterized by excessive hesitation, or the extrapolated volume (discussed later in calculations) may be excessive (i.e., greater than 5% of the FVC or 0.150 liter, whichever is greater). Figure 1.24 shows both a volume–time and a flow–volume display of efforts that had a poor start of test. However, the flow–volume display (as opposed to the volume–time display) is most useful in assessing the first 1 or 2 seconds of a maneuver. If it appears that the start of test is not acceptable, remind the patient about blasting out or not hesitating (or both).

FEV₁ is determined by using the back-extrapolation technique, which is discussed in detail later in the chapter. This technique, which helps define time zero, can be performed manually, but it is more commonly performed by the spirometer computer.
Coughing

The maneuver should contain no coughing during the first second. Many patients, however, cough with each effort toward the end of the test. If this happens, the technologist should comment that the patient coughed during the maneuver and whether or not the coughing interfered with obtaining accurate results. Figure 1.25 shows an example of a spirogram where the patient coughed.

Figure 1.24

Unacceptable spirometry because of poor start of test as illustrated in the volume–time and flow–volume spiromgrams. Note the rounded shape of the flow–volume graph at the highest point (peak flow).

Figure 1.25

Unacceptable spirometry because of significant coughing as illustrated in the volume–time and flow–volume spiromgrams.
The cough, however, can also be used as a tool. Occasionally a patient’s efforts are questioned because the individual does not appear to be blowing as hard or as fast as possible or because the peak flow rates vary considerably between maneuvers. Because submaximal efforts can result in errors and variability in the FEV₁, PEFR, and other measurements, a technique can be taught that helps the operator determine whether a patient is blowing out as fast as possible at the beginning of the test. This technique requires the patient to take a full deep breath and purposely cough into the spirometer tube. The cough should be forceful, and only a small amount of air should be coughed out, not the entire vital capacity. The resulting cough PEFR represents a good approximation of the peak flow that should be obtained during the FVC when the patient is instructed to blow the air out as fast and as hard as possible. If the difference between the cough PEFR and the FVC PEFR is more than 1 liter/sec, poor patient effort or technique is likely.

**Variable Flow**

The spirogram should not have variable flow rates. This means the flow should be consistent and as fast as possible throughout the exhaled vital capacity. Figure 1.26 shows an example of variable flow.

**Early Termination**

There should be no early termination of expiration, and patients should be coached to keep blowing and keep going. There are two main end-of-test criteria used to determine if the patient exhaled long enough: (a) the patient cannot or should not continue further exhalation, and (b) the volume–time spirogram shows a plateau or no change in volume for at least 1 second, and the patient has tried to exhale for at least 6 seconds for adults and 3 seconds for children younger than age 10 years (Figure 1.27). When the forced maneuver ends early (a common
problem in young children), there is no obvious plateau and there is a cliff-like appearance at
the end of the flow–volume curve (Figure 1.28). Pay close attention to the expiratory time and
the appearance of a plateau, and coach the patient to blow at least 6 seconds up to a maximum
of 15 to 20 seconds. Although some patients can blow longer than 15 to 20 seconds, the volume
collected beyond that point is probably not clinically significant. Not meeting this criterion is
frequently the result of poor coaching, so keep urging the patient to “keep blowing, keep
blowing, don’t stop yet, keep blowing.” The operator should note if a patient cannot meet this
criterion because of discomfort or another reason. Maneuvers that do not meet the end-of-test
criteria, while not acceptable in the strictest sense of the word, do provide useful information
about FEV₁ and PEFR.

The 2005 ATS/ERS standardization of spirometry guideline describes a “usable” curve
versus an acceptable curve. A usable curve or maneuver is one that has a good start of test and
no coughing in the first second. An acceptable curve or maneuver meets all acceptability cri-
teria. In clinical practice there are times when patients cannot meet all the acceptability criteria,
but there are still valuable spirometric data that can be used to evaluate respiratory problems
or response to treatment.

**Summary of Acceptability Criteria**

1. Good start of test
2. No artifacts, including coughing, during first second
3. No variable flow
4. No early termination of expiration
5. No evidence of glottis closure, leak at mouth, extra breaths, or obstruction of mouthpiece
Between Maneuver Repeatability

After at least three acceptable maneuvers have been obtained, the *repeatability between maneuvers* should be evaluated. Because spirometry is an effort-dependent test, repeatable FVC and FEV₁ values occur if the patient is trying as hard as possible with each maneuver. The two largest FVC values from acceptable maneuvers should agree within 0.150 liter, and the two largest FEV₁ values from acceptable maneuvers should agree within 0.150 liter. Figure 1.29 demonstrates three acceptable spirometric maneuvers where the two largest FVC values agree within 0.150 liter. Figure 1.30 demonstrates three acceptable maneuvers that are not repeatable and more maneuvers are needed.

Occasionally, a patient will have *spirometry-induced worsening* (bronchospasm), meaning that each effort is worse, in terms of airflow, than the previous one. Most patients with this characteristic will eventually stop getting worse with each trial and will reach a plateau, but the patient may be too short of breath at that point to go on. An interesting problem arises when spirometry worsens with each effort. Which maneuver should be selected for the final report? The best maneuver in terms of highest FVC and FEV₁ is likely the first, as shown in Figure 1.31. However, if before-and-after bronchodilator studies are being done, the last maneuver (maneuver 4), which is also the lowest in terms of FVC and FEV₁, might be more appropriate.

**Summary of Repeatability Criteria**

1. Two largest FVC values from acceptable maneuvers agree within 0.150 liter
2. Two largest FEV₁ values from acceptable maneuvers agree within 0.150 liter
Flow–Volume Loops

In many laboratories, a full expiratory and inspiratory loop is performed. The patient is asked to take a big deep breath and fill the lungs, blast the air out hard and fast until no more air can be exhaled, and follow up with a fast and deep inspiration (Figure 1.32). This procedure is slightly more involved, and not all spirometers have the ability to measure both inspiratory and expiratory flow. In some cases, patients are unable to perform a satisfactory inspiratory portion immediately following a maximal forced expiration. When this happens it may be necessary to have the patient perform the fast and deep inspiration before the forced expiration.
or record the inspiratory portion separately from the expiratory portion. There are two important criteria to examine in flow–volume loops: (a) the inspiratory vital capacity should be at least 95% of the expiratory vital capacity, and (b) the two highest peak inspiratory flows from several trials should agree within 1 liter/sec. A more detailed explanation of flow–volume loop patterns is provided later in this chapter.

**Summary and Reminders for Good Spirometry Testing**

- Assure spirometer has been checked for accuracy (calibration check)
- Assure proper patient preparation
  - Explain the test
  - Determine any contraindications
  - Obtain age, height, and possibly weight
  - Correctly position the patient
- Explain and demonstrate the maneuver
  - Keep explanation simple and brief
  - Demonstrate attaching to mouthpiece, proper chin and neck position, and the maneuver
  - Reemphasize key points
- Perform the maneuvers
  - Attach nose clip, place mouthpiece in mouth, and seal lips (closed circuit)
  - Have patient inhale completely and rapidly
  - Instruct patient to BLAST the air out as hard and fast as possible with minimal pause; provide enthusiastic coaching
  - Provide feedback to patient on quality of each maneuver
  - Repeat test to obtain at least three acceptable maneuvers
  - Assess repeatability and perform additional maneuvers, if necessary.
CHAPTER 1 Forced Spirometry and Related Tests

Calculations and Reporting Results

Most new pulmonary function equipment is equipped with a computer or microprocessor that eliminates the need for manual calculation. However, manual calculations are required for the many manual volume-displacement spirometers still in use. Additionally, both the student and the technologist should understand the basic calculations involved to validate the computer calculations and to better comprehend what the computer or microprocessor is doing.

The specific manual calculations vary depending on the type of volume-displacement spirometer and the chart paper it uses. Spirometers designed with zero time-and-volume starting points (i.e., no air in the spirometer) and supplied with temperature-corrected chart paper are the simplest and fastest to use. The calculations for spirometers that have a rotating chart for the spirogram or operate at volumes other than zero and do not have temperature-corrected chart paper take longer, but the results are considered more accurate. Before getting into these two different methods, you must first understand the issue of temperature correction.

Temperature Correction

When a patient blows into a spirometer tube, the exhaled air coming from the lungs is 37°C and saturated with water vapor. This exhaled air cools as it travels toward the spirometer. Charles’s law states that the volume occupied by a given quantity of gas is directly related to
temperature. The air exhaled into a volume-displacement spirometer will equilibrate, given enough time, at approximately the temperature of the spirometer (which is near room or ambient temperature). The air exhaled into a nonheated flow-sensing device does not totally equilibrate to room temperature until after it has passed out of the device.

It has long been the accepted practice to express the volumes and flows measured during spirometry at body temperature. To convert volumes measured at ambient temperature and pressure saturated with water vapor (ATPS) to volumes at body temperature and pressure saturated with water vapor (BTPS), a factor must be applied (i.e., $V_{BTPS} = V_{ATPS} \times \text{factor}$).

The formula for determining that factor is:

$$V_{BTPS} = V_{ATPS} \times \frac{PB - PH_2O}{PB - 47} \times \frac{310}{273 + Ta}$$

where

- $PB$ = Barometric pressure in mmHg
- $PH_2O$ = Water vapor pressure at spirometer temperature
- $Ta$ = Room (ambient) temperature (degrees C)
- 47 = Water vapor pressure in mmHg at 37° C
- 310 = Absolute body temperature (Kelvin $+37$, or $273 + 37$)
- $V_{ATPS}$ = Volume at ambient temperature and pressure saturated
- $V_{BTPS}$ = Volume at body temperature and pressure saturated

The laboratory must be equipped or able to measure or determine barometric pressure and temperature. The temperature can either be measured inside the spirometer or with a thermometer in the room near the spirometer. When the temperature and barometric pressure are determined, the $PH_2O$ is taken from a chart, and the correction factor can be calculated. When ATPS volumes are multiplied by this factor, BTPS volumes are obtained.

This method of correcting volumes is controversial. Can the ATPS-to-BTPS factor be correctly applied to both volume-displacing and flow-sensing spirometers? Does room temperature accurately reflect spirometer temperature at the end of the FVC maneuver? These and other issues have been the subject of several studies.

Despite these concerns, temperature correction of spirometric values is still the convention and is done in the manner previously described. The computerized devices make this correction automatically, some by assuming a barometric pressure and others by having the user enter a barometer reading.

To help the reader calculate the BTPS factor, Table 1.2 lists the water vapor pressures at various temperatures, which is needed for the preceding formula. Table 1.3 presents some common BTPS factors at two different altitudes.

### FVC and FEV1 Measurement

The manual calculation of FVC and FEV1 for the volume-displacement spirometer that begins the test at zero volume (i.e., empty) is relatively simple when special lined chart paper is used. Typically, this chart paper shows time on the x axis and volume at BTPS on the y axis. Figure 1.33 shows an example of three acceptable spirometry maneuvers starting from the zero time-and-volume point.
CHAPTER 1 Forced Spirometry and Related Tests

The largest FVC is easily identified and is shown as 4.25 liters. Note the repeatability and good end-of-test technique (i.e., plateau). The largest FEV₁ (2.75 liters) is easily selected from the three volumes and is found on the 1-second line (the curves started exactly from the zero point). The values are read in liters at BTPS, but note that the chart paper states the BTPS correction is for 23°C.

If the room or spirometer temperature varies by more than 2 degrees from 23 degrees, the BTPS correction may need to be recalculated.

<table>
<thead>
<tr>
<th>°C</th>
<th>°F</th>
<th>PH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>21</td>
<td>70</td>
<td>19</td>
</tr>
<tr>
<td>22</td>
<td>72</td>
<td>20</td>
</tr>
<tr>
<td>23</td>
<td>73</td>
<td>21</td>
</tr>
<tr>
<td>24</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td>25</td>
<td>77</td>
<td>24</td>
</tr>
<tr>
<td>26</td>
<td>79</td>
<td>25</td>
</tr>
<tr>
<td>27</td>
<td>81</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 1.3
Temperature Correction (ATPS to BTPS)

<table>
<thead>
<tr>
<th>Room or spirometer temperature</th>
<th>ATPS to BTPS factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Sea level*</td>
</tr>
<tr>
<td>20</td>
<td>1.101</td>
</tr>
<tr>
<td>21</td>
<td>1.096</td>
</tr>
<tr>
<td>22</td>
<td>1.091</td>
</tr>
<tr>
<td>23</td>
<td>1.086</td>
</tr>
<tr>
<td>24</td>
<td>1.080</td>
</tr>
<tr>
<td>25</td>
<td>1.074</td>
</tr>
<tr>
<td>26</td>
<td>1.069</td>
</tr>
<tr>
<td>27</td>
<td>1.062</td>
</tr>
</tbody>
</table>

*Barometric pressure = 760 mmHg
†Barometric pressure = 625 mmHg

The largest FVC is easily identified and is shown as 4.25 liters. Note the repeatability and good end-of-test technique (i.e., plateau). The largest FEV₁ (2.75 liters) is easily selected from the three volumes and is found on the 1-second line (the curves started exactly from the zero point). The values are read in liters at BTPS, but note that the chart paper states the BTPS correction is for 23°C. If the room or spirometer temperature varies by more than 2 degrees from 23 degrees, the BTPS correction may need to be recalculated.
Calculations and Reporting Results

The calculation of FVC and FEV₁ from spirometers that have kymographs that can continually rotate or that operate at zero or other-than-zero volumes involves slightly more work. The advantage of this type of spirometer is the ability to do the closed-circuit technique where the patient can attach to and breathe on the mouthpiece before the forced spirometric maneuver. Additionally, these spirometers can collect volume for an unlimited time. Usually the chart paper on these devices comes preprinted with ATPS volumes, although some have BTPS volume grids. To measure the FVC, subtract the starting volume from the ending volume as shown in Figure 1.34. If the value is read in liters at ATPS, then a correction to BTPS is needed.

The FEV₁ is determined by using the back-extrapolation technique. Because the FEV₁ is defined as the volume exhaled in the first second of the FVC, it is critical to identify the point from which time begins (i.e., the point when the patient started blowing as fast as possible). The back-extrapolation technique, which helps define time zero, is shown in Figure 1.35A. The computer will make this measurement; however, it is important to understand how it is done. To manually measure back-extrapolation volume, use a ruler and draw a line through the steepest portion of the forced expiratory volume–time curve. Where that line crosses the horizontal line drawn from maximum inhalation is the point known as time zero (t₀). When this point is known, measure 1 second over, and then measure the volume for FEV₁. The extrapolated volume, shown in Figure 1.35B, is the volume from the maximum inhalation line to the forced expiratory curve at time zero. An extrapolated volume greater than 5% of the total FVC, or greater than 0.150 liter (whichever is larger), is considered excessive, and any trial with excessive extrapolated volume should be considered unacceptable. When the extrapolated volume exceeds this limit, it is usually because the patient had a poor start of test.

Figure 1.33

Acceptable spirometry displayed in a volume–time format on chart paper frequently used on spirometers that are empty at the beginning of the test. The FVC is read in liters on the volume axis at the highest pen deflection. The FEV₁ is read in liters on the volume axis where the pen deflection line crosses the 1-second line.
When the FVC and FEV₁ have been determined and corrected to BTPS, you can calculate the FEV₁/FVC ratio. Simply divide FEV₁ by FVC and multiply by 100.

Other Spirometry Values

Many values and measurements can be calculated from the forced spirometry maneuver. This chapter will not demonstrate how each one is calculated by hand. Instead, it will discuss the more commonly used measurements in terms of what they measure and their pitfalls.

The FEF_{25–75%} is defined as the mean forced expiratory flow during the middle half of the FVC. In other words, it is the flow over the interval that starts after 25% of the FVC has been exhaled up to the point when 75% has been exhaled. It was originally described as the MMEF (maximal midexpiratory flow) and is reported in liters/sec. Many clinicians believe it comes from a part of the spirogram that is relatively effort independent and it describes the status of the small airways, which are thought to reflect early airway obstruction. For these reasons, it is frequently used to assess bronchodilator and provocation response. However, the FEF_{25–75%} has two major disadvantages: (a) it is highly variable from maneuver to maneuver in the same patient and (b) it depends heavily on the size of the FVC. Because it depends on the size of the FVC, it is somewhat common to see improvements in FEV₁ after bronchodilator administration but no change (or even a decrease) in the FEF_{25–75%}. Investigators have described a volume-adjustment technique (using the before-bronchodilator FVC to define the 25% and 75% points for the after-bronchodilator FEF_{25–75%} measurement). The volume-adjustment technique shown in Figure 1.36 merely transposes the 25% and 75% points from the before-bronchodilator curve to the after-bronchodilator curve. The resulting FEF_{25–75%} is sometimes referred to as isovolume FEF_{25–75%}.

In conjunction with the FEF_{25–75%} is the midexpiratory time (MET). Unlike the FEF_{25–75%}, this measurement is the time (not the flow) required to exhale the mid-50% of the expiratory curve.
An example of the MET can be seen in Figure 1.36, where it is approximately 2.25 seconds before bronchodilator (Rx) and 1.50 seconds after Rx.

The flow–volume display in conjunction with measuring lung volumes can be very useful. These graphic displays of flow and volume plotted at absolute lung volume (i.e., TLC, obtained by first measuring FRC and then immediately performing the FVC maneuver) are by far the best representation of pulmonary mechanics (Figure 1.37).

The PEFR, also called the maximal forced expiratory flow (FEFmax), is the highest flow achieved during the FVC maneuver. It is not apparent from the conventional volume–time spirogram because it is an instantaneous flow. It is usually reported in liters/sec. This parameter is a very effort-dependent value, and its poor repeatability in a series of maneuvers should alert the operator to questionable patient efforts. Figure 1.38 shows two flow–volume curves. Note the sharp point or peak with a good effort and the rounded pattern of a poor effort. Figure 1.38
also illustrates the \( FEF_{25\%} \), \( FEF_{50\%} \), and \( FEF_{75\%} \), which are also commonly reported expiratory flows. The 25%, 50%, and 75% modifiers refer to the amount of the exhaled FVC. Like the \( FEF_{max} \), these parameters are instantaneous flows and are usually reported in liters/sec.

**Inspiratory Flow and Flow–Volume Loop**

As noted earlier, inspiration is an active process caused by contraction of the respiratory muscles. The alveolar pressure \( (P_{alv}) \) becomes lower than atmospheric pressure \( (P_{atm}) \) and air rushes into the lungs. Thus,

\[
\text{Maximal inspiratory airflow} = \frac{P_{atm} - P_{alv}}{\text{Resistance}}
\]

During inspiration, airway resistance usually does not limit flow because the airways are pulled open and are wider.

When a patient inspires as fast as possible directly before or after a forced expiration, a maximal flow–volume loop is formed. **Figure 1.39** shows the flow–volume loop with commonly
reported instantaneous inspiratory flows: $F_{I\text{Fmax}}$, $F_{I\text{F25\%}}$, $F_{I\text{F50\%}}$, and $F_{I\text{F75\%}}$. The 25%, 50%, and 75% modifiers in these inspiratory flows usually refer to the volume inspired from residual volume. A commonly reported ratio when the flow–volume loop is performed is the $FE_{F50\%}/F_{I\text{F50\%}}$.

The flow–volume loop, as a picture, can be very informative. Figure 1.40 presents a flow–volume loop that shows a variable intrathoracic obstruction, commonly seen in patients with obstructive lung disease such as asthma or emphysema. During forced expiration, the airways collapse because of the high pleural pressure, and expiratory flow is reduced. Note the scooped-out appearance of the expiratory portion. During forced inspiration, the airways widen because of the negative intrathoracic pressure, and inspiratory flow is normal. The $FE_{F50\%}/F_{I\text{F50\%}}$ ratio in this case would be low (i.e., less than 0.8).

Figure 1.41 presents a flow–volume loop that shows a variable extrathoracic obstruction. The forced expiratory flow rates are normal and higher than those achieved during the forced inspiration. During the forced inspiration, flow rates are reduced because the airway pressure above the thoracic cage (extrathoracic) is less than atmospheric pressure, causing collapse. The $FE_{F50\%}/F_{I\text{F50\%}}$ ratio in this case would be increased (i.e., greater than 1.2).

Figure 1.42 presents a flow–volume loop that shows a fixed obstruction. The airway is minimally affected by airway pressure because of an intrathoracic or extrathoracic blockage. Airflow during forced inspiration and expiration is equally reduced, and the flow–volume loop

Figure 1.37
Flow–volume graph of forced spirometry showing the measured curves before and after bronchodilator (Rx). The placement of the curves is at absolute lung volumes, determined by first measuring FRC (e.g., through body box) and then immediately performing forced spirometry with the patient staying on the mouthpiece for both parts. The maximum inhalation level (i.e., TLC) can be measured (FRC + inspiratory capacity) and used as the absolute volume level to place the curve.
appears rectangular. The FEF_{50%}/FIF_{50%} ratio in this case may be normal (i.e., between 0.8 and 1.2), but the instantaneous flow rates are reduced.

Figure 1.43 presents some additional examples of abnormal and normal flow–volume loops. The severe emphysema pattern (Figure 1.43A) shows significant air trapping and a scooped-out appearance. This is contrasted with the more mild forms of intrathoracic obstruction (Figure 1.43B). Flow–volume curves in patients with a restriction process (Figure 1.43C) have no air trapping and a normal flow–volume shape, but there is a reduced FVC. When airflow obstruction is mainly in the large airways (e.g., tumor), a slightly different variable intrathoracic pattern is observed (Figure 1.43D).

**Reporting Results**

After obtaining at least three acceptable maneuvers, two of which are repeatable, which maneuver or values should be used on the report? Usually, just one FVC, one FEV₁, and one each of all the other values are reported. How does one choose?
The largest FVC and the largest FEV₁ (BTPS) should be reported, even if the two values come from different curves. Other measurements (e.g., FEF₂₅–₇₅% or instantaneous flows) should be obtained from the single best test curve. The best test curve is the acceptable curve that has the largest sum of FVC and FEV₁.

Figure 1.44 shows three acceptable efforts on a volume–time display. Effort 1 has the largest FVC, and effort 2 has the largest FEV₁. The best test curve (the curve with the largest sum of FVC and FEV₁) is effort 2, and it is the curve from which the FEF₂₅–₇₅% should be taken.

All results should be expressed in liters at BTPS, rounded to two decimal points.

Comments on Testing

Pulmonary function test reports should always contain comments from the technologist to aid in interpretation of data and to provide the reviewer additional information on the conditions.
Figure 1.40
Flow–volume loop showing a variable intrathoracic obstruction commonly seen in patients with obstructive lung disease. During forced inspiration, the airways widen because of the negative intrathoracic pressure, and inspiratory flow is normal. During forced expiration, the increased pleural pressure causes airways to collapse, resulting in an exaggerated reduction in airflow.


Figure 1.41
Flow–volume loop showing a variable extrathoracic obstruction. During forced inspiration, flow rates are reduced because airway pressure outside the thoracic cage (i.e., extrathoracic) is less than atmospheric pressure, as indicated by the arrows. During forced expiration, airflow is commonly normal.

Calculations and Reporting Results

47

of the patient at the time of testing and the quality of the test. The comments should be clear, concise, and accurate, including comments about test quality, reliability of data, and any deviations from recommended guidelines.

If the testing was well done and the data are good quality, make simple statement such as, “Excellent patient effort and technique.” If the testing was not done well you could state something like, “Good effort, but patient unable to perform spirometry maneuver consistently, resulting in considerable variability.”

Spirometry Reference (Predicted) Values

It is common practice to compare each measured or calculated variable in a patient’s pulmonary function test with a reference or predicted value. This comparison provides the basis for interpretation. An in-depth discussion of how reference values are established and determining the lower limit of normal are presented in Chapter 12.

Following Changes Over Time

It may also be important to observe and compare changes in spirometry over time (a longitudinal study). Sequential tests that are done monthly or yearly, for example, can determine whether a patient’s lung function is worsening, improving, or not changing—except for aging. Figure 1.45 demonstrates why observing and comparing changes in a patient over time can be more valuable than simply comparing results with a reference value. Figure 1.45A is a graph of two patients on a reference regression line for a pulmonary function test value. The regression line of the equation slopes downward (declines) with age, and the shaded area

Flow–volume loop showing a fixed obstruction, which can result from an intrathoracic or extrathoracic problem. Typically, airflow is equally limited during expiration and inspiration.

represents the 95% confidence interval. Patient 1 is above the regression line, and in fact is
above the 95% confidence interval. Patient 2, however, is below the 95% level, and the result
would likely be called abnormal. Figure 1.45B shows the same two patients measured again
2 years later. Patient 2 is still below the 95% level, and the result still would likely be called
abnormal, but the results are declining at the expected normal rate. Although the result for
patient 1 is still normal, it is declining much faster than expected.

When examining spirometric results over time, it is important to define a meaningful
change. The FVC and FEV₁ are the two variables used in this type of evaluation. The expected
decrease in these parameters from aging is approximately 25 to 30 mL/year. Additionally, there
is the factor of test variability. Hence, for FVC and FEV₁, week-to-week changes that exceed
11% and 12%, respectively, should be considered meaningful. For FVC and FEV₁, yearly
changes that exceed 15% should be considered meaningful. 34
Figure 1.44

Volume–time graph of three acceptable forced spirometry efforts. Effort 1 has the highest FVC (3.55 liters), and effort 2 has the highest FEV₁ (2.02 liters). Effort 2 also has the highest sum of FVC and FEV₁, and would thus be called the best curve.

Figure 1.45

Pulmonary function test (PFT) results and reference regression line (solid) with the 95% confidence intervals (dashed) on two patients (1 and 2) of the same age (45 years). A. Patient 1 is above the 95% confidence interval for this particular parameter, and the results would be called normal or even above normal. Patient 2 falls below the 95% confidence interval, and the results would be called abnormal. B. Two years later, both patients are aged 47 years. Patient 2 is still below the 95% confidence interval, and the results would again be called abnormal. Patient 1 is within the 95% confidence interval, and the results would be called normal. However, patient 1 is declining faster than the reference regression line and faster than patient 2. We should be concerned about patient 1.
Reversibility Testing

Bronchodilators are administered routinely in the pulmonary function laboratory to determine whether airflow obstruction is reversible. Some laboratories test all patients for reversible airways obstruction; others do so only if the patient has an abnormality. In the author’s opinion, all patients should undergo spirometry testing before and after receiving a bronchodilator because of the large variation in normal values and because even a patient with normal values may have significantly higher values after receiving a bronchodilator.

Drugs that reduce bronchospasm or airflow obstruction are called bronchodilators. These drugs are available for administration by several routes: (a) inhalation, (b) oral, (c) intramuscular, or (d) intravenous. This section will focus only on drugs administered by inhalation (i.e., aerosolized).

Bronchodilators increase airway caliber by relaxing airway smooth muscle. The aerosolized bronchodilators are usually sympathomimetic (adrenergic) and affect the two primary types of adrenergic receptors located in the bronchial smooth muscle and blood vessels: alpha and beta. The alpha receptors cause vasoconstriction. The beta receptors, which can be divided into two groups (beta 1 and beta 2), cause vasodilatation, bronchodilatation, and increased heart rate, among other things. The beta-1 receptors increase the heart rate more than they dilate bronchi, and the beta 2-receptors cause more bronchodilation than increased heart rate.

The ordering physician usually chooses the drug, dose, and mode of delivery, depending on the question being asked. However, many laboratories have a written procedure for bronchodilator administration if the physician has not specified such information.

Aerosolized bronchodilators can be given in several ways, including: (a) metered dose inhalers (MDI), (b) jet nebulizers powered by compressed air, and (c) ultrasonic nebulizer. The use of a spacer can increase the effectiveness of the MDI in some patients and is used frequently in the laboratory.

The method for using an MDI is important. The technologist should supervise or perform MDI actuation. The procedure is not standardized but should include the following: (a) shake the MDI and actuate it several times to prime; (b) attach spacer, if appropriate; (c) direct the patient to slowly exhale completely; (d) direct the patient to slowly inhale, and actuate the MDI just after the inhalation starts; (e) direct the patient to continue to inhale slowly; as deeply as possible; (f) direct the patient to hold his or her breath for 5 to 10 seconds and slowly exhale; and (g) wait 30 to 60 seconds before performing a repeat inhalation of the drug.

In many laboratories, more than two actuations of a beta agonist such as albuterol (a common clinical dose) are administered. The ATS/ERS recommendations are to deliver a high dose (e.g., four actuations) in the laboratory. In some laboratories the actuations continue until side effects are achieved (e.g., increased heart rate, shakiness, or headache). The reason for more than two actuations is to ensure that the patient received a good treatment, which is indicated by the side effects. Any laboratory considering such a method should write a protocol describing the contraindications and side effect limits.

After administering the bronchodilator, the technologist should wait at least 10 to 15 minutes before repeating the pulmonary function tests. This will ensure that the medication is approaching or is at peak effect.
In some cases anticholinergic medications (e.g., ipratropium bromide) are administered in the laboratory to assess bronchodilator response. If these medications are used, the technologist should wait at least 30 minutes before repeating the test.

**Summary of Key Points for Spirometry Reversibility Testing**

- Use an appropriate bronchodilator (i.e., one ordered by the physician, used clinically by the patient, or specified in the laboratory procedure manual).
- Administer or supervise patient administration of the ordered amount or an amount that is clinically useful.
- Wait at least 10 to 15 minutes before repeating pulmonary tests.
- Note how much of the drug was given, the method of administration, and responses, such as increased heart rate, shakiness, palpitation, or patient comments.

**Reporting Bronchodilator Therapy**

The pulmonary function test report should include the pulmonary medications taken by the patient before and as part of the test. As previously stated, note how much of the drug was given with the test and the method of administration. To report medications the patient used before testing, ask the patient or check the patient’s chart. Because there are numerous medications and combinations of medications, you must know the names of the different drugs (generic and trade names), mode of action, and route of administration. Additionally, because taking certain medications before a pulmonary function test may contraindicate performing the test, you must know the duration of action. **Table 1.4** is a list of medications frequently taken by patients with pulmonary disease.

**Table 1.4**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Withhold time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting beta agonists (e.g., albuterol, terbutaline)</td>
<td>4 to 6 hours</td>
</tr>
<tr>
<td>Long-acting beta agonists (e.g., salmeterol, formoterol)</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td>Short-acting anticholinergics (e.g., ipratropium bromide)</td>
<td>4 to 6 hours</td>
</tr>
<tr>
<td>Long-acting anticholinergics (e.g., tiotropium)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Theophyllines</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td>Leukotriene modifiers (e.g., montelukast [Singulair], zafirlukast [Accolate])</td>
<td>24 hours</td>
</tr>
<tr>
<td>Inhaled corticosteroids (e.g., beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, flunisolide)</td>
<td>Uncertain, but usually withheld day of testing</td>
</tr>
<tr>
<td>Inhaled corticosteroids + long-acting beta agonists (e.g., Advair)</td>
<td>12 to 24 hours</td>
</tr>
</tbody>
</table>
CHAPTER 1 Forced Spirometry and Related Tests

Basic Elements of Interpretation

The pulmonologist is usually responsible for interpreting the results of pulmonary function tests. However, the technologists should know the basic elements of spirometric interpretation to help them obtain better and more useful information when performing the test and to better understand the clinical implications of the results.

The forced spirogram provides information about the flow and volume of air moving in and out of the lungs in one rapid inhalation and forced expiration. When the airways are narrowed, the flow through them will be reduced. Airway narrowing can result from bronchospasm (smooth muscle contraction), inflammation, increased mucus, tumors (either internal or external to the airway), or loss of elasticity resulting in airway collapse. This reduction in airflow is referred to as airflow limitation. Another commonly used term is obstruction, as in airway obstruction and obstructive airway disease. However, the term obstruction implies that the reduction in airflow is from material inside the airway, which is only one of many reasons for airway narrowing.

Many parameters can be measured from the forced spirogram or flow–volume loop, but only a few are helpful in the interpretation process. Specifically, this section will address the FVC, FEV₁, and the FEV₁/FVC ratio.

Airflow Limitation Versus Restriction

The FVC is the maximum volume of air forcibly exhaled after a maximum inhalation. An FVC below the lower limits of normal, even though effort was maximal, can be due to: (a) airflow limitation wherein air is trapped in the alveoli due to collapsing airways and/or is caused by a reduced driving force due to decreased elasticity or (b) reduced lung size caused by a restrictive process (e.g., interstitial lung disease, neuromuscular disease, or chest wall disorders).

The FEV₁ is the volume exhaled in the first second of the FVC. It too can be reduced because of airflow limitation or a restrictive process.

The FEV₁/FVC ratio (usually multiplied by 100 and expressed as a percentage) is the primary variable used to determine the presence of airflow limitation. In patients with airflow limitation, the FEV₁/FVC ratio is reduced. When this ratio is borderline, other measurements (e.g., instantaneous and midflows) can be used to assist in the interpretation process. However, the use of the FEF₂₅₋₇₅% and instantaneous flows to diagnose small airway disease is not recommended.

Some clinicians prefer to quantitate the severity of airflow limitation, although there is no agreement on what is mild, moderate, or severe. If this is done, it should be based on FEV₁ rather than FEV₁/FVC%. Table 1.5 presents an example of assessment of airflow limitation severity and is based on FEV₁.

A restrictive process or pattern can be detected from a decreased FVC and FEV₁. However, the primary variable used to determine restriction is the TLC (which is not measured during spirometry). The FEV₁/FVC ratio is typically normal or increased in patients with a restrictive pattern. Thus, if a patient’s FVC and FEV₁ are reduced, and the FEV₁/FVC ratio is normal or increased, the interpretation should state that a restrictive pattern cannot be ruled out.

Additionally, there can be a mixed obstructive and restrictive disease process that is very difficult to confirm with spirometry alone. If a mixed disorder is suspected, the static lung volumes, including FRC, residual volume (RV), and TLC, must also be measured.
The written interpretation of the forced spirogram will vary depending on the interpreter. Some interpreters will make an observation only such as airflow limitation or reduced FEV₁, but others will quantify the observations by stating severe airflow limitation or moderately reduced FEV₁. However, as mentioned earlier, there is no agreement on what is mild, moderate, or severe. Additionally, the current practice is that the written interpretation should always contain a statement on the quality of the test. A very simple flowchart to interpret the forced spirogram with an inspiratory curve is shown in Figure 1.46.

### Interpretation of Bronchodilator Response

The response to a bronchodilator is determined by calculating percent change from the prebronchodilator values. Percent change is calculated as follows:

\[
\text{% change} = \frac{\text{Postbronchodilator value} - \text{Prebronchodilator value}}{\text{Prebronchodilator value}} \times 100
\]

When evaluating a patient’s bronchodilator response it is important to consider such factors as the response of healthy individuals to bronchodilators and the variability of the measurements. Additionally, it is important to consider which measurement(s) should be examined. In the general population, the response to a bronchodilator for FVC, FEV₁, and FEF₂₅₋₇₅% is an increase of approximately 11%, 8%, and 20%, respectively. The variability of the FVC, FEV₁, and FEF₂₅₋₇₅% measurements themselves in patients with asthma is 11%, 13%, and 23%, respectively.

Light and coworkers evaluated a number of pulmonary function measurements before and after bronchodilator. In comparing the magnitude of response with the variability, the FEV₁ had the highest discriminatory ability. Measurements such as specific airway conductance (sGaw) (see Chapter 4) and FEF₂₅₋₇₅%, although they increased more, were not better than FEV₁ in identifying responders. Berger and Smith and Sourk and Nugent also showed that the FEV₁ was the better parameter.

The use of FEV₁ and FVC in examining the response, as measured by spirometry, to a bronchodilator has been endorsed by the ATS/ERS. In 2010 a 12% increase in FEV₁ and a 200 mL (0.2 liter) increase in either FEV₁ or FVC are recommended as criteria for a positive bronchodilator response in adults. The FEF₂₅₋₇₅% and instantaneous flows should be used only

<table>
<thead>
<tr>
<th>Degree of Severity</th>
<th>FEV₁ Percent Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Moderate</td>
<td>60% to 69%</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>50% to 59%</td>
</tr>
<tr>
<td>Severe</td>
<td>35% to 49%</td>
</tr>
<tr>
<td>Very severe</td>
<td>&lt;35%</td>
</tr>
</tbody>
</table>
secondarily, and, if used at all, they should be adjusted for volume (i.e., measured at isovolume). The FEV1/FVC ratio should not be used to measure response to a bronchodilator.

Table 1.6 compares the spirometric data of two patients: one with airflow limitation and the other with a restrictive process. It can be seen that the FEV1/FVC ratio clearly distinguishes the patient with airflow limitation from the patient with a restrictive process. It can also be seen that the patient with airflow limitation responds to bronchodilator (23% improvement in FEV1 and 18% improvement in FVC), but the FEV1/FVC ratio does not change significantly.
Special Considerations

Obtaining acceptable and repeatable spirometry results is not an easy task. A number of patient, operator, and equipment constraints must be satisfied. What happens when the patient is not cooperative, is unable to follow directions, or is physically unable to do what is asked? When such problems occur, the operator may dismiss the patient and report that the patient is unable to perform spirometry. However, in many of these instances, spirometry can be adequately performed if the operator is skilled, patient, and willing to take extra time.

Patients Who Won’t

Most patients come to the hospital or office because they are sincerely seeking help. They are willing to do most things asked of them and are cooperative. A small percentage of patients are not willing to do what is asked of them and are not very cooperative. Sometimes such patients are involved in legal action, and a gain or loss may ride on the test outcome. What does one say to these uncooperative patients? How does one get them to do an effort-dependent test like spirometry? The first step is to have the ordering physician give the patient a pep talk, stressing the importance of trying as hard as possible. Next tell the uncooperative patient that “the data obtained thus far are not reportable, and therefore the doctors or litigation (or both) cannot proceed.” You can add, “You must try harder to blow faster and longer.” This direct, no-nonsense approach frequently works with these types of patients.

Patients Who Have Difficulty Following Directions

Some patients have difficulty following directions, for example, the very young, the very old, and the hearing impaired. Testing children is a particular challenge, and Chapter 10 discusses approaches to pediatric testing.

<table>
<thead>
<tr>
<th>Table 1.6</th>
<th>Examples of Data from Forced Spirometry Done on Two Patients Before and After Bronchodilator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted value</td>
<td>Patient with airflow limitation</td>
</tr>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.85</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.82</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>79</td>
</tr>
</tbody>
</table>

*The reference values are obtained from the NHANES III standards42 using a 45-year-old man who is 68 inches tall.

†Values in parentheses are percent predicted.
CHAPTER 1 Forced Spirometry and Related Tests

Very old patients may have many problems that can affect the outcome of spirometry (e.g., poor coordination, hearing impairment, fatigue, illness). The key to successful pulmonary function testing with these patients, as with children, is patience. Explain the instructions for the procedure carefully, repeat as frequently as the circumstances dictate, and be prepared and willing to take extra time.

Hearing impaired patients and those who do not speak English must be able to hear and understand what you want them to do. In some cases an interpreter is needed to relay instructions. For those who wear hearing aids and still do not hear well, or for those who just do not hear well enough to catch all the details, written instructions may work well. Hearing aids amplify all sounds, and in noisy environments discriminating speech from other sounds may be a problem. Because most hearing impaired people lip-read very well, speak slowly and clearly while looking directly at the patient. Again, patience is the key to success.

Patients Who Can’t

Another group of patients who need special considerations are those who are physically unable to perform the test in the standard manner (e.g., patients with tracheostomies, patients who cannot seal the mouthpiece tightly because of paralysis or malformation of the lips or mouth, and patients who have significant muscular weakness). Ingenuity is sometimes the key to working successfully with such patients. For example, an infant positive-pressure mask connected to the spirometer through a tubing adapter can be fitted over the tracheal stoma to assist in spirometry for the patient with a tracheostomy. The ordering physician can only expect the technologist to try as hard as possible to get as much valid information as possible. In some instances valid information cannot be obtained.

Maximum Voluntary Ventilation

The maximum amount of air that can be exhaled in a specified period during rapid and forced breathing is commonly referred to as the maximum voluntary ventilation (MVV). An older term for this volume is the maximum breathing capacity (MBC). MVV depends on a number of physiologic factors, including movement of the thoracic cage and the respiratory muscles and lung resistance.

In the past, the MVV test was commonly performed during routine pulmonary function tests. However, its clinical use declined over the years due to the fact that if FEV₁ is available, it adds little clinical information. Today, the MVV test is most commonly performed as part of the cardiopulmonary exercise test, where it is used as an index of maximum ventilatory capacity.

The test is performed on the same spirometer system used for forced spirometry. The patient should attach to the mouthpiece and place a nose clip on the nose. When directed, the patient should breathe in and out deeply and rapidly for 12 to 15 seconds. The tidal volume during this maneuver should approximate 50% of the vital capacity with a breathing frequency of approximately 90 breaths/min. The expired volume during this short period is extrapolated to 1 minute and reported at BTPS in liters/min. Obtain at least two trials, with a repeatability goal of ±10%. If the variability is greater than 20%, additional maneuvers should be obtained. The highest acceptable MVV and MVV rate should be reported.
Patients often settle at a rate and volume that is most comfortable for them. Emphasize in
the instructions that a smooth and rhythmic breathing pattern is critical to obtaining optimal results.

Reference (predicted) values for the MVV test have been published and are shown in Table 1.7. The MVV will be decreased in patients with airflow obstruction, respiratory muscle weakness, poor coordination, and poor effort. A calculation or approximation of MVV can be made using the following formula:

\[
\text{Calculated MVV} = \frac{40}{\text{FEV}_1}
\]

However some prefer to use \(\text{MVV} = 35 \times \text{FEV}_1\).

### Peak Expiratory Flow Rate Monitoring

PEFR is the highest flow achieved from a maximum forced expiratory maneuver. It can be
obtained in the laboratory using a spirometer and expressed at BTPS in liters/sec. Or it can be
obtained using small portable monitoring instruments and expressed in liters/min. These port-
able devices can be inexpensive, nonelectronic devices or more expensive electronic devices
that can also measure FEV\(_1\). This section will present information about measuring PEFR using
small portable instruments that have become an important part of asthma management and
monitoring. It is important for the respiratory care student and technologist to understand how
to use these devices and the test procedure.

PEFR meters measure flow, and most nonelectronic devices use a similar design. The
patient blows with maximum effort and force into a tube that has a movable indicator.
The indicator moves in proportion to the airflow through the device. PEFR can then be read
directly in liters/min from the calibrated scale on the device. High-flow ranges (e.g., 0 to 850
liters/min) for adults and low-flow ranges (e.g., 0 to 400 liters/min) for children are often
available. These devices vary in price from about $10 to $30.

Newer electronic devices measure flow using various flow-sensing technologies and are
almost miniature spirometers. PEFR can be read digitally, and these devices vary in price from
about $100 to $350.

PEFR greatly depends on patient effort and cooperation and lung volume. To achieve a
maximum value, PEFR must be measured when the lungs are completely full (i.e., maximum
inspiration) and without expiratory hesitation.\(^45\) Strong coaching and encouragement is important.
The patient’s neck should not be bent (neck flexion or extension can lower PEFR), and the

### Table 1.7

<table>
<thead>
<tr>
<th>Reference Values for the MVV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boren and colleagues(^43)</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>(3.39(\text{Height in inches}) - 1.26(\text{Age}) - 21.4)</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>(138 - 0.77(\text{Age}))</td>
</tr>
<tr>
<td>Grimby and Soderholm(^44)</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>(79.0(\text{Height in meters}) - 1.42(\text{Age}) + 76)</td>
</tr>
</tbody>
</table>

---

patient should not cough or spit during the maneuver (coughing or spitting can falsely increase PEFR in some devices). A nose clip is not necessary.

If PEFR is to be self-measured by the patient at home, it is important that adequate instructions on how to perform the test are provided. Regular checks of the patient’s technique and use of a PEFR meter are important quality control steps.

At least three acceptable PEFR maneuvers should be performed. PEFR maneuvers are considered acceptable when the patient takes a maximal inspiration, there is a good seal at the mouth, and no hesitation and no coughing or spitting occurred. The PEFR values and their order must be recorded. The highest two of three acceptable PEFR values should agree within 40 liters/min. If this repeatability is not achieved, additional maneuvers should be obtained. The largest PEFR value from at least three acceptable and two repeatable maneuvers is reported.

**Infection Control**

The role of respiratory therapy equipment in healthcare-associated infections usually receives great attention. However, the role of pulmonary function equipment in the transmission of infections is not well documented.

Several studies reported that a range of nonpathogenic flora existed in spirometers and associated tubing. Burgos and coworkers reported that bacterial colonization of water-sealed spirometers occurred within 3 days of use, but they could not demonstrate any transmission from spirometer to patient. Hiebert and coworkers reported in an interesting study that transfer of *Escherichia coli* organisms does not occur during routine spirometry as long as an interval of at least 5 minutes is allowed between tests. In one case, the transmission of microorganisms to other patients and operators was reported.

Hence it is probably safe to speculate that there is a small risk of cross-contamination when pulmonary function equipment is used. It also seems safe to speculate that this risk is inversely proportional to the frequency of cleaning or changing equipment parts. The use of barrier filters to trap microorganisms might reduce this risk; however, the filters may interfere with accuracy and may cause small reductions in peak flow (although these reductions are probably not clinically meaningful).

The Centers for Disease Control and Prevention has published guidelines for preventing transmission of infectious agents in healthcare settings. In addition, Kendrick and coworkers published an excellent review and practical approach to infection control in the pulmonary function laboratory.

**Recommendations for Infection Control in the Pulmonary Function Laboratory**

- Disposable mouthpieces or flow sensors should be discarded after single patient use. Reusable mouthpieces should be washed, disinfected, and dried after use. The choice of disinfection method varies from laboratory to laboratory. Acceptable methods are chemical disinfection, dishwasher-type systems, and steam.
Case Presentations

Case 1.1
A 16-year-old boy was tested in the pulmonary function laboratory. The ordering doctor noted that the diagnosis is asthma. The results of each spirometry trial are shown in Table 1.8 and Figure 1.47.

Table 1.8
Spirometric Results of Each Trial Before and After Bronchodilator (Rx) on 16-year-old Male in Case 1.1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time</th>
<th>FVC (L)</th>
<th>FEV₁ (L)</th>
<th>FEV₁/FVC %</th>
<th>FEF₂₅–₇₅% (L/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Rx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1</td>
<td>9:05</td>
<td>4.13</td>
<td>3.01</td>
<td>73</td>
<td>2.03</td>
</tr>
<tr>
<td>Trial 2</td>
<td>9:07</td>
<td>3.61</td>
<td>2.48</td>
<td>69</td>
<td>1.63</td>
</tr>
<tr>
<td>Trial 3</td>
<td>9:08</td>
<td>3.42</td>
<td>2.41</td>
<td>70</td>
<td>1.69</td>
</tr>
<tr>
<td>Trial 4</td>
<td>9:10</td>
<td>3.12</td>
<td>2.01</td>
<td>64</td>
<td>1.48</td>
</tr>
<tr>
<td>Trial 5</td>
<td>9:12</td>
<td>3.09</td>
<td>2.02</td>
<td>65</td>
<td>1.51</td>
</tr>
<tr>
<td><strong>After Rx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1</td>
<td>9:40</td>
<td>4.33</td>
<td>3.30</td>
<td>76</td>
<td>2.59</td>
</tr>
<tr>
<td>Trial 2</td>
<td>9:42</td>
<td>4.29</td>
<td>3.31</td>
<td>77</td>
<td>2.63</td>
</tr>
<tr>
<td>Trial 3</td>
<td>9:43</td>
<td>4.32</td>
<td>3.33</td>
<td>77</td>
<td>2.58</td>
</tr>
</tbody>
</table>
Figure 1.47: Spirometric results in flow-volume graph format showing five maneuvers before bronchodilator (Rx) and three maneuvers after Rx.

<table>
<thead>
<tr>
<th>Flow (L/sec)</th>
<th>Before Rx</th>
<th>After Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>642</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>100</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>800</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>500</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>Before Rx</th>
<th>After Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>900</td>
<td>800</td>
</tr>
<tr>
<td>900</td>
<td>800</td>
<td>700</td>
</tr>
<tr>
<td>800</td>
<td>700</td>
<td>600</td>
</tr>
</tbody>
</table>

Flow (L/sec) vs. Volume (L) graph showing the relationship before and after bronchodilator administration.
Questions
1. What is the interpretation/evaluation of these spirometric tests?
2. Which before-and-after efforts should be reported?

Answers and Discussion
The first FVC effort (9:05) shows mild airflow limitation based on the reduced FEV₁/FVC% and FEF₂₅₋₇₅% (43% of predicted). The remaining before-Rx efforts show significant deterioration.

The after-Rx forced expiratory efforts show marked improvement in airflow. The amount of improvement depends on which before-Rx effort is used for comparison.

The deterioration of flow rates in the before-Rx test could be caused by poor effort or spirometry-induced bronchoconstriction. Poor effort is a factor the operator must assess. The diagnosis of asthma makes the spirometry itself the likely cause of the airflow deterioration.

The effects of deep inspiration have been studied and have shown varying effects on airflow. In some asthmatics, a deep inspiration causes bronchoconstriction that comes on rapidly and may disappear spontaneously in 1 or 2 minutes. In nonasthmatics a deep inspiration has shown a bronchodilatation effect.

Traditionally, one maneuver from the before-bronchodilator testing and one maneuver from the after-bronchodilator testing are reported. In Case 1.1, if the first before-Rx maneuver is selected (based on highest value), the comparison to after-Rx maneuvers would show only a small improvement. However, if the fifth before-Rx maneuver is selected, which best represents the patient’s airflow before the bronchodilator, the interpretation is quite different. Alternatively, both the first and fifth maneuvers could be reported to show the deterioration, or a comment could be made noting the deterioration.

Case 1.2
A 42-year-old Caucasian woman was seen in the pulmonary function laboratory. The ordering doctor had noted asthma as the diagnosis and noted that she was being treated with theophylline and inhaled bronchodilators. The results from her pulmonary function tests are shown in Table 1.9.

Table 1.9
Pulmonary Function Results Before and After Bronchodilator (Two Actuations of Albuterol from a Metered Dose Inhaler)

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Before*</th>
<th>After</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.26</td>
<td>2.90 (89)</td>
<td>3.00</td>
<td>3</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.73</td>
<td>2.02 (74)</td>
<td>2.18</td>
<td>8</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>84</td>
<td>70</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/sec)</td>
<td>3.26</td>
<td>2.41 (74)</td>
<td>2.62</td>
<td>9</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent predicted.
CHAPTER 1 Forced Spirometry and Related Tests

Questions

1. What is the interpretation/evaluation of these spirometric tests?
2. What issues would be raised with these results, given the diagnosis and medication regimen?

Answers and Discussion

The spirometry data reveal airflow limitation with only minimal response to the two puffs of the albuterol MDI.

One question is whether bronchodilators were withheld before this spirometric test. A short-acting bronchodilator taken within 8 hours of spirometry can affect the results and interpretation. Inhaled short-acting bronchodilators should be withheld for their duration of action (usually 4 to 8 hours) before such a test. Long-acting bronchodilators should be withheld for 12 to 24 hours. The advisability of withholding oral or inhaled bronchodilators for pulmonary function tests is controversial; follow the physician’s directive.

Another question is whether the patient has airflow limitation that improves with bronchodilators. If not, she may not need the medications with which she is being treated. A bronchial provocation test (e.g., methacholine) would determine the presence or absence of bronchial hyperreactivity (asthma).

In this particular case, a methacholine challenge revealed moderate airway hyperreactivity, which is surprising given her poor response to the bronchodilator during spirometry. However, patients with hyperreactive airways (asthma) may not respond to inhaled bronchodilators for several reasons:

• The medication delivered by MDI is trapped in the mouth and does not reach the airways.
• The large airways are physically narrowed, with decreased amounts of medication reaching the lower airways.
• The patient has a bronchospastic reaction to the propellant used in the MDI.
• The patient has problems with the technique of MDI administration (e.g., coordination, breath holding, or rate of inhalation).

It is possible that, in this patient, any or several of these reasons played a role. Although the usual clinical dose of albuterol using an MDI is two actuations, it may be necessary to deliver more medication to demonstrate bronchodilator improvement.

The spirometry was repeated several days later. This time, however, the order was for six actuations unless the patient developed side effects (e.g., tremors, tachycardia, palpitations, headache). The results are shown in Table 1.10.

These results clearly show that this patient responds to the bronchodilator, which is consistent with the methacholine challenge. In this case, six actuations were enough; possibly four or five would have been enough. The usual dose of two actuations has been established as the dose that usually does not cause side effects and usually results in improvement, but some patients require more actuations.

Table 1.10
Self-Assessment Questions

1. During a forced expiration, the point in the airways where the pleural pressure equals the airway pressure is called the:
   a. Equal airway pressure
   b. Null pressure point
   c. Equal pressure point
   d. Transpulmonary pressure

2. All the following are examples of a volume-displacement spirometer except:
   a. Water seal
   b. Bellows
   c. Balloon
   d. Rolling seal

3. All the following are examples of flow-sensing spirometers except:
   a. Pneumotachograph
   b. Thermistor
   c. Wedge
   d. Ultrasonic

4. Calibration of spirometers should be done with a good quality syringe of known volume:
   a. Before every patient
   b. Every day it is used
   c. Once per week
   d. Once per month

5. All the following are acceptability criteria for valid spirometry except:
   a. No coughing
   b. No early termination
   c. Good repeatability of FVC and FEV₁
   d. Good start of test
   e. None of the above

Table 1.10

Pulmonary Function Results Before and After Bronchodilator (Six Actuations of Albuterol from a Metered Dose Inhaler)

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Before</th>
<th>After</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.26</td>
<td>2.83</td>
<td>3.19</td>
<td>13</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.73</td>
<td>1.98</td>
<td>2.47</td>
<td>25</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>84</td>
<td>70</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>FEF25–75% (L/sec)</td>
<td>3.26</td>
<td>2.46</td>
<td>3.39</td>
<td>38</td>
</tr>
</tbody>
</table>
6. When calibrating a spirometer with a known-volume calibration syringe, the volume measured should be within what percentage of the known volume?
   a. ± 1%
   b. ± 3.5%
   c. ± 5%
   d. ± 7%

7. Spirometric values are reported as the volume at:
   a. ATPS
   b. BTPS
   c. STPD
   d. ATPD

8. Several concerns have been raised about the use of reference values. Which of the following is not a concern?
   a. Not enough values for certain races and age groups
   b. Use of different types of instrumentation
   c. Inclusion of current and ex-smokers in some studies
   d. Not all values are contained in one study
   e. None of the above

9. When performing reversibility testing, how long after bronchodilator administration should you wait before performing postbronchodilator testing?
   a. 1–5 minutes
   b. 3–6 minutes
   c. 10–15 minutes
   d. 30–35 minutes

10. According to the 2005 ATS/ERS Standardization of Spirometry, the acceptable limit for back-extrapolated volume as a percentage of the vital capacity is less than:
   a. 5% of FVC
   b. 7% of FVC or 0.150 liter, whichever is greater
   c. 5% of FVC or 0.150 liter, whichever is greater
   d. 3% of FVC

11. When performing PEFR measurements using a peak flow meter, the largest two of three acceptable blows should be repeatable within:
   a. 10 liters/min
   b. 20 liters/min
   c. 40 liters/min
   d. 80 liters/min

12. According to the 2005 ATS/ERS Standardization of Spirometry, the repeatability requirement for valid spirometry is:
   a. The two largest FVC values must be within 3% of each other, and the two largest FEV1 values must be within 3% of each other.
   b. The two largest FVC values must be within 5% of each other, and the two largest FEV1 values must be within 5% of each other.
The two largest FVC values must be within 0.150 liter of each other, and the two largest FEV$_1$ values must be within 0.150 liter of each other.

d. The two largest FVC values must be within 0.200 liter of each other, and the two largest FEV$_1$ values must be within 0.200 liter of each other.

13. What is the most likely interpretation of the following spirometric data?
FVC = 2.30 (63% of predicted)
FEV$_1$ = 2.00 (70% of predicted)
FEV$_1$/FVC = 87%

a. Normal
b. Unacceptable
c. Airflow limitation
d. Possible restrictive process

14. The minimum number of acceptable spirometric trials that should be obtained is:
a. One
b. Two
c. Three
d. Eight

15. The pneumotachograph measures flow by:
a. Sensing the pressure drop across a fixed resistance
b. Sensing resistance through the tube
c. Measuring volume
d. Measuring volume and time

References


Introduction

In the pulmonary function laboratory, the measurement of lung volumes or measurement of static lung volumes usually refers to the measurement of total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC), and vital capacity (VC). These measurements are essential for analyzing lung function; they provide information to further the diagnostic process and assess therapy. There are two major steps in measuring lung volumes: (a) determining FRC and (b) measurement of slow vital capacity (SVC) and its subdivisions.

FRC is most commonly determined with one of three basic techniques: (a) body plethysmography, (b) multiple-breath closed-circuit helium (He) dilution, or (c) multiple-breath open-circuit nitrogen (N₂) washout. This chapter will discuss these techniques in detail focusing on instrumentation, relevant physiology, calculations, and testing techniques. In addition, this chapter will discuss the measurement of SVC and its subdivisions.

Other methods of measuring static lung volumes include the single-breath N₂ test, the single-breath He (or other inert gas) test, the chest roentgenogram (x-ray), and computed tomography (CT). The single-breath N₂ and chest x-ray methods were much less commonly used as of 2010 and thus will be discussed only briefly. The single-breath He (or other inert gas) method...
is performed in conjunction with the single-breath carbon monoxide diffusing capacity test (DL\textsubscript{CO}) and is discussed only briefly in this chapter. It is discussed more extensively in Chapter 3. The use of CT scans has increased significantly and will be briefly discussed.

**Lung Subdivisions: Volumes and Capacities**

The total lung volume can be divided into several subdivisions or compartments (Figure 2.1), which can then be grouped into volumes and capacities. There are four volumes: inspiratory reserve volume (IRV), tidal volume (TV), expiratory reserve volume (ERV), and residual volume (RV). Two or more of these volumes make up a capacity. For example, the sum of IRV and TV is inspiratory capacity (IC). There are four capacities: vital capacity (VC), inspiratory capacity (IC), functional residual capacity (FRC), and total lung capacity (TLC).

TV (Figure 2.2A) is the volume of air inspired and expired with each breath during normal breathing. The end of the inspiratory phase is called the end-inspiratory level, and the end of the expiratory phase is called the end-expiratory level.

IRV (Figure 2.2B) is the maximum volume of air that can be inhaled from the end-inspiratory level during quiet or normal tidal breathing. The ERV (Figure 2.2C) is the maximum volume.
Lung Subdivisions: Volumes and Capacities

Volume of air that can be exhaled from the end-expiratory level during quiet or normal tidal breathing (i.e., from FRC).

RV is the volume of air remaining in the lungs at the end of a maximum expiration. Unlike the other three volumes, RV must be measured indirectly using a two-step process. First, the

Figure 2.2
The three volumes that can be measured directly from the spirogram. A. Tidal volume (TV). B. Inspiratory reserve volume (IRV) C. Expiratory reserve volume (ERV).

A

Volume

Time

TV

B

Volume

Time

IRV

C

Volume

Time

ERV

TV
FRC is measured using one of several techniques. Then an SVC is obtained and subdivided (i.e., TV, IRV, ERV). When the FRC and SVC have been obtained, RV can be calculated in the following way:

\[ RV = FRC - ERV \]

The VC is the volume change at the mouth and can be an expiratory VC or an inspiratory VC. The expiratory VC is the volume of air that can be exhaled from the lungs after a maximum inspiration. The inspiratory VC is the volume of air that can be inhaled from a position of full expiration to full inspiration.

The VC can also be performed forcefully or slowly. When done forcefully it is called the forced vital capacity (FVC), which is defined as the volume of air that is exhaled forcefully starting from a position of full inspiration and ending at complete expiration. When the VC is exhaled slowly, it is called the SVC, which is defined as the volume of air that is exhaled without force from a position of full inspiration to full expiration. The VC can also be described as the sum of the TV, IRV, and ERV. In a healthy individual, the VC makes up approximately 70% of the TLC.

The IC is the maximum amount of air that can be inhaled from the TV end-expiratory level. It is the sum of the TV and IRV. This capacity usually makes up 60% to 70% of the VC in healthy individuals.

The FRC is the volume of air remaining in the lungs at the TV end-expiratory level. At this point in the respiratory cycle (i.e., end expiration), the elastic force of the chest wall (acting to expand the chest) is exactly balanced by the elastic force of the lungs (acting to deflate the lungs). As shown in Figure 2.1, the FRC consists of the ERV and RV, and its determination is a critical step in measuring lung volumes.

The TLC is the volume of air in the lungs after a maximum inspiration. It consists of all four volumes (IRV, TV, ERV, and RV) and two capacities (IC and FRC).

The size of the lung volume compartments varies among individuals, depending on age, gender, height, weight, race, and disease. In healthy individuals the lung volume compartments vary from the factors previously described, but the proportional relationships are similar. Typically, in healthy individuals the FRC is approximately 40% to 50% of the TLC, and the RV is approximately 25% to 30% of the TLC (Figure 2.3). In individuals with lung disease, forced spirometry alone does not always provide adequate information. For example, in individuals with airflow obstruction (e.g., emphysema), it is common to see a reduced FVC and forced expiratory volume in 1 second (FEV₁) and a reduced FEV₁/FVC ratio. Similarly, an individual with a restrictive process (e.g., interstitial lung disease) will also have a reduced FVC and FEV₁; however, the FEV₁/FVC ratio is typically increased. Although the FEV₁/FVC ratio may be helpful in differentiating obstructive and restrictive diseases, it is not the acid test. The only true way to differentiate the two disease processes is to measure all the lung volume compartments.

In addition to a reduced FVC, FEV₁, and FEV₁/FVC ratio, patients with airflow obstruction usually have an increased FRC and a decreased ERV. Hence, the RV and the TLC are increased (Figure 2.3). The amount of increase depends on the severity of obstruction.

As noted earlier, in individuals with restrictive patterns, the FVC and FEV₁ are reduced and the FEV₁/FVC ratio is usually increased. Additionally, the lung volume compartments are all proportionally reduced (Figure 2.3).
In mixed obstructive and restrictive disorders, some compartments are normal, some are increased, and some are reduced, making interpretation difficult. Table 2.1 shows the various static lung volume compartments and their status for a particular disease pattern.

Measurement of VC

The SVC is the maximum volume of air that can be slowly exhaled from the lungs after a maximum inspiration to a full expiration. In healthy individuals, there is little difference between the SVC and the FVC. However, in individuals with airflow obstruction, the FVC maneuver causes gas trapping and thus is smaller than the SVC.
CHAPTER 2 Lung Volumes

The same instrumentation is used to measure SVC and FVC. Many computerized pulmonary function testing systems contain software that can measure the SVC and its subdivisions. It is recommended that if both SVC and FVC are to be measured, SVC should be performed before FVC maneuvers because of the potential for muscular fatigue and gas trapping.\(^1\) The SVC can be done as an inspiratory SVC (often referred to as IVC) or as an expiratory SVC (often referred to as EVC).

As in forced spirometry and prior to testing, provide the patient with instructions on the appropriate technique, and demonstrate the SVC maneuver. It is important to stress that the maneuver is not forced but is done in a relaxed manner except near end-inspiration and end-expiration. A nose clip should be worn by the patient during the maneuver. The maneuver for performing the expiratory SVC (or EVC) should include several tidal breaths to establish a stable FRC level, followed by a maximum inspiration and then a slow, complete expiration (Figure 2.4). The maneuver for performing the inspiratory SVC (or IVC) includes several tidal breaths to establish a stable FRC level, followed by a maximum expiration and then a slow, complete inspiration (Figure 2.5).

One additional variation of measuring the SVC that is less commonly used employs the concept that the VC is the sum of the TV, IRV, and ERV. After breathing at TV for several breaths, the patient inspires maximally and then returns to quiet breathing at the tidal breathing level. After again breathing at TV for several breaths, the patient slowly expires maximally. This two-step technique (Figure 2.6) measures the SVC in parts, which then can be summed.

Repeatability and Reporting

As with forced spirometry, at least three acceptable VC maneuvers should be obtained. The two highest SVC values should agree within 0.150 liters. If this is not achieved, additional maneuvers should be performed.\(^1\) The largest value from at least three acceptable maneuvers should be reported. For IC, the mean of at least three acceptable maneuvers should be reported.

Table 2.1

| Lung Volume Compartments and Their Status for Obstructive, Restrictive, and Mixed Obstructive and Restrictive Lung Disease Patterns |
|---|---|---|
| | Obstructive | Restrictive | Mixed |
| VC | D or N | D | D |
| TLC | I | D | N or D |
| IC | N | D | N or D |
| FRC | I | D | N or D |
| ERV | D or N | D | D |
| RV | I | D | N or D |

I, increased; D, decreased; N, normal.

The same instrumentation is used to measure SVC and FVC. Many computerized pulmonary function testing systems contain software that can measure the SVC and its subdivisions. It is recommended that if both SVC and FVC are to be measured, SVC should be performed before FVC maneuvers because of the potential for muscular fatigue and gas trapping.\(^1\) The SVC can be done as an inspiratory SVC (often referred to as IVC) or as an expiratory SVC (often referred to as EVC).

As in forced spirometry and prior to testing, provide the patient with instructions on the appropriate technique, and demonstrate the SVC maneuver. It is important to stress that the maneuver is not forced but is done in a relaxed manner except near end-inspiration and end-expiration. A nose clip should be worn by the patient during the maneuver. The maneuver for performing the expiratory SVC (or EVC) should include several tidal breaths to establish a stable FRC level, followed by a maximum inspiration and then a slow, complete expiration (Figure 2.4). The maneuver for performing the inspiratory SVC (or IVC) includes several tidal breaths to establish a stable FRC level, followed by a maximum expiration and then a slow, complete inspiration (Figure 2.5).

One additional variation of measuring the SVC that is less commonly used employs the concept that the VC is the sum of the TV, IRV, and ERV. After breathing at TV for several breaths, the patient inspires maximally and then returns to quiet breathing at the tidal breathing level. After again breathing at TV for several breaths, the patient slowly expires maximally. This two-step technique (Figure 2.6) measures the SVC in parts, which then can be summed.

Repeatability and Reporting

As with forced spirometry, at least three acceptable VC maneuvers should be obtained. The two highest SVC values should agree within 0.150 liters. If this is not achieved, additional maneuvers should be performed.\(^1\) The largest value from at least three acceptable maneuvers should be reported. For IC, the mean of at least three acceptable maneuvers should be reported.
**Figure 2.4**

Typical SVC maneuver as expressed on a volume–time spirogram with **tidal breathing** followed by a maximum **inspiration** and then a slow, complete **expiration**.

**Figure 2.5**

The reverse of the typical expiratory SVC is the inspiratory SVC. On a volume–time spirogram, **tidal breathing** is followed by a slow, complete **expiration** and then a maximum **inspiration**.
The determination of RV and TLC can be complicated. There are two recommended methods to determine these values after FRC has been determined. The first and preferred method is to measure ERV immediately after the acquisition of the FRC measurement followed by slow inspiratory vital capacity. All measurements should be performed as a linked maneuver, that is, without the patient coming off the mouthpiece prior to completion of the maneuvers. The reported values for RV and TLC are:

\[
\begin{align*}
RV &= \text{Mean of FRC} - \text{Mean of ERV} \\
TLC &= \text{Reported value for RV} + \text{Largest IVC}
\end{align*}
\]

The second recommended method includes the measurement of IC immediately after the FRC determination. This method may be necessary in patients with severe dyspnea who cannot perform the ERV immediately after the FRC measurement. With this approach, patients can come off the mouthpiece between successive linked FRC and IC determinations and also between the separate VC maneuvers. The reported values for RV and TLC using this second approach are:

\[
\begin{align*}
RV &= \text{Mean TLC} - \text{Largest VC measured} \\
TLC &= \text{Mean of the three largest sums of FRC values and linked IC values}
\end{align*}
\]
Measurement of FRC

As noted previously, determining FRC is one of two main steps in determining lung volumes. The three most commonly used FRC determination techniques are: (a) body plethysmography (also called body box and abbreviated $FRC_{\text{pleth}}$), (b) multiple-breath He dilution (abbreviated $FRC_{\text{He}}$) and (c) multiple-breath N₂ washout (abbreviated $FRC_{\text{N₂}}$). In healthy subjects and individuals with pure restrictive lung disease, these three methods show good agreement.³⁶ In individuals with obstructive lung disease, however, there is generally poor agreement between gas dilution values (He dilution and N₂ washout) and values from the body box.

The body plethysmograph or body box measures the volume of gas in the thoracic cage and is considered the most accurate method of measuring FRC. However, the body box is more expensive, technically more complicated, and requires more patient cooperation and effort than gas dilution–washout methods. Additionally, the body box may overestimate FRC slightly.⁷⁻¹¹ The suspected overestimation error stems from the fact that in severe obstructive lung disease, alveolar pressure may be underestimated. This matter is discussed later in this chapter.

The multiple-breath gas dilution–washout methods are relatively simple to perform and require little effort from the patient. However, in individuals with obstructive lung disease, the gas dilution–washout methods underestimate the true FRC because they measure only those areas of the lung in communication with the mouth. They do not measure areas of the lung that contain trapped gas. A large number of obstructive lung disease patterns are thus falsely classified as mixed obstructive–restrictive lung disease patterns because FRC is underestimated.

Both the gas dilution–washout and plethysmographic methods for determining FRC are considered acceptable.²⁻³,¹² The gas dilution methods underestimate the true FRC in patients with airflow obstruction. The plethysmograph method includes those air spaces not measured by gas dilution–washout methods and thus is the method of choice in patients with airflow obstruction. The use of both methods provides useful information about the volume of noncommunicating gas (i.e., trapped gas).

Measuring FRC with Body Plethysmography

The body plethysmograph or body box is the first of three methods that will be discussed to measure FRC. According to Comroe,¹³ Pflüger was the first to apply Boyle’s law to measure RV in 1882 by constructing a large metal container. The English translation of the German name for Pflüger’s device was man-box or man-can. However, DuBois and coworkers are usually credited with the modern application.⁶

To measure $FRC_{\text{pleth}}$, the patient, sitting inside a sealed box, breathes quietly for several breaths and then pants against a closed shutter. The gas volume trapped in the lungs when the shutter is closed can then be measured by applying Boyle’s law. As previously mentioned, this method is generally considered the most accurate of the three methods for measuring FRC because it measures the total gas volume in the thoracic cage or thoracic gas volume (TGV).

The body box is also used to measure airway resistance (Raw). The patient uses the same panting technique, or even a quiet breathing technique in some systems, but first with the shutter open and then with the shutter closed. Raw is used to assess airflow obstruction rather than lung volumes. It is discussed in Chapter 4.
CHAPTER 2 Lung Volumes

The discussion of FRC pleth determination includes: (a) physiology and instrumentation and (b) testing technique.

**Physiology and Instrumentation**

The operating principle of the body box is based on Boyle’s law, which states that a volume of gas at constant temperature varies inversely with the pressure applied to it. In other words, when gas in a closed container is compressed, the volume decreases while the pressure inside the container increases. The reverse is true if the gas in the closed container is decompressed. Mathematically, Boyle’s law is written as:

\[ P_1 V_1 = P_2 V_2 \]  
(Eq. 2.1)

The individual to be tested sits in the sealed body box, attaches to the mouthpiece, wears a nose clip, and breathes quietly. When a valve (i.e., shutter) to which the mouthpiece is connected is closed at the TV end-expiratory position (i.e., FRC), it traps that volume of gas in the lungs. By trying to pant in and out against the closed shutter, the patient compresses and decompresses that trapped volume of gas in the thorax while the temperature remains constant. By panting out (i.e., against the shutter), the chest wall moves inward, which compresses the thoracic gas. Because the chest wall moves inward there is a proportional decompression of the gas in the sealed body box. Conversely, the decompression of the thoracic gas results in a proportional compression of the gas in the box. Because there is no airflow, the pressure changes inside the lung (measured at the mouth) and volume changes in the TGV (measured by changes in body box volume) allow the trapped TGV to be determined by applying Boyle’s law. The derivation of the formula for determining TGV using Boyle’s law is shown in Appendix C.

The final form of the formula as shown in Appendix C is:

\[ V = \frac{P_1 \Delta V}{\Delta P} \]  
(Eq. 2.2)

where

- \( P_1 \) = Alveolar pressure
- \( \Delta V \) = Change in body box volume when panting
- \( \Delta P \) = Change in alveolar pressure (measured at the mouth) when panting against a closed shutter
- \( V_f \) = TGV when the shutter is closed, usually at FRC

In practice, the operator observes a computer monitor that displays the relationship between alveolar pressure measured at the mouth and body box volume or pressure (Figure 2.7). The \( \Delta V \) and \( \Delta P \) are measured as the slope of the line fitting the panting lines. The slope (rise over run) is \( \Delta P/\Delta V \), but equation 2.2 requires \( \Delta V/\Delta P \). Thus, the inverse of the slope is required. The inverse of the slope is then multiplied by the calibration factors for body box volume and mouth pressure. Thus, equation 2.2 can be rewritten as:
Measurement of FRC

\[ TGV = P \times \frac{1}{\text{Slope}} \times \frac{\text{Body box calibration factor}}{\text{Mouth pressure calibration factor}} \]

where

- \( TGV \) = Thoracic gas volume
- \( P \) = Barometric pressure in cm H2O less water vapor
- \( \text{Slope} = \frac{\Delta P}{\Delta V} \)

Let us use some hypothetical numbers. The closed shutter panting produced the display shown in Figure 2.7. Angle \( \alpha \) is measured to be 45 degrees, and the slope or tangent of 45 degrees is 1.00. The body box pressure calibration factor, which is typically determined by injecting a known volume into the sealed body box and measuring the horizontal deflection, is 10 mL/cm. The mouth pressure calibration factor, which is typically determined by applying a known pressure to the mouth pressure transducer and measuring the vertical deflection,
is 2.5 cm H$_2$O/cm. If the barometric pressure is 760 mmHg and the water vapor pressure at 37°C is 47 mmHg, then

$$P = 760 - 47 = 713 \text{ mmHg} = 970 \text{ cm H}_2\text{O}$$

Plugging these values into the rewritten equation 2.2 results in the following:

$$\text{TGV} = P \times \frac{1}{\text{Slope}} \times \frac{\text{Body box calibration factor}}{\text{Mouth pressure calibration factor}}$$

$$\text{TGV} = 970 \text{ cm H}_2\text{O} \times \frac{1}{1} \times \frac{10 \text{ mL/cm}}{2.5 \text{ cm H}_2\text{O/cm}}$$

$$\text{TGV} = 970 \text{ cm H}_2\text{O} \times 4 \text{ mL/cm H}_2\text{O}$$

$$\text{TGV} = 3,880 \text{ mL or } 3.880 \text{ liters}$$

The alveolar pressure changes caused by the compression and decompression of air in the lungs are estimated at the mouth. As mentioned earlier, the assumption that alveolar pressure equilibrates and is correctly measured at the mouth when the glottis is open and the cheeks are held firmly has been questioned.\textsuperscript{7-10} In the presence of severe airflow obstruction there is a phase lag between pressures at the mouth and in the alveoli. This leads to underestimation of alveolar pressure and overestimation of TGV. This problem can be minimized by reducing the patient’s panting frequency to 0.5 to 1.0 breaths/sec.

The TGV changes caused by the compression and decompression of the chest wall during the panting maneuver are estimated by measuring changes in the body box volume. The sealed box allows for measurement of the small changes in volume (e.g., 200 to 500 mL). The three major types of body boxes (variable-pressure box, flow box, and volume-displacement box) are classified based on how each type measures the body box volume change.

**Variable-Pressure Box**

The variable-pressure box (Figure 2.8) uses a pressure transducer to measure body box pressure changes that are caused by the compression and decompression of the chest in a constant volume container. Hence, it is also known as a constant-volume box. This transducer, which is attached to the wall of the box, is calibrated by injecting known volumes into the sealed box, creating a relationship between box volume change and box pressure change. This type of box requires a correction for body weight and frequent venting of excess pressure caused by rising temperatures when the patient is inside.

**Flow Box**

The flow box (Figure 2.9) measures box volume changes within a constant pressure chamber using a large pneumotachograph (which measures flow) placed in the box wall. When the thorax compresses and decompresses, the air in the body box will flow in and out of the box.

*1.36 converts mmHg to cm H$_2$O.
Measurement of FRC

The measured flow is then integrated to obtain volume. The frequency response can be corrected. The flow and mouth pressure signals must be in phase, either by mechanical adjustments or computer software.

The flow box can be converted into a pressure box simply by occluding the pathway through this pneumotachograph. The measured flow is then integrated to obtain volume. The frequency response can be corrected. The flow and mouth pressure signals must be in phase, either by mechanical adjustments or computer software.

The flow box can be converted into a pressure box simply by occluding the pathway through the pneumotachograph, which combines the flow and pressure box approaches. This type of body box is commonly sold commercially. This combination allows for the measurement of TGV using the pressure box mode (the pathway to the pneumotachograph is closed) and the flow–volume curve using the flow box mode (the pathway to the pneumotachograph is open).
Volume-Displacement Box

The volume-displacement box (Figure 2.10) measures box volume changes within a constant pressure chamber with an attached spirometer. It is easily calibrated by injecting a known volume into the sealed box. The frequency response of the spirometer must be taken into account or corrected, and the warming of the air in the plethysmograph can be overcome by air conditioning. The volume-displacement box can measure large volume changes (e.g., VC) and both the volume expired at the mouth and the volume compressed by the chest wall. There
can be a considerable difference between these two volumes in individuals with severe airway obstruction.14

In the past, the relationship between mouth pressure (which estimates alveolar pressure) and box volume changes was hand measured. Today, excellent software can calculate this measurement and make the body box easier to use. Additionally, software and instrumentation advances for the body box allow for the performance and measurement of many pulmonary function tests, including spirometry (SVC and FVC), diffusing capacity, single- and multiple-breath N2 washout, pressure–volume characteristics, and maximal inspiratory and expiratory pressures.

**Figure 2.10**

Volume-displacement body plethysmograph (variable volume). The patient, wearing a nose clip, attaches to the mouthpiece and breathes through a shutter–pneumotach apparatus, which is usually located outside the plethysmograph (body box). The shutter (S) is open for tidal breathing, measurement of Raw, and spirometry. It is closed for measurement of TGV. When the shutter is closed, mouth pressure is measured by a transducer (T2). The pneumotach (P) measures flow through transducer T1. The flow can then be electronically integrated to obtain volume. Changes in body box volume, which occur with chest-wall movement, are measured by a volume-displacement spirometer (VS) and a linear volume-displacement transducer (LVDT). The type of spirometer shown is a Krogh water-sealed spirometer. Signal processing is done by a computer, and modern systems allow the user to perform SVC and FVC.
CHAPTER 2  Lung Volumes

Testing Technique
The testing technique for measuring FRCpleth includes: (a) equipment preparation and calibration, (b) patient preparation and instructions, (c) testing, and (d) quality control.

Equipment Preparation and Calibration
Calibrate the body box every day it is used. Follow the calibration process described in the operator’s manual provided by the manufacturer. Usually the process consists of calibrating the box volume with a calibration syringe and the mouth pressure transducer with a water manometer. Additionally, calibrate any flow-sensing device attached to the breathing tube with a calibration syringe. Maintain a log of calibration results showing date and time, calibration values, barometric pressure, and the identification of the individual performing the calibration. It is common to print the calibration pages and store them in a notebook for review.

Patient Preparation and Instructions
Give the patient some instructions before he or she enters the box, such as how to use the mouthpiece and nose clip. Tell the patient that after he or she sits inside the door will be closed. Many patients are apprehensive about being closed in a small space. Assure the patient that the door can be opened at any time between maneuvers. Additionally, most boxes today are constructed with clear plastic walls, which promote a feeling of openness.

Patients who are receiving intravenous (IV) or O2 therapy present a problem. If the patient is receiving IV therapy, the bags and pumps must be temporarily disconnected before testing in the body box. Similarly, patients receiving O2 therapy (including transtracheal) should have their O2 temporarily turned off while measurements are made.

Carefully explain the panting maneuver. Usually the patient is asked to pant (shallow breaths) at a rate of 0.5 to 1 breath/sec. When the shutter closes and the airflow stops, panting is more difficult. Explain that although air movement really stops when the shutter closes, the pressure of the panting is being measured, and therefore the patient must try to continue the panting maneuver. Next, demonstrate the open (if Raw is to be measured) and closed-shutter maneuvers.

Practicing with the patient is the next step. With the door closed and sealed, communication is hampered. Most of the intercom systems on the boxes do not provide good sound quality and therefore can cause delays as the patient tries to understand and perform this tricky maneuver. One recommendation is to leave the door open and show the patient what it feels like to pant against the closed shutter and give additional instructions or suggestions. When you think the patient is ready, seal the door and proceed with the testing. The patient still may have some problems with the maneuver (described next), but you can do any fine-tuning over the intercom system.

Testing
The common problems encountered in getting the patient to do the panting maneuver correctly include incorrect panting frequency (i.e., too fast or too slow), failure to inspire and expire against the closed shutter, panting too hard, lips failing to seal around mouthpiece, and glottis closure. Additionally, unsatisfactory results may occur when the patient allows the cheeks to puff in and out with the closed-shutter panting. Correct this by having the patient place his or her hands on the cheeks and prevent them from moving (Figure 2.11).
Careful instruction and good feedback can reduce problems. During the closed-shutter panting maneuver, carefully monitor the graphic plot showing the change in mouth pressure and box volume. Ideally, you will observe a series of superimposed lines (Figure 2.12). Looping or bending can occur with glottis closure or box leaks or when the cheeks move (Figure 2.13).

As noted earlier, the relationship (i.e., the slope) of mouth pressure and body box volume changes during the closed-shutter maneuver was hand measured in the past. Current body box systems contain software that can estimate this slope. The advantage of allowing the computer to analyze all the data points and fit a line include: (a) faster analysis, (b) analysis of each individual panting breath, (c) greater accuracy by elimination of observer bias, and (d) better consistency.15

It has been recommended that the operator acquire at least three to five satisfactory panting maneuvers, with at least three FRCpleth values that agree within 5% (i.e., the difference between the highest and lowest value divided by the mean is less than 0.05).2 If significant variability exists, obtain additional values. The mean value of all acceptable and repeatable FRCpleth values should be reported in liters at BTPS, rounded to two decimals (e.g., 3.13 liters).
Figure 2.12

Plethysmograph display of a properly done closed-shutter panting maneuver. It demonstrates the relationship between mouth pressure and body box pressure as a series of overlapping straight lines.

Figure 2.13

Plethysmograph displays of poorly done panting maneuvers. The relationship between mouth pressure and body box pressure is a series of open (A) or bent loops (B), usually caused by thermal drifting or patient technique (panting too rapidly or panting too deeply), which makes measurement difficult. The dashed lines represent the best fit if these measurements were used, but the operator should work hard with the patient to correct the problems and achieve a better measurement.
Measurement of FRC

Mouth pressure vs. Body box pressure

A

B
CHAPTER 2 Lung Volumes

Quality Control
The accuracy of the body plethysmograph in measuring FRC using a mechanical model has been described.\textsuperscript{16,17} This technique uses a container of known volume as a model lung (e.g., 3- or 4-liter glass flask filled with copper wool, with a two-holed rubber stopper at the opening). One hole is connected to the body box mouthpiece, and the second hole is connected to a rubber bulb. The bulb can be squeezed at the appropriate frequency by an individual sitting inside the box (holding his or her breath). The volume measured should equal the volume in the flask less the volume of copper wool (calculated from weight and density) within 50 mL or 3%, whichever is greater based on a mean of five determinations.\textsuperscript{18} Some manufacturers of body plethysmographs provide variations of this early mechanical model.

Biological controls (healthy nonsmoking individuals) should be tested at least monthly or whenever errors are suspected. Measurements should include FRC\textsubscript{pleth}, RV, and TLC. Values that differ by more than 10\% for FRC\textsubscript{pleth} and TLC, or more than 20\% for RV from previously established means on the same biological control, suggest errors.

Another approach to ensure accuracy is to measure FRC\textsubscript{pleth} and compare the value to FRC\textsubscript{He} and/or FRC\textsubscript{N\textsubscript{2}}. Values for FRC using the different techniques should be very similar in healthy individuals.

Measuring FRC by Multiple-Breath Closed-Circuit He Dilution
The second method for determining FRC is by multiple-breath closed-circuit He dilution (FRC\textsubscript{He}).\textsuperscript{19,20} This method involves diluting He, an inert gas, in the lungs by rebreathing the gas in a closed system over a short time (usually 2 to 10 minutes).

This method is widely used in pulmonary function laboratories because: (a) it is a very easy test for the patient to perform, since it requires only tidal breathing and minimal learning and effort, and (b) the instrumentation is simple and inexpensive. However, as mentioned earlier, a major drawback of this method is that it measures only the lung volume in communication with the mouth. This becomes a problem in individuals with airflow obstruction because significant amounts of lung volume may not communicate with the mouth. The result underestimates FRC, which leads to an underestimation of RV and TLC.

The discussion of this method includes: (a) instrumentation, (b) physiology and calculations, and (c) testing technique.

Instrumentation
The most commonly used He analyzer operates on a thermal conductivity principle. This principle is based on the facts that gases are able to conduct heat and different gases conduct heat at different rates. By introducing gas molecules into a sampling chamber containing a heated wire, the temperature of that wire decreases, allowing more current to flow through the wire. To be specific for He, other gases must either be removed or be compared with a reference. Therefore, CO\textsubscript{2} is scrubbed from the sample gas using a chemical absorber, and O\textsubscript{2} and N\textsubscript{2} are negated by comparing the thermal conductivity of the sample gas with a dry room-air reference. A Wheatstone bridge is incorporated to measure the resistance difference of the sample and reference chambers. Moisture in the circuit gas results in changes in H\textsubscript{2}O vapor pressure, which affects the He analyzer. Thus, H\textsubscript{2}O is also removed with a chemical absorber.
A small pump draws the gas from the breathing circuit and passes it over the chemical absorbers (one for CO\textsubscript{2} and one for H\textsubscript{2}O), passes it to the He analyzer, and then passes it back into the breathing circuit. A volume-displacement spirometer with a capacity of at least 7 liters is commonly used. A mixing fan is incorporated to circulate and mix the air throughout the breathing circuit. A breathing valve, corrugated tubing, and mouthpiece are used and become part of the circuit dead space. These items are usually disassembled and disinfected or sterilized between uses. The complete system is shown in Figure 2.14.

**Figure 2.14**

Closed-circuit He dilution for determining FRC. A. The known concentration and volume of He in the spirometer system is separated from the patient by a closed valve. B. The valve is opened, and He (dots) is redistributed by rebreathing until it is equilibrated in the lungs and the circuit.
Physiology and Calculations

The closed-circuit He dilution technique uses a spirometer and breathing circuit that contains a known volume ($V_S$) and concentration ($C_S$) of He (Figure 2.14). The patient, wearing a nose clip, is connected to the mouthpiece. After a valve is opened (connecting the patient to the spirometer and test gas, which contains He, O$_2$, and N$_2$), the patient breathes into and out of this closed spirometer circuit. The initial concentration of He in the spirometer ($C_S$), commonly 10%, is diluted proportionately by adding the patient’s lung volume ($V_L$), resulting in a final He concentration that reflects the concentration in both the spirometer circuit and the lungs ($C_{LS}$).

If the patient is turned in to the spirometer at TV end-expiratory level (FRC), then the $V_L$ that will be measured is FRC. However, the patient could be turned in above or below FRC, allowing a lung volume other than FRC to be measured. If this occurs, it is referred to as a switching error, and a mathematical correction is usually made to ensure that FRC is correctly measured (see more discussion on switching error in the next section).

When the patient is turned in to the spirometer circuit and begins to breathe and rebreathe the circuit gas, the rebreathing will continue until the He concentration is equilibrated (Figure 2.14). In healthy individuals, the equilibration time takes approximately 2 to 3 minutes. However, in individuals with obstructive lung disease, it may take as long as 5 to 10 minutes, but it rarely exceeds 10 minutes. One technique that is sometimes used to speed up the equilibration process and thus reduce testing time is a periodic deep breath.

Looking at the calculation more closely, it can be seen that:

\[
\frac{V_S C_S + V_L C_L}{V_S C_S + V_L C_L} = \frac{V_S C_{LS} + V_L C_{LS}}{V_S C_{LS} + V_L C_{LS}}
\]

Because $C_L = 0$ at the beginning of the test:

\[
V_S C_S = V_S C_{LS} + V_L C_{LS}
\]

Solving for $V_L$:

\[
V_L = \frac{V_S C_S - C_{LS} V_L}{C_{LS}}
\]

\[
V_L = \frac{V_S (C_S - C_{LS})}{C_{LS}}
\]

If the concentration of He in the spirometer at the start of the test ($C_S$) is called $C_i$, and the concentration of He in the spirometer and patient’s lungs at the end of the test ($C_{LS}$) is called $C_f$, and $V_L$ is called FRC, then:
Measurement of FRC

\[
FRC = \frac{V_S (C_1 - C_3)}{C_2 - C_3} \times \text{He Abs Corr}
\]  
(Eq. 2.3)

where

- \( FRC \) = Functional residual capacity
- \( V_S \) = Volume in spirometer and circuit
- \( C_1 \) = Concentration of He in spirometer
- \( C_2 \) = Concentration of He at the end of the test after equilibration of lungs and spirometer
- \( \text{He Abs Corr} \) = Volume of theoretical He absorption by the blood during rebreathing (usually 0.1 liter); this is a controversial correction.

The volume in the spirometer and circuit \((V_S)\) includes the known volume of He and a dead space that consists of the tubing, the analyzer, and the space in the \( CO_2 \) absorber. This dead space must be measured. In most automated systems, this is accomplished by initially adding a small amount of He to the closed circuit and taking an initial reading. A known volume of air is then added, and after a short time to allow equilibration, a second He concentration reading is taken. This additional step modifies equation 2.3. Because the initial volume in the spirometer and circuit \((V_S)\) can be calculated by taking another He concentration reading, the equation for FRC by He dilution then becomes:

\[
FRC = \frac{C_1 \times C_2 - C_3 \times V_{\text{added}}}{C_1 - C_2} \times \text{He Abs Corr}
\]  
(Eq. 2.4)

where

- \( FRC \) = Functional residual capacity
- \( C_1 \) = Concentration of He in spirometer and circuit at the start of the test
- \( C_3 \) = Concentration of He in spirometer and circuit at the end of the test after equilibration of lungs and spirometer system
- \( V_{\text{added}} \) = Volume of air added to spirometer and circuit between \( C_1 \) and \( C_2 \)
- \( \text{He Abs Corr} \) = Volume of theoretical He absorption by the blood during rebreathing (usually 0.1 liter); this is a controversial correction.

An example of calculating an FRC by closed-circuit He dilution \((FRC_{\text{He}})\) is as follows:

<table>
<thead>
<tr>
<th>Volume of air added</th>
<th>1.20 liters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial He concentration ((C_1))</td>
<td>10.0%</td>
</tr>
<tr>
<td>He concentration after air added ((C_2))</td>
<td>8.6%</td>
</tr>
<tr>
<td>He concentration after subject equilibration ((C_3))</td>
<td>6.2%</td>
</tr>
<tr>
<td>Spirometer temperature</td>
<td>23° C</td>
</tr>
<tr>
<td>He absorption correction</td>
<td>0.1 liter</td>
</tr>
<tr>
<td>Switching error</td>
<td>0</td>
</tr>
</tbody>
</table>

He Abs Corr
CHAPTER 2 Lung Volumes

FRC_{He} = \frac{C_1 - C_2}{C_1} \times \frac{V_{\text{End}}}{{\text{He Abs Corr}}}

FRC_{He} = \frac{10.0}{6.2} \times \frac{8.6 - 6.2}{10.0 - 8.6} \times 1.200 \text{ at ambient temperature and pressure,}

\text{saturated with water vapor (ATPS) - 0.10}

FRC_{He} = 1.61 \times \frac{2.4}{1.4} \times 1.20 - 0.10

FRC_{He} = 3.21 \times \text{ATPS to BTPS factor of 1.084}

FRC_{He} = 3.48 \text{ liters}

**Testing Technique**

The testing technique for measuring FRC_{He} includes: (a) equipment preparation and calibration, (b) patient preparation and instruction, (c) testing, and (d) quality control.

**Equipment Preparation and Calibration**

Calibrate the spirometer used for He dilution systems as recommended by the manufacturer and test it for leaks every day it is used. The CO₂ and H₂O absorbers should be fresh. These absorbers usually contain color indicators. The CO₂ absorber (soda lime) is usually white with color indicators that change to blue as they become saturated with CO₂. The H₂O absorber (calcium sulfate) is usually light blue with color indicators that change to pink as they become saturated with H₂O. Have an adequate supply of He and O₂ available.

**Patient Preparation and Instruction**

The patient should be seated comfortably and told how to use the mouthpiece and nose clip. Tell the patient that the test requires sitting quietly and breathing through the mouthpiece with the lips tightly sealed for several minutes. Remind the patient not to remove the mouthpiece until you say so. Because perforated eardrums can result in leaks to the system circuit and thus result in erroneous FRC values, ascertain if the patient has this condition. If so, supply earplugs.

**Testing**

With the patient wearing a nose clip and breathing room air while attached to the mouthpiece, observe tidal breathing for 30 to 60 seconds as the patient becomes accustomed to breathing on a mouthpiece. When a stable breathing pattern exists, turn the valve that connects the patient to the spirometer system and test gas at TV end-expiratory level (FRC). Often, the switch-in of the valve to connect the patient to the spirometer system is not done exactly at FRC. The patient may be a little above or a little below FRC. This is not a problem because a mathematical correction for this switching error is made in the calculations. Because it can be difficult to see the patient’s chest movement to turn him or her into the system exactly at FRC, try placing your hand on the patient’s back or shoulder to feel the chest movement and help determine the correct turn-in point.

The calculation of FRC_{He} by the closed-circuit He dilution technique (equations 2.3 and 2.4) assumes that the volumes in the spirometer and lungs will not change between the start and end of the test. The CO₂ produced by the patient will increase the spirometer volume.
Measurement of FRC

The O₂ consumed by the patient will decrease the spirometer volume. Hence, CO₂ must be absorbed, and O₂ must be added.

The CO₂ produced by the patient is continually being absorbed by chemical absorption as the He mixture circulates in the spirometer, circuit, and patient. The O₂ is added by one of two techniques. The first and most common technique is a \textit{continuous-addition technique}, which keeps the spirometer system volume constant by continually adding O₂ in small quantities that equal the volume loss caused by the patient’s O₂ consumption. Typically, an adult individual on this type of system has an O₂ consumption of 300 to 600 mL/min.

The second O₂ addition technique, found on some older systems, is the \textit{bulk-addition technique}. Systems that use this technique put a bolus of O₂ (e.g., 1000 mL) into the spirometer before the patient is turned in. When the patient is turned in, all of the added O₂ must be consumed before the test can conclude. Otherwise, the volume of the spirometer and circuit will have changed, causing a greater He concentration change than would normally be seen.

The patient should continue to breathe on the mouthpiece until equilibration is reached. The He concentration is monitored every 15 seconds. Equilibration is usually defined by a plateau in the He concentration (i.e., the change in He concentration is less than 0.02% over 30 seconds). If the He concentration continues to fall steadily with no trend toward equilibration, suspect a leak. Leaks typically occur around the patient’s mouth or from a loose nose clip. If equilibration has not been reached 10 minutes after the beginning of the test, end the test. For patients who may become hypoxic, use pulse oximetry monitoring.

At the end of the test (i.e., equilibration), perform an SVC maneuver before removing the mouthpiece (linked to FRC determination); some patients, however, may not be able to perform this additional test after being on the mouthpiece for several minutes. If the patient cannot perform the linked SVC maneuver before being disconnected, have the patient perform it as soon as possible after FRC determination and disconnection.

When the patient comes off the mouthpiece, saliva and secretions spill out, so have a good supply of tissues nearby.

Perform at least one technically acceptable FRC₉₆ determination. If more than one determination is performed, allow at least 5 minutes between them. For practical purposes, differences of less than 10% between two FRC₉₆ determinations are acceptable. Report the mean FRC₉₆ in liters at BTPS rounded to two decimals (e.g., 3.13 liters).

\textbf{Quality Control}

The accuracy of the He dilution device can be determined by using a 3-liter calibration syringe. The He dilution system should be prepared to test a patient. Connect the 3-liter syringe and inject a known amount of air (e.g., 3 liters) into the spirometer. Close the valve to the syringe, if possible, to avoid mixing the dead space of the syringe after injecting the volume of air. After approximately 30 seconds, when the meter reading is stable, end the test. The calculated volume (at ATPS) should equal the injected volume within 3%. If this is not the case, evaluate the system. Perform this quality control check at least weekly.

In addition, the measurement of values in biological controls is useful and assures the testing values are stable. At least monthly, test two or three reference individuals (i.e., non-smoking and healthy) on the system. Values obtained for FRC₉₆ that differ by more than 10% from previously established means for a given individual should alert you to investigate the system.
Measuring FRC by Multiple-Breath Open-Circuit N₂ Washout

The third method of determining FRC is the multiple-breath open-circuit N₂ washout (FRC\textsubscript{N₂}). This method involves removing or washing out the N₂ gas in a patient’s lungs while the patient breathes 100% O₂ for several minutes. It is easy for the patient to perform and requires minimal learning and effort. Like the He dilution method, the N₂ washout method has the drawback of measuring only the lung spaces that communicate with the mouth. Thus it also underestimates FRC in individuals with air flow obstruction. The discussion of this method includes: (a) physiology and instrumentation and (b) testing technique.

Physiology and Instrumentation

The early modern technique\textsuperscript{23} for the open-circuit method used the apparatus shown in Figure 2.15. This technique is cumbersome compared to today’s techniques. It involved acquiring three gas samples (an alveolar sample prior to starting the test, a second alveolar sample after the test, and a sample of the exhaled gas during the 100% O₂ breathing period). The first sample was taken with the patient attached to the system mouthpiece and breathing room air. The patient was instructed to exhale maximally, at which time the alveolar gas sample was taken, which represented the average lung N₂ concentration on room air. Following this sample, the patient breathed room air for 2 more minutes to restore quiet breathing. Then a valve was turned at FRC so the patient could breathe 100% O₂ from a reservoir bag for 7 minutes. The exhaled gas was collected in a 100-liter gasometer (Tissot). After 7 minutes, the patient was instructed to exhale fully, and the second alveolar sample was taken. The patient was then disconnected, the breathing circuit was flushed, and the third gas sample was taken from the gasometer.

The three N₂ samples were analyzed using the volumetric methods (e.g., Van Slyke manometer), which depended on chemical absorption. This analyzation process, which was common in the early 1960s, took 10 to 20 minutes for each sample and was extremely technique dependent.

Today, the large gasometer has been replaced by flow meters, and the volumetric gas analyzers have been replaced by electronic N₂ analyzers that can analyze the N₂ concentration of each breath. Additionally, the second alveolar sample at the end of the O₂ breathing period has been eliminated from the technique.\textsuperscript{24}

The concept of the N₂ washout is based on the fact that at the start of the test the unknown FRC contains 80% N₂ and an unknown concentration of O₂ (probably between 16% and 21%)

Figure 2.15

The early modern open-circuit N₂ washout circuit for determining FRC. The patient breathes through a two-way valve to which a vacuum bottle (A) is connected for collecting the alveolar sample. The inspiratory side is connected to a 100% oxygen reservoir, and the expiratory side is connected to a large water-sealed spirometer (T). This spirometer, which is also known as a Tissot (pronounced TEE-so), is usually 100 to 200 liters, which is large enough to collect the expired air during 7 minutes of quiet breathing.
Measurement of FRC

Two-way valve

100% oxygen
and CO₂ (probably between 0.4% and 5.0%). By measuring the volume of N₂ in the FRC and applying a concentration dilution formula, the FRC volume can be determined. Thus,

\[ C_1 V_1 = C_2 V_2 \]

where

- \( C_1 \) = N₂ concentration at start of test
- \( V_1 \) = FRC volume
- \( C_2 \) = N₂ concentration in exhaled volume
- \( V_2 \) = Total exhaled volume during O₂ breathing period

As stated earlier, the N₂ washout measures the lung volume that can be ventilated by the mouth. Thus, it will underestimate FRC in those individuals with large amounts of trapped air or areas of lung that are poorly ventilated. Early data showed that increased breathing periods (i.e., 11 to 15 minutes) obtained larger FRCs in individuals with obstructive lung disease. However, longer durations are more uncomfortable for the patient, and in some patients (e.g., those with COPD) who breathe 100% O₂ for more than a few minutes, it may result in CO₂ retention.

The measurement of N₂ can be performed using N₂ analyzers (most common), mass spectrometers, or indirectly by subtracting measurements of O₂ and CO₂. The N₂ analyzers used with modern systems operate on a photoelectric principle. Gas is pulled through a needle valve into an ionization chamber by a vacuum pump. The molecules are ionized and emit light. This light is then filtered and collected by a photo resistor, which converts the light into an electrical signal. The intensity of the light is directly related to the concentration of N₂ in the sample. The use of computers has allowed for the signal from the N₂ analyzer to be combined with the volume signal from a spirometer to provide instantaneous or breath-by-breath measurements of N₂ and volume. This technology allows for faster detection of leaks, which is an advantage over the He dilution technique.

The basic equation used with the early technique was:

\[ \text{FRC}_{N_2} = \frac{(\text{Tissot volume}) (\text{FIN}_2 - \text{FIN}_1)}{\text{FAN}_{\text{initial}} - \text{FAN}_{\text{final}}} - \text{DS} \]

An example of calculating an FRC by N₂ washout using the previous equation is as follows. An open-circuit N₂ washout was performed with the patient inspiring 100% O₂, and the exhaled air was collected in a 120-liter Tissot gasometer. The following information was obtained:

- Barometric pressure (PB) = 631 mmHg
- Tissot temperature (T) = 24°C
- Tissot volume after 7 minutes of breathing = 56.3 liters ATPS
- FIN₂ (fractional concentration of expired N₂ in Tissot) = 0.0368
- FIN₁ (fractional concentration of inspired N₂) = 0.001
- FAN₂ initial (alveolar N₂ concentration at start of test) = 0.80
- FAN₂ final (alveolar N₂ concentration at end of test) = 0.015
- DS (valve dead space, liters) = 0.090
Measurement of FRC

\[ FRC_{N_2} = \frac{(\text{Tissot volume})(FEN_2 - FIN_2)}{FAN_{N_2,\text{initial}} - FAN_{N_2,\text{final}}} - DS \]

\[ VE\ Tissot \ (i.e., \ Tissot\ volume\ @\ ATPS\ including\ system\ dead\ space) = 56.3 \text{ liters} \]

\[ VE\ Tissot @ BTPS = \frac{VE\ Tissot @ ATPS \times 310}{273 + T} \times \frac{PB - PH_2O\ at\ 24^\circ C}{PB - PH_2O\ at\ 37^\circ C} \]

\[ VE\ Tissot @ BTPS = 56.3 \times \frac{310}{273 + 24} \times \frac{631 - 22}{631 - 47} \]

\[ VE\ Tissot @ BTPS = 61.30 \text{ liters} \]

\[ FRC_{N_2} = \frac{(61.30)(0.0368 - 0.0001)}{0.80 - 0.015} \]

\[ FRC_{N_2} = \frac{(61.30)(0.0358)}{0.785} = 2.80 \text{ liters} @ BTPS \]

Today, the computerization and simplification of this technique has greatly shortened the time needed to calculate \( FRC_{N_2} \).

**Testing Technique**

The testing technique for measuring \( FRC_{N_2} \) includes: (a) equipment preparation and calibration, (b) patient preparation and instruction, (c) testing, and (d) quality control.

**Equipment Preparation and Calibration**

Calibrate the flow-meter device and \( N_2 \) analyzer every day of use, following the manufacturers instructions. There should be an ample supply of \( O_2 \).

**Patient Preparation and Instruction**

The patient should be seated comfortably and given instructions on how to use the mouthpiece and nose clip. Tell the patient that the test requires sitting quietly and breathing on the mouthpiece with the lips tightly sealed for several minutes. Remind the patient to keep the mouthpiece in place with the lips sealed until you say to remove it. Because perforated eardrums can result in leaks to the system circuit and thus result in erroneous FRC values, ascertain if the patient has this condition. If so, supply earplugs.

**Testing**

The patient breathes on the mouthpiece for 30 to 60 seconds to become comfortable on the mouthpiece and to assure a stable FRC level. When a stable FRC level has been established, the patient is turned in to the system and starts breathing 100% \( O_2 \). The \( N_2 \) concentration and the patient are monitored during the washout period to assure that no leaks occur. A large increase in \( N_2 \) concentration indicates a leak. If this occurs, the test should be stopped and repeated after the appropriate waiting period (i.e., 15 minutes). The test is usually stopped when the expired \( N_2 \) concentration falls below 1.5% for at least three successive breaths.²
Monitor the $N_2$ concentration throughout the test. When no leaks are present, the $N_2$ concentration appears as shown in Figure 2.16A. If a leak occurs, $N_2$ from room air enters the system, and the $N_2$ concentration abruptly rises (Figure 2.16B).

**Figure 2.16**
A. A typical display of an $N_2$ washout test using an $N_2$ analyzer. B. When leaks occur (e.g., the patient does not keep the lips sealed tightly), room air enters the circuit, and the $N_2$ concentration spikes to near ambient levels (i.e., near 80%).
At least one technically satisfactory measurement should be obtained. If additional washouts are performed, allow at least 15 minutes between maneuvers. Repeat the N₂ washout procedure with a 15-minute interval between trials until you obtain two FRC measurements that agree within 10%. The mean FRCₜ₉₅ measurements that agree within 10% should be reported in liters at BTPS, rounded to two decimals (e.g., 3.78 liters).

Quality Control
The main cause of erroneous results with the open-circuit N₂ washout test is leaks. These can be easily detected during the test by observing the N₂ signal. As with the He dilution and body box techniques, the testing of biological controls is recommended at least monthly.

Measurement of Lung Volumes by Other Methods
There are other less commonly used methods for measuring lung volumes, and these will only be briefly discussed.

The single-breath N₂ method can be used to estimate RV and TLC. The test involves diluting the ambient N₂ in the lungs by inhaling a VC (from RV to TLC) of 100% oxygen. An analysis of the single-breath N₂ curve produced in this test yields several other parameters of pulmonary function, including closing volume and slope of phase III. However, this method has never been standardized and is not widely used.

The single-breath He method estimates TLC and is performed during the single-breath carbon-monoxide uptake (DL,CO) (discussed in Chapter 3). This DL,CO test employs an inert tracer gas (e.g., He), which is diluted into the lung volume, and an estimate of TLC can be calculated. This estimate of TLC is referred to as alveolar volume (VA) and is lower than the true TLC in individuals with airflow obstruction.

The TLC can also be estimated from the chest roentgenogram (radiograph) using the posteroanterior (PA) and lateral (LAT) views when the patient is at full lung inflation. The two basic methods that use the chest radiograph to measure lung volumes are (a) the planimeter method and (b) the ellipse method. A planimeter is a device with two arms that pivot around a fixed joint, allowing one to trace over the lines of any two-dimensional shape (Figure 2.17). By outlining all the lung fields on the PA and LAT films, including the heart but excluding the sternum, the radiographic chest volume can be calculated. Digital technology has been developed to replace the manual method.

The ellipse method assumes that the lungs can be divided into a large number of elliptical cross sections (Figure 2.18). The area of the elliptical sections is determined from the PA and LAT view chest films and then converted to volume. The area of the heart, the domes of the diaphragm, and the pulmonary blood and tissue are subtracted out.

Both methods compare well with each other as well as with TLC measured by plethysmographic and dilution–washout techniques.

The drawbacks of using the chest film are: (a) only TLC can be measured and (b) TLC can be underestimated if the patient does not maximally inspire when the film is exposed. Additionally, the technique depends on good-quality film to define the lung boundaries.
However, the advantages of being unaffected by poorly ventilated areas and the ability to compare films retrospectively when pulmonary function tests are not available or comparable make this technique valuable. The use of computers has shortened the time required to measure and calculate the data.

CT scans can provide estimates of lung volumes and can estimate the volume of the lung with increased or decreased density. Magnetic resonance imaging (MRI) offers the advantage of scanning specific regions of the lung. However, MRIs are costly, so their use for measuring lung volumes is limited.

**Reference Values**

As in forced spirometry, it is common practice to report reference or predicted values for static lung volumes. Unfortunately, no one set of lung volume reference values was recommended by the most recent guidelines. One survey found that the most commonly used study for lung volume reference values was that of Goldman and Becklake. This study used hydrogen (H) dilution (similar to He dilution) to measure FRC on 44 male and 50 female subjects near Johannesburg, South Africa (altitude 5,700 feet).
The techniques used in the many reference studies vary and include He dilution, H dilution, \( \text{N}_2 \) washout, single-breath \( \text{N}_2 \), and body plethysmography. This fact complicates the task of selecting reference equations for one’s laboratory. When selecting reference values, consider the following criteria: (a) use of similar equipment and methods and (b) similar populations (i.e., age, body size, gender, and race). When a tentative selection has been made, a laboratory should consider comparing the measurements from 10 to 20 healthy individuals selected from a representative sample of the laboratory’s population with the tentative reference values. If the differences between the values of the 10 to 20 healthy individuals and reference values are small (e.g., within \( \pm 10\% \)), then the laboratory can be reasonably confident that the chosen reference values are appropriate. If the differences are greater, consider using other reference values.

**Figure 2.18**
Measurement of TLC from chest roentgenograms using the ellipse method. The PA and LAT views of the chest at full inspiration are divided into five elliptical cross sections or segments. The area of each section is measured (arrows indicate the points between which to measure) and then converted to volume.

The techniques used in the many reference studies vary and include He dilution, H dilution, \( \text{N}_2 \) washout, single-breath \( \text{N}_2 \), and body plethysmography. This fact complicates the task of selecting reference equations for one’s laboratory. When selecting reference values, consider the following criteria: (a) use of similar equipment and methods and (b) similar populations (i.e., age, body size, gender, and race). When a tentative selection has been made, a laboratory should consider comparing the measurements from 10 to 20 healthy individuals selected from a representative sample of the laboratory’s population with the tentative reference values. If the differences between the values of the 10 to 20 healthy individuals and reference values are small (e.g., within \( \pm 10\% \)), then the laboratory can be reasonably confident that the chosen reference values are appropriate. If the differences are greater, consider using other reference values.

**Infection Control**

In determining FRC and the lung volume compartments, the patient continually rebreathes on the breathing circuit. Thus, the possibility of cross contamination exists. The laboratory should have procedures in place to help ensure patient and technologist safety.

The Centers for Disease Control and Prevention has published guidelines for preventing transmission of infectious agents in healthcare settings. In addition, Kendrick and coworkers published an excellent review and practical approach to infection control in the pulmonary function laboratory.
If the patient has known *Mycobacterium tuberculosis* and is considered infectious, several additional precautions are recommended. Test the patient at the end of the day to ensure no other patient uses the instrument that day. The room in which the test is performed should at least meet current Centers for Disease Control and Prevention guidelines for air changes and ventilation. The airflow should be biased into the contaminated area from adjacent hallways and rooms (i.e., negative pressure). The use of ultraviolet light is controversial, but some centers use it. The technologist performing the testing should wear a personal respirator that meets current Occupational Safety and Health Administration (OSHA) recommendations. After testing is complete, disassemble the tubing and removable parts from the testing system and clean them with a high-level disinfectant. Reassemble the system the next day after all the parts have thoroughly dried.

**Case Presentations**

**Case 2.1**

A 68-year-old Caucasian woman with a complaint of worsening dyspnea was seen in the pulmonologist’s office. She admitted to having been a heavy smoker (90 pack years, where one pack year is defined as one package of cigarettes per day for 1 year) but had recently quit. This office was equipped to measure spirometry and lung volumes, and the results of her tests are shown in Table 2.2 and Figure 2.19. Her chest film had an emphysematous appearance with increased diameters.

After seeing the results of the office pulmonary function test, the doctor ordered another pulmonary function test at the area hospital, and the results are shown in Table 2.3 and Figure 2.20.

**Table 2.2**

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Before*</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (L)</td>
<td>4.82</td>
<td>4.63 (96)</td>
<td></td>
</tr>
<tr>
<td>FRC&lt;sub&gt;H&lt;/sub&gt; (L)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.80</td>
<td>2.58 (92)</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.91</td>
<td>2.08 (109)</td>
<td></td>
</tr>
<tr>
<td>SVC (L)</td>
<td>3.59</td>
<td>2.55 (71)</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.63</td>
<td>2.18 (60)</td>
<td>2.38</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>2.57</td>
<td>1.08 (42)</td>
<td>1.18</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC (%)</td>
<td>71</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>FEF25–75% (L/sec)</td>
<td>2.50</td>
<td>0.65 (26)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent predicted

<sup>1</sup>Measured by He dilution
Figure 2.19
Volume–time spirogram from patient in Case 2.1 performed in the doctor’s office before and after administration of a bronchodilator.

Table 2.3
Hospital Pulmonary Function Laboratory Data Before and After a Bronchodilator

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (L)</td>
<td>4.82</td>
<td>5.76 (120)</td>
<td></td>
</tr>
<tr>
<td>FRC&lt;sub&gt;pleth&lt;/sub&gt; (L)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.80</td>
<td>3.97 (142)</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.91</td>
<td>3.13 (164)</td>
<td></td>
</tr>
<tr>
<td>SVC (L)</td>
<td>3.59</td>
<td>2.63 (73)</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.63</td>
<td>2.28 (63)</td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>2.57</td>
<td>1.11 (43)</td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC (%)</td>
<td>71</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;(L/sec)</td>
<td>2.50</td>
<td>0.59 (24)</td>
<td></td>
</tr>
<tr>
<td>Raw (cm H&lt;sub&gt;2&lt;/sub&gt;O/L/sec)</td>
<td>2.93</td>
<td>2.34</td>
<td></td>
</tr>
<tr>
<td>sGaw (L/cm H&lt;sub&gt;2&lt;/sub&gt;O/L/sec)</td>
<td>0.07</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>DL&lt;sub&gt;co&lt;/sub&gt; (mL/min/mmHg)</td>
<td>23.4</td>
<td>17.30 (74)</td>
<td></td>
</tr>
<tr>
<td>DL&lt;sub&gt;co/VA&lt;/sub&gt;</td>
<td>4.85</td>
<td>3.64 (75)</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses are percent of predicted

†Measured by body plethysmograph
CHAPTER 2 Lung Volumes

Questions

1. How would you interpret the pulmonary function tests done in the doctor’s office?
2. How would you interpret the pulmonary function tests done in the hospital?
3. How do you explain the difference in data?

Answers and Discussion

Data from the pulmonary function test done in the office and shown in Table 2.2 reveal normal lung volumes (TLC, FRC_{He}, and RV) and a reduced SVC. These data also reveal severe airflow limitation with minimal response to a bronchodilator. A concern is why the lung volumes do not reveal hyperinflation that would be consistent with this degree of obstruction and the chest film interpretation. Therefore, the final interpretation would most likely state a mixed obstructive and restrictive disorder.

The pulmonary function test data from the hospital (Table 2.3), which used the body plethysmograph, show a different picture. There is still severe airflow limitation and the diffusing capacity is reduced, but the lung volumes are all markedly increased. There is good response to a bronchodilator. The final interpretation from these data is severe airflow limitation, but there is certainly not a mixed disorder.
The major difference between the two interpretations depends on the measurement of FRC. In the doctor’s office, the FRC\textsubscript{He} was 2.55 liters. In the hospital laboratory, the FRC\textsubscript{pleth} was 3.97 liters, which is significantly higher.

Why are the two FRC determinations so different? Measurement of FRC\textsubscript{He} uses a gas dilution technique. It requires the patient to breathe into a system that contains a known volume and concentration of He. During the breathing period, the He diffuses and equilibrates into the gas spaces of the lung that communicate with the mouth. Noncommunicating spaces are not measured. Thus, the FRC\textsubscript{He} can be underestimated.

The body plethysmograph (body box) is another method to determine FRC. Although it is more expensive and requires more technical expertise, it is quick and accurate. It measures the TGV in the thoracic cage when a shutter is closed. This volume includes non-communicating areas and therefore is more accurate than the gas dilution technique.

The difference between the two sets of lung volumes in this patient can be accounted for by the presence of trapped gas spaces or poorly communicating airways. The correct interpretation is that the patient is hyperinflated and does not have a mixed disorder.

**Case 2.2**

A 58-year-old African American male office worker was tested in the pulmonary function laboratory. Spirometry at a recent physical examination in the doctor’s office detected some abnormal results. He denied shortness of breath or cough but claimed to be a 40 pack year smoker. His laboratory results are shown in Table 2.4 and Figure 2.21.

**Table 2.4**

| Pulmonary Function Values Before and After a Bronchodilator in the Pulmonary Function Laboratory |
|---|---|---|
| Predicted | Before* | After |
| FVC (L) | 5.04 | 3.78 (75) | 3.93 |
| FEV\textsubscript{1} (L) | 3.51 | 2.00 (57) | 2.12 |
| FEV\textsubscript{1}/FVC (%) | 70 | 53 | 54 |
| FEF\textsubscript{25-75%} (L/Sec) | 3.97 | 2.34 (59) | 2.79 |
| FRC\textsubscript{pleth} (L) | 4.01 | 2.89 (72) | 2.69 |
| RV (L) | 1.88 | 1.94 (103) | |
| TLC (L) | 6.88 | 5.85 (85) | |
| SVC (L) | 5.01 | 3.91 (78) | |
| Raw (cm H\textsubscript{2}O/L/sec) | 2.13 | 1.92 | |
| sGaw (L/cm H\textsubscript{2}O/L/sec) | 0.15 | 0.19 | |

*Values in parentheses are percent predicted
Questions

1. What is the interpretation and evaluation of these pulmonary function tests?
2. What issues should be raised with the reference values?

Answers and Discussion

The data from Table 2.4 and Figure 2.21 reveal airflow limitation without meaningful response to a bronchodilator. Additionally, the lung volumes are reduced, suggesting a mixed obstructive and restrictive disorder.

The predicted or reference values used by the laboratory do not state whether they are race specific. If they are based on a Caucasian population, then the apparent restrictive process could be an artifact.

Healthy, predicted, or normal values for pulmonary function tests are frequently based on entirely Caucasian populations. The predicted values for the lung volumes (TLC, RV, FRC) shown in Table 2.4 come from a study by Goldman and Becklake, and the other predicted values come from a study by Morris and coworkers. Neither of these particular studies state the race or ethnic background of the subjects who participated.

Several studies have documented that people of African descent have lower lung volumes than do Caucasians. This is attributed to the fact that people of African descent have longer...
legs and shorter trunks. Thus, standing height, which is a major factor in predicting pulmonary function values, is biased.

When the predicted values are recalculated (shown in Table 2.5) based on the studies of Rossiter and Weil\(^47\) and Stinson and colleagues,\(^48\) which used black populations, the interpretation changes to airflow limitation.

In practice, some pulmonary function laboratories use scaling factors when testing African Americans. The process adjusts the Caucasian population’s predicted values down approximately 12%. This approach has a major pitfall in that the 12% correction is an average. The difference between Caucasian and African American values varies with each parameter. For TLCs, for example, African Americans have approximately 11% lower predicted values.\(^47\)

A pulmonary function laboratory must carefully consider selecting predicted values. The use of race-specific predicted equations raises the issue of whether the available studies are adequate, because they do not provide criteria for determining race. Many studies assume that racial identity is evident through color distinctions. However, this may not always be true in practice.

The alternative to race-specific predicted values is to take racial issues into consideration at interpretation. For example, in this case, the interpretation of the data in Table 2.4 might have read “airflow limitation without meaningful response to a bronchodilator and normal lung volumes when adjusted for race.”

The important consideration is that there is a weakness in using healthy reference equations based on Caucasian populations for non-Caucasian patients. If race-specific reference equations are used, note so on the report.

### Table 2.5

<table>
<thead>
<tr>
<th>Pulmonary Function Values Before and After Bronchodilator</th>
<th>Predicted</th>
<th>Before*</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.98</td>
<td>3.78 (95)</td>
<td>3.93</td>
</tr>
<tr>
<td>FEV(_1) (L)</td>
<td>2.82</td>
<td>2.00 (71)</td>
<td>2.12</td>
</tr>
<tr>
<td>FEV(_1)/FVC (%)</td>
<td>71</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>FEF(_25-75%) (L/Sec)</td>
<td>3.60</td>
<td>2.34 (65)</td>
<td>2.79</td>
</tr>
<tr>
<td>FRC(_{pleth}) (L)</td>
<td>3.28</td>
<td>2.89 (88)</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>2.04</td>
<td>1.94 (95)</td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>6.03</td>
<td>5.85 (97)</td>
<td></td>
</tr>
<tr>
<td>SVC (L)</td>
<td>3.99</td>
<td>3.91 (98)</td>
<td></td>
</tr>
<tr>
<td>Raw (cm H(_2)O/L/sec)</td>
<td>2.13</td>
<td></td>
<td>1.92</td>
</tr>
<tr>
<td>(s)Gaw (L/cm H(_2)O/L/sec)</td>
<td>0.15</td>
<td></td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent predicted
Self-Assessment Questions

1. All the following are techniques for determining FRC except:
   a. Closed-circuit He dilution
   b. Open-circuit N₂ washout
   c. Single-breath N₂ washout
   d. Body plethysmography

2. Which of the following is the most accurate concerning the ERV?
   a. The maximum amount of air that can be exhaled from the VC
   b. The maximum amount of air that can be exhaled from the TV end-expiratory level
   c. The maximum amount of air that can be inhaled from the TV end-expiratory level
   d. The maximum amount of air that can be exhaled from RV

3. A patient has the following lung volumes:

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Predicted</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC (L)</td>
<td>3.50</td>
<td>4.30</td>
<td>81</td>
</tr>
<tr>
<td>FRCpleth (L)</td>
<td>3.80</td>
<td>3.00</td>
<td>127</td>
</tr>
<tr>
<td>RV (L)</td>
<td>3.00</td>
<td>2.00</td>
<td>150</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>6.50</td>
<td>6.30</td>
<td>103</td>
</tr>
</tbody>
</table>

The interpretation would most likely state:
   a. Normal lung volumes
   b. Hyperinflation
   c. Restrictive pattern
   d. Mixed obstructive and restrictive pattern

4. In patients with obstructive lung disease, the gas dilution methods for FRC determination:
   a. Overestimate FRC
   b. Equal body plethysmograph FRC
   c. Underestimate FRC
   d. Equal radiographic FRC

5. In the body plethysmograph, alveolar pressure changes caused by the compression and decompression of the lungs are estimated by:
   a. Measuring mouth pressure
   b. Measuring body box pressure
   c. Measuring transpulmonary pressure
   d. Measuring transdiaphragmatic pressure

6. The calculation of FRC using the body plethysmograph is based on:
   a. Murphy’s law
   b. Boyle’s law
   c. Charles’s law
   d. Poiseuille’s law
7. Which of the following methods for determining TLC best agrees with the results of the radiographic technique in patients with obstructive lung disease?
   a. Body box FRC + IC
   b. Closed-circuit He dilution FRC + IC
   c. Open-circuit N\textsubscript{2} washout FRC + IC
   d. Open-circuit He dilution FRC + IC

8. Which of the following is most accurate about the FRC?
   a. It is the volume of air remaining in the lungs at TV end-expiratory level
   b. It consists of residual volume and expiratory reserve volume
   c. It can be determined by gas dilution and body plethysmography
   d. All of the above
   e. a and c

9. In restrictive lung disease, which lung volume compartment is not decreased?
   a. VC
   b. FRC
   c. TLC
   d. IC
   e. None of the above

10. In obstructive lung disease, the SVC will probably be:
    a. Larger than the TLC
    b. Smaller than the RV
    c. Larger than the FVC
    d. Smaller than the IC

11. Lung volume values for TLC, FRC, and RV should be reported at:
    a. BTPS
    b. ATPS
    c. STPD (standard conditions)
    d. ATPD (ambient temperature and pressure, dry)

12. Which of the following statements best explains why it is important to wait at least 5 minutes between He dilution FRC determinations?
    a. The subject must recover from breathing on the mouthpiece
    b. The subject’s CO\textsubscript{2} production must return to resting levels
    c. The He must be cleared from the subject’s lungs
    d. To ensure that O\textsubscript{2} saturation has returned to baseline

13. Which of the following should be done to ensure that the volume in the spirometer during a closed-circuit FRC determination remains unchanged?
    a. Ensure adequate He absorption
    b. Ensure adequate CO\textsubscript{2} absorption
    c. Ensure adequate O\textsubscript{2} absorption
    d. Ensure subject starts test at FRC

14. When the N\textsubscript{2} concentration abruptly rises near the end of an open-circuit N\textsubscript{2} washout, it usually means:
    a. The computer has an error
    b. The N\textsubscript{2} analyzer is not calibrated
c. The system has developed a leak
d. The O₂ concentration is varying

15. Which of the following are methods to estimate TLC?
   a. Single-breath N₂
   b. Single-breath He
   c. Measurement of chest radiographs
   d. a, b, and c
   e. a and c

References

3. Tierney DF, Nadel JA. Concurrent measurements of functional residual capacity by three 
4. Reichel G. Differences between intrathoracic gas measured by the body plethysmograph and 
   functional residual capacity determined by gas dilution methods. Prog Respir Res. 
5. Cobeel LJ. Comparison between measurement of functional residual capacity and thoracic 
   thoracic gas volume: a comparison with a nitrogen washout method for measuring 
7. Rodenstein DO, Stanescu DC. Reassessment of lung volume measurement by helium 
   1982;126:1040–1044.
8. Rodenstein DO, Stanescu DC, Francis C. Demonstration of failure of body plethysmography 
9. Shore SA, Huk O, Mannix S, Martin JG. Effect of panting frequency on the plethysmographic 
   determination of thoracic gas volume in chronic obstructive pulmonary disease. 
10. Shore S, Milic-Emili J, Martin JG. Reassessment of body plethysmographic technique for 
    the measurement of thoracic gas volume in asthmatics. Am Rev Respir Dis. 
    1982;126:515–520.
    Report working party. Standardization of lung function tests, European Community for 
    Steel and Coal. Eur Respir J. 1993;6(suppl 16):5–40.


Three
CHAPTER 3

Single-Breath Carbon Monoxide Diffusing Capacity

Introduction

The process of diffusion is defined as the flow of particles from an area of higher concentration to an area of lower concentration. The measurement of diffusion, as performed in pulmonary function laboratories, provides information about the transfer of gas between the alveoli and the pulmonary capillary blood and is referred to as the diffusing capacity. The term transfer factor (TL,CO), which is preferred in Europe, might be better because the term diffusing capacity is somewhat misleading for two reasons: (a) many factors in addition to diffusing characteristics affect the outcome of this test, and (b) the outcome of the test is related to metabolic rate, and the test is usually done at rest; thus the outcome is submaximal and not a capacity. However, the term diffusing capacity of the lung for carbon monoxide (DL,CO) is used in this text to be consistent with the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) standardization guideline.¹

The measurement of diffusing capacity using carbon monoxide (CO) can be performed using three general techniques: (a) steady state, (b) rebreathing, and (c) single breath. Because...
CHAPTER 3 Single-Breath Carbon Monoxide Diffusing Capacity

this book focuses on commonly performed tests, only the single-breath technique is discussed in detail.

The single-breath DL,CO was first measured by Marie and August Krogh in 1914. Forster and coworkers described a modification of Krogh’s technique and used helium (He) in the inspired gas mixture as a tracer gas. The tracer gas allowed measurement of the dilution of the inspired gas into the lung residual volume.

Over the years many controversies developed, including: (a) how to measure breath-hold time, (b) whether there should be a correction for hemoglobin (Hb), (c) what the oxygen (O2) concentration should be in the inspired test gas, and (d) whether there should be an adjustment for carboxyhemoglobin, carbon dioxide (CO2) absorption, and valve dead space. The ERS made recommendations on standardizing the diffusing capacity test in 1983. These recommendations were updated in 1993. The ATS made recommendations on a standardized technique in 1987 and updated those recommendations in 1995. The most current guideline at the time of this writing is largely based on the previous statements.

Physiology

This section on relevant physiology includes: (a) diffusion of gases and (b) the methods for measuring diffusing capacity.

Diffusion of Gases

The diffusion of gases in the lungs occurs between alveoli and pulmonary capillary blood. The two major gases involved in lung diffusion (O2 and CO2) must move through two barriers: (a) the alveolar-capillary (A-C) membrane and (b) the blood plasma–red blood cell barrier.

The rate of diffusion across these primarily liquid barriers is limited by: (a) the surface area for diffusion, (b) the distance the gas molecules must travel, (c) the solubility coefficient of the gases in liquid, (d) the partial pressure difference (gradient) between air and blood for each gas, and (e) the density of each gas.

O2 and CO2 are more soluble in blood than in the A-C membrane and have a strong affinity for Hb. But because these gases are found in venous blood, they are not suitable for measuring diffusion capacity. CO is more advantageous than other gases because: (a) it has a great affinity for Hb (210 times that of O2), (b) it is soluble in blood, and (c) its concentrations in venous blood is insignificant. Although CO can be toxic if it combines with a large amount of Hb, it is not dangerous in low concentrations. Thus, the measurement of DL,CO involves the rate of consumption (uptake) of CO by the blood from the alveoli.

The diffusion or transfer of CO from alveoli to Hb can be separated into four components: (a) diffusion across the A-C membrane, (b) transfer to red blood cells, (c) passage through the red blood cell membrane, and (d) the COHb reaction rate.

The rate of diffusion of a gas across the A-C membrane (Dm) depends on: (a) the difference between the gas tension (or partial pressure) in the alveolus and in the plasma, (b) the surface area available for diffusion, (c) the distance the gas molecules must travel, and (d)
tissue characteristics. Thus, Dm is altered or decreased when there is increased interstitial fluid,
increased fibrotic tissue, increased interalveolar fluid, mismatching of perfused capillaries and
ventilated alveoli, pulmonary emboli, or poor ventilation.

The transfer to the red blood cell depends on the volume of red blood cells in the pulmo-
nary capillary bed (Qc). Qc is altered by position, exercise, and pulmonary circulation.

The passage through the red blood cell membrane and combination with the hemoglobin
molecule (Θ CO) are the final two processes that complete the diffusion of a gas from alveolus
to hemoglobin molecule.

The relationship of these components can be expressed as follows:

\[
\frac{1}{DL_{CO}} = \frac{1}{Dm} + \frac{1}{\Theta Qc}
\]

where
- DL = Lung’s diffusing capacity
- Dm = Diffusing capacity of the A-C membrane
- Θ = Reaction rate of the gas with the Hb molecule
- Qc = Volume of blood in the alveolar capillaries

The lung’s diffusing capacity (DL) for CO is the rate of uptake of CO/min (VCO) per mean
gradient of CO across the A-C membrane. This can be stated mathematically as:

\[
DL_{CO} = \frac{(VCO)}{P_{A CO} - P_{C CO}} \text{ mL/min/mmHg}
\]

where
- DL_{CO} = Diffusing capacity of the lung for CO
- VCO = CO uptake from the alveolar gas to the blood/min
- P_{A CO} = Mean alveolar CO pressure
- P_{C CO} = Mean capillary CO pressure

There are a number of physiological and pathological changes that can alter the DL_{CO}.

Conditions or changes that can lower the DL_{CO} include the following:

- Respiratory muscle weakness or deformity preventing maximal inflation
- Reduced Hb
- Pulmonary emboli
- Increased CO or inspired O₂ concentration
- Lung resection
- Emphysema
- Interstitial lung disease
Conditions or changes that can increase the \( DL_{CO} \) include the following:

- Increased Hb (polycythemia)
- Decreased intrathoracic pressure (resistance breathing)
- Exercise
- Asthma
- Supine position

**Measuring Diffusing Capacity**

As noted earlier, the three general methods for measuring the diffusing capacity of the lung are: (a) steady state, (b) rebreathing, and (c) single breath.

**Steady-State Technique**

There are several steady state-techniques, including the Filley method, end-tidal CO method, and assumed dead-space method. These techniques are infrequently used today but can be useful in measuring diffusing capacity during exercise.

**Rebreathing Technique**

The rebreathing technique is often considered another form of the steady-state technique. It promotes the mixing of the test gas when ventilation-perfusion disturbances are present. It, too, is rarely used in the clinical setting because of technique and computation complexity.

**Single-Breath Method**

The single-breath method is the most commonly used. The standard technique has the patient first empty the lungs, then inhale as deeply as possible a test gas mixture containing known concentrations of CO, an inert tracer gas such as He, neon, or methane (\( CH_4 \)), and O\(_2\) and N\(_2\), and then hold the breath for approximately 10 seconds. Then the patient exhales, and a sample of the exhaled gas is collected and analyzed for CO and the inert tracer gas.

The inert tracer gas used in the single-breath method has an interesting function. The test gas (CO and inert tracer gas) is drawn into the lungs and distributed to the alveoli including the residual volume. When it is in the gas exchange units, the CO diffuses across the A-C membrane. The CO concentration in the inhaled gas is lower than the CO concentration in the inhaled gas for two reasons: (a) diffusion and (b) dilution into the total lung volume. The inert gas acts as a tracer, and its dilution can be used to determine how much reduction in the CO concentration occurred because of dilution into the total lung volume.

Although the single-breath method is quick and does not require blood samples, it is criticized because it measures the diffusing capacity at maximal inspiration and during breath holding, neither of which is a normal breathing state.

**\( DL_{CO} \) Instrumentation**

The technique described by Ogilvie and colleagues, which has become known as the classic technique, uses a closed-circuit bag-in-box connected to a spirometer (Figure 3.1). The patient
Figure 3.1
Closed-circuit bag-in-box system with connections to spirometer and four-way valve. A. The bag (sometimes called balloon) holds the inspired test gas mixture. One of the four openings can be used (i.e., connected to the mouth port) at any one time. For example, if the valve is turned so that P4 is connected to the mouth port, the patient can inhale the test gas. If P4 is connected to the bag, the patient inhales the test gas mixture (P4 is connected to the mouth port), resulting in a decrease in bag volume. This causes a negative pressure inside the box (but outside the bag). A volume of air equal to the quantity of test gas inhaled then enters the box. B. What happens to the bag-in-box system when a patient inhales the test gas mixture. The patient inhales the test gas mixture (P4 is connected to the patient mouth port), resulting in a decrease in bag volume. This causes a negative pressure inside the box. A volume of air equal to the quantity of test gas inhaled then enters the box.
is attached to a valve through the *patient mouth port*, which allows breathing from one of four circuits (thus it is sometimes called a four-way valve). The operator manually turns the valve to connect the patient to the desired circuit. Some commercial systems have modified this setup by using a demand valve connected to a gas cylinder containing the test gas mixture and a flow sensor to estimate the inspired volume.

As previously noted, two gases are used with the classic technique: (a) an inert gas, such as He, and (b) CO. Specific analyzers for these gases are connected to the system.

### Analyzers

There are several types of CO analyzers, including infrared absorption, electrochemical cell, gas chromatograph, and mass spectrometer. The infrared CO analyzer has been the analyzer of choice in the DLCO test for many years and is based on the principle of infrared absorption. In this analyzer two identical infrared beams are directed through two parallel chambers (Figure 3.2). One chamber contains a known gas and is referred to as the *reference chamber*. The second chamber contains the sample or unknown gas. The infrared beams pass through the chambers and are directed to a single detector unit that converts the beams to an electronic signal.

**Figure 3.2**

The infrared analyzer is commonly used to measure gas concentrations of CO₂, CO, N₂O, and others. It operates by emitting infrared light aimed toward a detector cell. The light passes through a rotating chopper blade, which causes a pulsed pattern and helps stabilize the circuit. As specific gas molecules absorb the infrared light, the detector measures the differences between the reference and gas sample chambers, and the results are sent to amplifiers and linearization circuits.
The major criticisms of the infrared absorption CO analyzer are its alinearity characteristic, relatively large dead space, and somewhat slow response time. Alinearity arises from the fact that two molecules of gas can exist in the sample gas chamber, one directly behind the other. The molecule closest to the infrared light source absorbs the light, but the second molecule does not. Thus, there can be more molecules of gas (i.e., a higher concentration) than are shown. However, most manufacturers have solved this problem by passing the output signal through a linearizing network.

The gas chromatograph requires a smaller sample of gas than the infrared analyzer but has a somewhat slower response time. The gas chromatograph also requires an inert gas (He is commonly used) to act as a carrier (i.e., move the gas to be analyzed through the analyzer columns). Note that the same inert gas cannot be used as both the carrier gas in the chromatograph and the tracer gas in the test gas mixture.

The most common type of He analyzer used in the DL,CO test is based on the thermal conductivity principle, that is, that different gases conduct at different rates. Introducing gas molecules into a sampling chamber containing a heated wire causes the temperature of that wire to decrease, allowing more current to flow. To be specific for He, other gases (e.g., CO₂ and N₂) must be removed or compared to a reference.

Another method used by some systems employs a rapidly responding multigas analyzer. This analyzer uses the infrared principle for CO and methane (which is employed as the tracer gas), measures rapidly and continuously, and has a very small dead space and sample volume requirement.

**Calibration**

As with other pulmonary function tests, a calibration check of the DL,CO instrumentation is vital. Check the calibration of the spirometer or flow-sensing device with a known-volume syringe, and check for volume-displacement spirometer leaks daily. Keep calibration-check results in a laboratory log book or on a computer.

Because calculation of DL,CO is based on the ratio of the inspired to expired concentrations of the two gases, the analyzers must be linear. Because infrared CO analyzers are nonlinear, they must be linearized by the laboratory or the manufacturer. He analyzers are linear and usually do not require linearization conditioning. The analyzers should be zeroed prior to each test.

**Inspired Gas Composition**

The test gases include a tracer gas, CO, O₂, and N₂. Commonly used tracer gases include He, neon, and CH₄. The CO concentration should be approximately 0.3%. The exact concentration of CO is not critical because a ratio of inspired and expired concentrations are used to determine DL,CO. Most DL,CO systems use a balance of air in the inspired gas. With the tracer gas this actually results in a concentration of O₂ of approximately 19%. Because of the effect of O₂ concentrations on DL,CO, it has been recommended that laboratories use gas mixtures with inspired O₂ partial pressure values similar to the reference set used in the interpretation of data.
CHAPTER 3 Single-Breath Carbon Monoxide Diffusing Capacity

**DL\textsubscript{CO} Testing Techniques**

The testing technique section for measuring DL\textsubscript{CO} includes: (a) patient preparation, (b) explanation of the basic maneuver, (c) technique recommendations, and (d) some practical hints.

**Patient Preparation**

The first and sometimes most important component of the testing technique for this and most pulmonary function tests is proper patient preparation. The laboratory should make a strong effort to develop methods that inform patients about restrictions regarding medications, smoking, and meals. For the DL\textsubscript{CO} test, the following is recommended\textsuperscript{1}:

- Supplemental O\textsubscript{2} should be discontinued 10 minutes or more before the test—if this is not appropriate, note the patient’s O\textsubscript{2} use in the comments.
- The patient should be seated for approximately 5 minutes before the test is performed to assure that the patient has had time to recover from any walking around or other testing. The patient should remain seated throughout the test.
- Smoking should be stopped on the day of the test. The time of the last cigarette smoked should be recorded.

**Basic Maneuver**

Carefully instruct the patient about the maneuver. After the patient is comfortable and seated, demonstrate how to properly place the mouth on the mouthpiece and use the nose clip. After the patient is on the mouthpiece with the nose clip in place and breathing normal tidal breaths, coach the patient as follows:

1. Slowly exhale to maximum expiratory level (i.e., RV).
2. Upon signal, quickly inhale the test gas to maximum inhalation level (i.e., TLC).
3. Hold the breath for approximately 10 seconds.
4. Exhale at a moderate speed.
5. Continue exhaling while a sample of exhaled gas (called alveolar gas sample) is collected.
6. Come off the mouthpiece and remove the nose clip while the alveolar gas sample is analyzed.
7. Repeat the procedure after waiting at least 4 minutes.
8. Perform as many maneuvers as needed to obtain at least two acceptable maneuvers that agree within the repeatability criteria.

**Technique Recommendations**

The 2005 ATS/ERS\textsuperscript{1} recommendations are summarized in the following sections:
**Inspiratory Maneuver**

- 85% of the inspired volume should be inspired within 4 seconds. If longer times are needed, this should be noted.
- The inspiratory volume should be from RV to TLC (i.e., inspiratory vital capacity [IVC]).
- The IVC at body temperature, ambient pressure, and saturated with water vapor (BTPS) conditions should be \( \geq 85\% \) of the largest previously measured VC at BTPS conditions.
- No stepwise changes should be made in inspiration (Figure 3.3).

**Breath Hold**

- Patient should not create excessive positive or negative intrathoracic pressures during the breath hold (i.e., keep intrathoracic pressure close to atmospheric levels). Increases in intrathoracic pressure above atmospheric levels may decrease the DL,CO value, and decreases in intrathoracic pressure below atmospheric levels may increase the DL,CO value.
- The breath hold must last 8 to 12 seconds.

**Expiratory Maneuver**

- After the breath hold, the expiration should be smooth, and the expiratory time should be \( \leq 4 \) seconds.

**Figure 3.3**

Graphic illustration of an acceptable and unacceptable inspiratory maneuver. The unacceptable maneuver shows a pause in inspiration, resulting in a step-like pattern. The inspirations should be rapid and performed in less than 4 seconds without a stepwise appearance.
Washout Volume
The washout volume is the volume of gas that must be expired and discarded to clear anatomic and mechanical dead space before the alveolar sample is collected. If the alveolar sample is contaminated with dead space gas, the resulting DL,CO will likely be underestimated. Some measuring systems provide a graphical display of exhaled gas concentrations to assure that dead space gas is not present in the alveolar sample.

- The washout volume should be 0.75 to 1.00 liter.
- For patients with a VC < 2.00 liters, use a washout volume of 0.50 liter.

Alveolar Sample
An alveolar sample volume of 0.5 to 1.00 liter should be collected for analysis.

Number of Maneuvers and Repeatability
- Perform at least two acceptable maneuvers that agree within ± 10% or 3 mL/min/mmHg, whichever is larger. More than five maneuvers is not recommended.

Reporting Values
- The average of at least two acceptable maneuvers should be reported with outliers excluded.1
- The report should always include the unadjusted measured DL,CO, adjusted DL,CO (e.g., DL,CO Hbcorr) if an adjustment is made, the predicted and predicted DL,CO, and the predicted and percent predicted DL,CO/VA. Including the lower limit of normal is also valuable.
- If adjustments are made to the DL,CO value (e.g., for Hb or COHb), the Hb or COHb value used for the adjustment should be reported.1
- The average VA should be reported.

Practical Hints
The DL,CO test can be performed at a variety of times depending on the laboratory protocol (e.g., before spirometry, between spirometry and the determination of static lung volumes, or after spirometry). I recommend that the DL,CO test be performed after spirometry or static lung volume determinations for two reasons: (a) the DL,CO maneuver is somewhat more complicated to perform than other pulmonary function tests, and it can be done more quickly and with fewer attempts after other pulmonary function tests, when the patient is more experienced and (b) the spirometric results provide information needed (i.e., VC) to satisfy acceptability requirements.

In patients with severe airflow limitation, after-bronchodilator DL,CO measurements might be easier than before-bronchodilator measurements. In some cases where a significant response to a bronchodilator has occurred, before- and after-bronchodilator DL,CO measurements can be useful. If performing after-bronchodilator DL,CO measurements, remember that beta agonists can increase heart rate and cardiac output and thus can affect the DL,CO value.
The amount of available Hb affects the DL,CO test. The more Hb available, the higher the DL,CO value; the less Hb available, the lower the DL,CO value. Thus, the correction for Hb is an essential part of the calculation process (see the next section). I recommend that a Hb value be obtained on each patient who has a DL,CO test. Unless the patient has serious bleeding problems, an Hb value obtained within 7 to 10 days of the test can be used. Report the Hb value used for any corrections.

Calculations

The basic formula to calculate single-breath DL,CO is:

\[
DL,CO = VA_{STPD} \times \frac{60}{t} \times \ln \left( \frac{FA_{COo} - FA_{COt}}{PB - 47} \times \frac{FA_{COo}}{FA_{COt}} \right)
\]

where

- \(VA_{STPD}\) = Alveolar volume at STPD
- \(60\) = Conversion to minutes
- \(PB - 47\) = Barometric pressure minus water vapor pressure at 37°C
- \(\ln\) = Natural logarithm
- \(FA_{COo}\) = Fractional concentration of CO in alveoli at start of test
- \(FA_{COt}\) = Fractional concentration of CO in alveoli at end of test
- \(t\) = Breath hold time

This basic equation can be simplified into the following:

\[
DL,CO = VA_{STPD} \times \frac{60}{(PB - 47) \times t} \times \ln \left( \frac{HeE \times COI}{HeI \times COE} \right)
\]

where

- \(VA_{STPD}\) = Volume inspired at ATPD - \(VD \times HeI \times (ATPD\ to\ STPD\ factor)\)
- \(HeE\) = Expired He concentration after breath hold
- \(HeI\) = Inspired He concentration
- \(COI\) = Inspired CO concentration
- \(COE\) = Expired CO concentration after breath hold
- \(VD\) = System and anatomic dead space

Example Calculation of DL,CO

A 45-year-old man performs a DL,CO test. His Hb is 15.7 g/dL, and he claims to be a non-smoker. The following data are obtained from the test:

- Barometric pressure = 729 mmHg
- Volume inspired (Vi) = 5130 mL at 23°C
He inspired concentration = 10.0
CO inspired concentration = 0.309

He expired concentration = 7.3
CO expired concentration = 0.102

Breath hold time = 10.7 seconds

System and patient dead space (VD) = (100 + 170 = 270 mL)

The DL\textsubscript{CO} can be calculated in two steps:

**Step 1:** Calculate the alveolar volume.

\[
V_{A_{STPD}} = \frac{\text{HeI}}{\text{HeE}} \times (V1 - VD) \times (\text{ATPD to STPD factor})
\]

\[
V_{A_{STPD}} = \frac{10.0}{7.3} \times (5130 - 270) \times 0.8847
\]

\[V_{A_{STPD}} = 1.3699 \times 4860 \times 0.8847
\]

\[V_{A_{STPD}} = 5890 \text{ mL at STPD}
\]

**Step 2:** Calculate the DL\textsubscript{CO}.

\[
DL_{CO} = \frac{V_{A_{STPD}} \times 60}{(PB - 47) \times t} \times \ln \left[ \frac{\text{HeE} \times \text{COI}}{\text{HeI} \times \text{COE}} \right]
\]

\[DL_{CO} = \frac{5890 \times 60}{(729 - 47) \times 10.7} \times \ln \left[ \frac{7.3 \times 0.309}{10.0 \times 0.102} \right]
\]

\[DL_{CO} = 353,400 \times \ln 2.2115
\]

\[DL_{CO} = 48.43 \times 0.7937
\]

\[DL_{CO} = 38.44 \text{ mL/minute/mm Hg}
\]

**Calculation Recommendations**

The 2005 ATS/ERS recommendations\(^1\) are summarized in the following sections:

**Breath-Hold Time**

- The Jones-Meade technique\(^14\) is the preferred method for determining breath-hold time. This technique starts the breath-hold time when 30% of the inspiratory time has elapsed, and it ends the breath-hold time at 50% or in the middle of the sample collection time (Figure 3.4A).
- The Ogilvie technique,\(^12\) which starts the breath-hold time at the beginning of inspiration of the test gas and ends it at the beginning of the alveolar gas sample (Figure 3.4B), was widely used in the past but is thought to overestimate DL\textsubscript{CO} when flow rates are reduced.
Another approach is to use three separate equations, or the three-equation method, for DL\textsubscript{CO} during inspiration, breath hold, and expiration. This approach may be more theoretically accurate in evaluating changes in volume over time, and it is commercially available with some instrumentation. However, it is not widely used.
Inspired Volume (VI)
- Instrument dead space (including filters) will vary and should be reported by the manufacturer and subtracted from VI.
- Anatomic dead space (2.2 mL/kg of body weight) should also be subtracted from VI. It seems reasonable to limit the anatomic dead space to 150 mL or to use an ideal body weight in overweight individuals. Another approach recommended by the ATS/ERS guideline in obese patients is to use the following formulas:

\[
\text{Anatomic dead space} = 24 \times \text{height in cm} \times \text{height in cm} / 4545, \text{ or}
\]

\[
\text{Anatomic dead space} = 24 \times \text{height in inches} \times \text{height in inches} / 703
\]

Alveolar Volume (VA)
- Adjustments for sample-bag dead space (VDs) can be made. If at the start of the test the sample bag contains room air, the expired He (or tracers gas) concentration should be adjusted using the following formula:

\[
\text{Adjusted expired He} = \frac{\text{Measured He}}{\left(\frac{\text{sample volume}}{\text{sample volume} - \text{VDs}}\right)}
\]

- CO₂ and H₂O in the exhaled gas must be removed if they interfere with analyzer function, and this will increase the CO and tracer gas concentrations. Thus, adjustments are required for the increase in tracer gas concentration to calculate VA, and formulas are provided in the ATS/ERS standardization document.

Hb Concentration
- For adolescents and adult males the correction equation for adjusting predicted DL\textsubscript{CO} is:

\[
\text{Predicted DL}_{\text{CO}}, \text{corrected for Hb} = \text{Predicted DL}_{\text{CO}} \times \frac{(1.7 \times \text{Hb})}{(10.22 + \text{Hb})}
\]

This correction assumes a standard Hb of 14.6 g/dL. Thus, DL\textsubscript{CO} values in patients with Hb values higher than 14.6 g/dL will be lowered after adjustment. Conversely, DL\textsubscript{CO} values in patients with Hb values lower than 14.6 g/dL will be higher after adjustment.

- For children younger than age 15 years and adult women the correction equation is:

\[
\text{Predicted DL}_{\text{CO}}, \text{corrected for Hb} = \text{Predicted DL}_{\text{CO}} \times \frac{(1.7 \times \text{Hb})}{(9.38 + \text{Hb})}
\]

This correction assumes a standard Hb of 13.4 g/dL.

Carboxyhemoglobin (COHb)
- COHb levels of less than 2% from ordinary environmental exposures are already incorporated into reference values based on healthy nonsmoking individuals.
• If an adjustment for increased levels of COHb is made, the recommendation is that DL,CO be increased by approximately 1% for each 1% of COHb. The following formula can be used:

$$\text{Predicted DL}_{\text{CO, corrected for COHb}} = \text{Predicted DL}_{\text{CO}} \times (102\% - \text{COHb}\%)$$

**Altitude and P_{O2}**

• Adjustments to the predicted DL,CO for patients on supplemental O2 can be made using the following formula (which assumes P_{O2} on room air of 100 mmHg at sea level):

$$\text{Predicted DL}_{\text{CO, corrected for P_{O2}}} = \frac{\text{Predicted DL}_{\text{CO}}}{1.0 + 0.0035 (P_{O2} - 100)}$$

• Adjustments for altitude can be made using the following formula (which assumes a P_{O2} of 150 mmHg at sea level):

$$\text{Predicted DL}_{\text{CO, corrected for altitude}} = \frac{\text{Predicted DL}_{\text{CO}}}{1.0 + 0.0031 (P_{O2} - 150)}$$

**Quality Control**

To calculate the DL,CO value, you must obtain information from the instrumentation components (i.e., spirometer, timer, and gas analyzers). Thus, quality control considerations should include assessing the individual components and the system as a whole (collective assessment). Collective assessments are done using a 3-liter syringe, biological controls, and commercial DL,CO simulator, if available.

**Individual Components**

The individual components are the gas analyzers, timing device, and volume-measuring device.

**Gas Analyzers**

Gas analyzers must be linear because the calculation uses the ratio of the inspired and expired tracer gas (e.g. HeI/HeE) and the ratio of the inspired and expired CO concentrations (i.e., COI/COE). Gas analyzers should have linearity checks at least every 3 months. Prior to each test, the analyzers should be zeroed.

**Timing Device**

Small inaccuracies in breath-hold time can result in meaningful errors in the DL,CO value. Thus, the timing device must be accurate (within 1%, 100 ms over 10 seconds) and should be checked every 3 months.

**Volume-Measuring Device**

Use a 3-liter calibration syringe daily to calibrate the volume-measuring system. If a volume-displacement spirometer is used, leak testing is also necessary.
Other Considerations
The dead space of the system (including filters) must be known. The CO₂ and H₂O absorbers should be fresh and, for many systems, be positioned so that gas passes through them before entering the analyzers. The CO₂ absorber should precede the H₂O absorber in the gas analyzer circuit. Selectively permeable tubing can also be used to remove water vapor, but it may not remove all the water vapor and have a limited life expectancy. Follow the manufacturer’s replacement schedule for water-vapor permeable tubing.

Collective Components
The three collective quality control checks for the DL₃CO system are: (a) a DL₃CO test with a 3-liter syringe for leak testing and measurement of VA; (b) DL₃CO measured in laboratory biological controls to assure no changes are occurring in the system, and (c) DL₃CO and VA measured using a simulator.

DL₃CO with 3-Liter Syringe
This check ensures that the volume-measuring device and tracer gas analyzer are correct and no leaks are present. Connect the 3-liter syringe to the patient port of the valve with minimal space between the syringe and the port. With the syringe partially empty (e.g., in a 3-liter syringe, set at 2 liters so that 1 liter has been ejected), withdraw enough test gas to fill the syringe. Wait approximately 5 to 10 seconds and eject enough volume to satisfy dead space clearance requirements and to obtain an alveolar sample of adequate volume. The tracer gas concentration before and after this maneuver and volume inspired by the syringe can be used to calculate the expected VA (i.e., the volume of the syringe, which is 3 liters in this example). The formula for calculating the known VA is the same as the one used to calculate VA during patient testing, except temperature correction is not done:

\[
VA = \frac{HeI}{HeE} (V I - VD).
\]

where

- \(VA\) = Expected syringe volume
- \(VI\) = Volume inspired using syringe
- \(HeI\) = Initial He concentration
- \(HeE\) = Final He concentration
- \(VD\) = Valve and quality control setup dead space.

The following example illustrates this method. A 3-liter syringe is attached to the patient port of the DL₃CO system with a rubber connector. The valve and connector dead space is 0.2 liter. The syringe is set so that it contains 1 liter (i.e., one-third full) and is connected to the patient port of the DL₃CO system. This mimics a patient with a 1-liter RV and a 2-liter VC. Thus the VA (RV + VC) is approximately 3 liters, which is the value we are trying to achieve.

Withdraw 2 liters of test gas, thereby filling the syringe, and pause approximately 5 to 10
seconds and then eject 0.5 liter before collecting an alveolar sample. The following data are obtained:

- Inspired VC (V_{1 atm}) = 2 liters
- Initial He reading (He_I) = 9.95
- Final He reading (He_E) = 6.11
- Dead space (valve + connector) = 0.2 liter

\[
V_A = \frac{\text{He}_E}{\text{He}_I} \times (V_I - V_D)
\]

\[
V_A = \frac{9.95}{6.11} \times (2.00 - 0.2)
\]

\[
V_A = \frac{1.6285 \times 1.80}{9.93}\text{ liters at ATPD (because a room temperature syringe was used)}
\]

One suggestion is to use a ±3% checking criterion, and therefore the range of acceptability in this example would be 2.91 to 3.09 liters at ATPD. Hence, the system used in the previous example appears to be accurately determining alveolar volume. Note, the measured DL,CO for this test would be approximately zero (typically -1.0 to +1.0) because tracer gas dilution equals CO gas dilution and no diffusion takes place.

**Biological Controls**

The use of biological controls (healthy, nonsmoking individuals) in the pulmonary function laboratory is widespread and is a valid collective method for quality control in the DL,CO system. Although it does not provide a known true value, it does provide a value that remains reasonably constant over time, which allows the laboratory to detect changes. One recommendation is to measure the DL,CO on biological controls at least weekly. If a biological control’s measured DL,CO value (i.e., the mean of at least two acceptable trials that are repeatable) varies by more than 10% from the average DL,CO value, the test should be repeated. If the repeat test confirms the finding, consider the system out of control, and carefully evaluate the system’s individual components.

**DL,CO Simulator**

The DL,CO simulator is a somewhat new tool and provides a method to check the accuracy of the DL,CO device. One such device, the Hans Rudolph, 5560 Series (Figure 3.5), is supplied with software and precision gases. The gases are used to mimic patient testing and create exact target DL,CO and VA values. Measured values can then be compared to target values to determine if the DL,CO instrument is in control. The DL,CO target value range for this device includes low, medium, and high values. The target value depends on the VT used. An acceptable level of agreement between the measured DL,CO value and target value is ±3 units. The ATS/ERS standardization guideline does not provide recommendations on using a DL,CO simulator, but it could be used weekly or on a similar schedule as biological controls.
CHAPTER 3 Single-Breath Carbon Monoxide Diffusing Capacity

Basic Elements of Interpretation

Examination of Reference Studies

As with other pulmonary function values, the DLCO is compared with reference values generated from studies on healthy populations. Many such studies have been published, and there are differences in the DLCO values. For example, the reference or predicted DLCO value is calculated for a 45-year-old man, 68 inches (173 cm) tall, using the reference equations of Cotes,\textsuperscript{18} Crapo and Morris,\textsuperscript{19} Paoletti and coworkers,\textsuperscript{20} Knudson and coworkers,\textsuperscript{21} Miller and colleagues,\textsuperscript{22} and Gulsvik and coworkers,\textsuperscript{23} and the results are shown in Table 3.1.

The reference equations for these studies can be found in Chapter 12. One reason for some of the differences in the expected DLCO values is variation in techniques. The equations published by Cotes in his many editions of \textit{Lung Function} were from unpublished work, and little is known about the methods. The reference values of Crapo and Morris (published in 1981)\textsuperscript{19} incorporated a bag-in-box technique with He as the inert gas. The breath-hold time was calculated using the technique of Ogilvie\textsuperscript{12} (beginning of inspiration to the beginning of alveolar gas sample collection). They used 25\% \textit{O}_2 in the test gas and studied 123 men (age range 16 to 91 years) and 122 women (age range 17 to 84 years).

Miller and coworkers\textsuperscript{22} studied smokers and nonsmokers in their 1983 study. They employed a demand valve to deliver the inspired test gas and a pneumotachograph instead of the bag-in-box. The breath-hold time was calculated using the technique recommended by the Epidemiology Standardization Project (ESP),\textsuperscript{24} which begins when half the inspired VC has been inhaled and ends at the beginning of alveolar gas sample collection. The average of two tests was reported, and they studied 74 male nonsmokers and 130 female nonsmokers.

Paoletti and coworkers\textsuperscript{20} studied the general population of the Po River delta near Venice, Italy, in 1985 using an automated-demand valve system with a pneumotachograph. The
breath-hold time was calculated using the ESP technique. They studied 163 men aged 8 to 18 years and 80 men aged 19 to 65 years. They also studied 178 women aged 8 to 18 years and 291 women aged 19 to 65 years. The test gas contained 20% O₂.

Knudson and coworkers studied a Caucasian population in Tucson, Arizona, from 1981 to 1984. A commercially modified bag-in-box system was used—a double water-sealed spirometer. The test gas contained 0.3% CO, 10% He, 21% O₂, and balance N₂. The breath-hold time was measured using the ESP technique. They studied 28 men younger than age 25 years and 71 men older than age 25 years. They also studied 30 women younger than age 20 years and 99 women older than age 20 years.

Gulsvik and coworkers studied a Norwegian population from 1987 to 1988. They used a Gould 2100 automated system consisting of a flow-sensing device, a demand valve connected to the cylinder of test gas, and an alveolar gas sample bag. The test gas contained approximately 0.3% CO, 10% He, 21% O₂, and balance N₂. The breath-hold time was measured using the Jones-Meade technique. They studied 119 men and 185 women aged 18 to 73 years. They reported the TL,CO in mmol/min/kPa, which is multiplied by 2.987 to obtain mL/min/mmHg.

Choosing a Reference Equation

Because the techniques and expected values vary so widely, selecting reference values for one’s laboratory is a difficult task. It is best to choose a reference study with similar techniques to those used in your laboratory. Likewise, choose a reference study that included a population similar to your patient population (e.g., age range, body size). When you have one or two candidate studies that match as many criteria as possible, measure the DL,CO in 10 to 15 healthy, nonsmoking individuals of each gender and compare the results with the predicted or reference values from the candidate reference study. If the difference between the measured DL,CO values of the healthy individuals and the predicted value from a candidate reference study is zero or near zero, the reference equation fits the laboratory population. The best reference equation is the one with the smallest difference between predicted and measured values in the 10 to 15 healthy subjects.

### Table 3.1

<table>
<thead>
<tr>
<th>Study</th>
<th>DL,CO (mL/min/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotes</td>
<td>29.62</td>
</tr>
<tr>
<td>Crapo</td>
<td>35.77</td>
</tr>
<tr>
<td>Paoletti</td>
<td>36.20</td>
</tr>
<tr>
<td>Knudson</td>
<td>37.75</td>
</tr>
<tr>
<td>Miller</td>
<td>31.03</td>
</tr>
<tr>
<td>Gulsvik</td>
<td>31.12</td>
</tr>
</tbody>
</table>

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.
Interpretation and Clinical Applications

When a normal or predicted value has been determined, abnormal DL\textsubscript{CO} values can be identified. The DL\textsubscript{CO} should be interpreted in conjunction with other pulmonary function measurements. The DL\textsubscript{CO} can be abnormally increased or abnormally decreased. Increased DL\textsubscript{CO} values can occur when the pulmonary capillary blood volume increases. This occurs with exercise, left-to-right intracardiac shunts, left heart failure, and in the supine position. The DL\textsubscript{CO} value is also increased when there is an increase in the number of red blood cells (e.g., polycythemia) and during pulmonary hemorrhage. An increased DL\textsubscript{CO} in asthmatic patients is sometimes seen; one possible mechanism is an increase in the pulmonary capillary blood volume as a result of high negative intrathoracic pressure created during the rapid inspiratory maneuver.

Decreased DL\textsubscript{CO} values are usually of more interest and concern. A DL\textsubscript{CO} value can be reduced primarily because of: (a) a small lung volume and (b) a diffusion defect.

Because the total A-C membrane surface area depends on lung size, the DL\textsubscript{CO} value depends on lung volume. When a patient has a pneumonectomy, lung volume is decreased and the DL\textsubscript{CO} value is low compared with the predicted value. However, the other lung’s diffusion capability in such a patient can be perfectly normal. This problem is commonly handled by correcting the DL\textsubscript{CO} for the lung volume that was measured in the test (i.e., the VA). This correction takes the form of DL\textsubscript{CO}/VA, which is defined as the diffusion of the lung per amount of lung volume. This adjustment for lung volume is controversial because the relationship between DL\textsubscript{CO} and lung volume is not linear. The ATS/ERS\textsuperscript{25} recommends examining DL\textsubscript{CO}/VA and VA separately because it can provide information on disease pathophysiology.

In patients with emphysema, the DL\textsubscript{CO} is characteristically low. The loss of A-C membrane surface area occurs as alveoli rupture and form large alveolar spaces. In emphysema, the DL\textsubscript{CO} is decreased in the face of increased lung volumes, and thus the DL\textsubscript{CO}/VA ratio is also decreased.

In patients with interstitial lung disease (e.g., idiopathic pulmonary fibrosis, scleroderma, sarcoidosis, and asbestosis), the DL\textsubscript{CO} is commonly low. The A-C bed and alveoli are typically involved, reducing the number of functional A-C units. In these patients, the lung volumes are commonly reduced, and although the DL\textsubscript{CO} may be low, the DL\textsubscript{CO}/VA ratio may be normal or reduced.

Patients with pulmonary vascular and cardiovascular diseases can also have low DL\textsubscript{CO} values. In patients with pulmonary embolism or primary pulmonary hypertension, the pulmonary capillary blood volume is reduced and ventilation-perfusion matching is affected. In patients with congestive heart failure and mitral valve stenosis, the interstitial edema appears to be the main cause for the low DL\textsubscript{CO}. Usually the low DL\textsubscript{CO} value is accompanied by a normal VA, and thus the DL\textsubscript{CO}/VA ratio is reduced.

Other causes of low DL\textsubscript{CO} values include: (a) anemia, (b) renal failure, (c) marijuana smoking, and (d) cigarette smoking.\textsuperscript{26}

A scheme for quantifying the severity of a decrease in DL\textsubscript{CO} has been suggested by the ATS/ERS.\textsuperscript{25} Mild severity is suggested when the DL\textsubscript{CO} is between 60% and the lower limit of normal. Moderate severity is suggested when the DL\textsubscript{CO} is between 40% and 60% of predicted. Severe reductions in DL\textsubscript{CO} are less than 40% of predicted.
Case Presentations

Case 3.1

A 56-year-old white woman who claimed to be a nonsmoker and to have had a pneumonectomy 4 years ago was tested in the pulmonary function laboratory. Her pulmonary function test results are shown in Figure 3.6 and Table 3.2.

Questions

1. What is the interpretation of the pulmonary function data?
2. Is there adequate information for interpreting all the results?

Answers and Discussion

The pulmonary function data can be partially interpreted. The total lung volume (as measured by TLC) is decreased. There is also some airflow limitation that does not significantly improve with a bronchodilator. These findings suggest a mixed restrictive and obstructive process.

The DLCO is decreased, but there is not enough information to interpret this finding adequately. To interpret the single-breath DLCO value accurately, VA must be considered.

Figure 3.6

Flow–volume curves before and after administration of a bronchodilator on the 56-year-old woman in Case 3.1.
Because the surface area available for diffusion depends on the size of the lungs, the measured DL,CO will depend on lung volume. If a patient has only one lung, the DL,CO value will be low when compared to a patient with two lungs. Likewise, the DL,CO of a patient with one lung will be low when compared to a reference value based on height and age. But if the DL,CO is divided by the VA that the CO was distributed to, the ratio (DL,CO/VA) is normal. In this patient, the result of this correction is shown in Table 3.3.

If the DL,CO is normal or greater than normal, correction for VA is not important. But if the DL,CO is low, the DL,CO/VA should be considered. In this patient, the measured DL,CO is low, but when corrected for VA, it is normal. This suggests that lung diffusion is normal in the remaining lung.

### Table 3.2

| Pulmonary Function Data Before and After a Bronchodilator in a 56-Year-Old Woman (Case 3.1) |
|---------------------------------|--------|--------|
| Predicted | Before | After |
| FVC (L) | 3.74 | 1.76 (47) | 1.87 |
| FEV₁ (L) | 2.90 | 1.22 (42) | 1.31 |
| FEV₁/FVC (%) | 78 | 69 | 70 |
| FEF₂₅₋₇₅ (L/sec) | 2.96 | 0.80 (27) | 0.85 |
| TGV (L) | 2.85 | 2.94 (103) | |
| TLC (L) | 5.04 | 3.73 (74) | |
| RV (L) | 1.28 | 1.66 (130) | |
| DL,CO (mL/min/mmHg)† | 26.4 | 14.8 (56) | |

*Values in parentheses are percent predicted
†Corrected for Hb using Cotes’s method

### Table 3.3

| Single-Breath CO Diffusing Capacity and DL,CO Corrected for VA (DL,CO/VA) in a 56-Year-Old Woman (Case 3.1) |
|---------------------------------|--------|
| DL,CO (mL/min/mmHg) | 14.8 (56)* |
| DL,CO/VA | 5.7 (106)† |
| DL,CO/VA | 5.7 (110)‡ |

*Values in parentheses are percent predicted
†Percent predicted using Crapo and Morris’s predicted equations
‡Percent predicted using predicted TLC divided into predicted DL,CO

Because the surface area available for diffusion depends on the size of the lungs, the measured DL,CO will depend on lung volume. If a patient has only one lung, the DL,CO value will be low when compared to a patient with two lungs. Likewise, the DL,CO of a patient with one lung will be low when compared to a reference value based on height and age. But if the DL,CO is divided by the VA that the CO was distributed to, the ratio (DL,CO/VA) is normal. In this patient, the result of this correction is shown in Table 3.3.

If the DL,CO is normal or greater than normal, correction for VA is not important. But if the DL,CO is low, the DL,CO/VA should be considered. In this patient, the measured DL,CO is low, but when corrected for VA, it is normal. This suggests that lung diffusion is normal in the remaining lung.
Case 3.2

A 21-year-old man who claimed to be a nonsmoker was tested in the pulmonary function laboratory. The results are shown in Table 3.4.

Question

1. How do you interpret the DL_{CO}?

Answer and Discussion

The spirometry results are normal, and no response to a bronchodilator is seen. The lung volumes (TLC, FRC, and RV) are slightly low but still within normal limits.

The DL_{CO} value is low. When corrected for VA, it is also low, suggesting a diffusion abnormality. However, the DL_{CO} has not been corrected for Hb. When corrected for Hb, the DL_{CO} becomes 38.9 mL/min/mmHg, or 87% of predicted, which is within normal limits.

Table 3.4

Pulmonary Function Data Before and After a Bronchodilator on a 21-Year-Old Man (Case 3.2)

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Before*</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.30</td>
<td>4.77 (90)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.13</td>
<td>4.21 (102)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>FEF_{25-75%} (L/sec)</td>
<td>4.66</td>
<td>5.13 (110)</td>
</tr>
<tr>
<td>FRC_{pleth} (L)</td>
<td>3.56</td>
<td>3.03 (85)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>6.56</td>
<td>5.97 (91)</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.58</td>
<td>1.20 (76)</td>
</tr>
<tr>
<td>DL_{CO} (mL/min/mmHg)†</td>
<td>44.5</td>
<td>32.9 (74)</td>
</tr>
<tr>
<td>DL_{CO}/VA</td>
<td>6.90</td>
<td>5.59 (81)</td>
</tr>
</tbody>
</table>

Arterial blood gases

| pH | 7.43 |
| PaCO2 (mmHg) | 39 |
| PaO2 (mmHg)  | 87 |
| SaO2 (%)     | 94 |
| COHb (%)     | 2.1 |
| Hb(g/dL)     | 10.1 |

* Values in parentheses are percent predicted
† Not corrected for Hb
CO has a very high affinity for Hb. Thus, the diffusion of CO is affected by the amount of Hb in the pulmonary capillaries. Patients with anemia have low DL,CO values because of the low reservoir available for binding with CO. Likewise, patients with polycythemia (increased Hb values) have high DL,CO values because of high reservoirs. Two methods for normalizing the DL,CO value to a standard Hb value are widely used. The ATS/ERS standization guideline recommends the use of the following equation for adolescents and adult males:

\[
\text{Predicted DL,CO, corrected for Hb} = \frac{\text{Predicted DL,CO}}{(1.7 \times \text{Hb}) / (10.22 + \text{Hb})}
\]

The uncorrected DL,CO should always be reported, even if the Hb-corrected DL,CO is also reported.

**Case 3.3**

A 57-year-old woman was referred for evaluation of shortness of breath and hypoxemia. She claims to develop shortness of breath with walking a half flight of stairs or less than one block. She states she has an intermittent cough, uses two to three pillows while sleeping, and develops some chest heaviness during dressing and other activities of daily living (e.g., vacuuming). She claims to have had some near syncope, especially with exertion, and some edema. She appears to be in the *WHO Class II-III* functional status. She has no history of deep vein thrombosis, pulmonary emboli, liver disease, HIV exposure, illicit drug use, or smoking. There is no family history of pulmonary hypertension. Her pulmonary function data are presented in Table 3.5 and Figure 3.7.

**Questions**

1. How would you interpret data from the pulmonary function test?
2. What other tests would you recommend?

**Answers and Discussion**

The spirometry and lung volume results are normal with no response to bronchodilator. The DL,CO is markedly reduced, and after correcting for Hb and lung volume it is still markedly reduced. Given the nonsmoking history and normal spirometry and lung volumes, a chest x-ray was ordered.

The chest x-ray shows considerable enlargement of the central pulmonary arteries, consistent with pulmonary hypertension. There is also attenuation of the peripheral vascular markings (pruning) and signs of right ventricular enlargement (visible on the lateral film).

An echocardiogram was ordered to evaluate the possibility of pulmonary hypertension. The heart rate was 84 beats/min, blood pressure was 115/70 mmHg, and the ECG showed normal sinus rhythm, right axis deviation, and right ventricular hypertrophy. The results of the echocardiogram show moderate–severe right ventricular enlargement with moderate–severe decreased right ventricle systolic function (right ventricular index of myocardial performance $= 0.78$, and
estimated right ventricular systolic pressure = 82 mmHg). There was normal left ventricular chamber size and normal left ventricular systolic function (ejection fraction = 64%). There was no evidence of regional wall motion abnormalities, intracardiac mass, thrombus, or intracardiac shunt. There was mild–moderate tricuspid valve regurgitation.

Because idiopathic pulmonary artery hypertension was suspected, a right-heart catheterization was scheduled to confirm the diagnosis because data from the echocardiogram can sometimes be unreliable. The results of the right-heart catheterization confirmed the elevated pulmonary artery pressure (Ppa: mean = 50 mmHg, systolic = 80 mmHg). A 6-minute walk test was also performed. The distance walked was 325 meters, with a Borg scale value of 5. During the 6-minute walk test on room air, the patient desaturated to 82%.

An oxygen titration study with pulse oximetry was ordered and performed at rest and during exercise. She desaturated during the exercise, and she was treated by titrating the oxygen to maintain a saturation of at least 90%. As a result, she was placed on 1 liter/min of oxygen at rest and 5 liters/min with an Oxymizer pendant when active.

The final diagnosis was idiopathic pulmonary hypertension, and the patient was started on an oral phosphodiesterase 5 (PDE5) inhibitor.

### Table 3.5: Pulmonary Function Data Before and After a Bronchodilator on a 57-Year-Old Woman (Case 3.3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predicted</th>
<th>LLN</th>
<th>Before*</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.42</td>
<td>2.68</td>
<td>3.48 (102)</td>
<td>3.49</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.73</td>
<td>2.18</td>
<td>2.66 (98)</td>
<td>2.71</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>79</td>
<td>68.7</td>
<td>76.5</td>
<td>77.5</td>
</tr>
<tr>
<td>FEF₂₅–₇₅% (L/sec)</td>
<td>2.40</td>
<td>1.1</td>
<td>2.00 (84)</td>
<td>2.40</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>101</td>
<td>68</td>
<td>108 (106)</td>
<td></td>
</tr>
<tr>
<td>FRCₚₑₚh (L)</td>
<td>3.00</td>
<td>2.05</td>
<td>2.70 (90)</td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.39</td>
<td>4.29</td>
<td>5.64 (105)</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.97</td>
<td>2.56</td>
<td>2.22 (113)</td>
<td></td>
</tr>
<tr>
<td>DLₜ₟₂₅₋₇₅% (mL/min/mmHg)</td>
<td>22.7</td>
<td>16.2</td>
<td>8.0 (35)</td>
<td></td>
</tr>
<tr>
<td>VA (L)</td>
<td>5.16</td>
<td>4.29</td>
<td>4.73 (92)</td>
<td></td>
</tr>
<tr>
<td>DLₜ₟₂₅₋₇₅%/VA</td>
<td>4.40</td>
<td>1.69 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>14.1</td>
<td>92</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (rest)</td>
<td>96</td>
<td>92</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Pulse (rest)</td>
<td></td>
<td></td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses are percent predicted.
Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease that often results in right-heart failure and death. Idiopathic PAH occurs more in women than in men, the mean age at diagnosis is approximately 35 years, and the mean survival from diagnosis is less than 3 years. Pulmonary function data from a US-based registry of 1360 patients shows that patients have little or no airway obstruction, a reduced total lung capacity (TLC), and a reduced DL\textsubscript{CO}. The mean DL\textsubscript{CO} was 55 ±23\% of predicted. These data are mostly consistent with the pulmonary function test results obtained on the patient in this case (i.e., normal spirometry, normal TLC, and a DL\textsubscript{CO} that was 38\% of predicted). As of 2010, the treatment for PAH includes different types of PDE5 inhibitors, prostanoids, and endothelin-receptor antagonists. These agents have been shown effective in relieving shortness of breath, improving exercise tolerance, and possibly extending survival.
Self-Assessment Questions

1. CO has an affinity for Hb that is:
   a. 210 times that of O₂
   b. 210 times that of CO₂
   c. 2 times that of O₂
   d. 210 times that of N₂

2. All the following are components of the diffusion or transfer of CO from the alveoli to Hb except:
   a. Diffusion across the A-C membrane
   b. Passage through the red blood cell membrane
   c. COHb reaction rate
   d. Arterial–alveolar oxygen gradient
   e. Transfer to red blood cells

3. In the single-breath DL_CO test, an inert gas is included in the inspired gas mixture to:
   a. Measure FRC
   b. Measure the dilution of CO into the lung residual volume
   c. Ensure quality control
   d. Measure the diffusion across the A-C membrane

4. In the single-breath DL_CO test, the V̅a is calculated from:
   a. The volume inspired and the dilution of the inert gas
   b. The volume inspired and the dilution of CO
   c. The volume inspired and the FRC
   d. The volume inspired and the dilution of N₂

5. After the breath hold in the single-breath DL_CO test, the first portion of the exhaled gas is discarded because:
   a. It contains CO₂.
   b. It contains gas that did not reach the alveoli.
   c. It contains He.
   d. It contains gas that has water vapor.

6. To be considered acceptable according to the 2005 ATS/ERS standardization guideline, the inspired VC of test gas during the single-breath DL_CO test should be:
   a. At least 85% of the largest previously measured VC
   b. At least 80% of the largest previously measured VC
   c. Inhaled in less than 4 seconds
   d. a and c
   e. b and c

7. Which of the following does not affect the single-breath DL_CO value?
   a. Elevated COHb level
   b. Increased Hb level
   c. Decreased Hb level
   d. None of the above

8. When performing a single-breath DL_CO test on a patient whose VC is 3.00 liters, the minimum acceptable V̅t would be:
a. 2.70 liters  
b. 3.00 liters  
c. 2.55 liters  
d. 2.10 liters

9. What is the typical concentration of CO in the inspired test gas for the single-breath DL\textsubscript{CO} test?  
a. 0.03%  
b. 0.3%  
c. 3.0%  
d. 10.0%

10. All the following are criteria for an acceptable DL\textsubscript{CO} maneuver except:  
a. Rapid inspiration of less than 4 seconds  
b. Inspiratory VC of at least 85% of the largest previously measured VC  
c. A breath-hold time between 8 and 12 seconds  
d. Smooth expiration that is more than 4 seconds

11. The most accurate description of the Jones-Meade technique for determining breath-hold time for DL\textsubscript{CO} is:  
a. Start of the inspiration to start of alveolar gas sampling  
b. When 30% of the inspiratory time has elapsed to the point when 50% of the alveolar gas sample has been collected  
c. When 50% of the inspiratory time has elapsed to the point when 30% of the alveolar gas sample has been collected  
d. Start of the inspiration to the point when 50% of the alveolar gas sample has been collected

12. DL\textsubscript{CO} testing produced the following DL\textsubscript{CO} values: 28.8, 23.3, 23.1 mL/min/mmHg. What value should the laboratory report?  
a. 25.0  
b. 28.8  
c. 23.2  
d. Perform another maneuver

References


Airway Resistance by Body Plethysmography

Introduction

The measurement of resistance can be applied to the various parts of the respiratory system, including the chest wall, lung tissue, and airways. Lung resistance (RL) refers to the resistance of the lung tissue and airways. It is usually done in conjunction with the measurement of elastic properties (i.e., pressure volume) and requires a catheter–balloon system to measure esophageal pressure, which is then used to estimate pleural pressure. Total respiratory resistance (RTOT) is the sum of the chest wall, lung tissue, and airway resistances. It can be measured with the subject breathing spontaneously on an interrupter device or by the forced oscillation technique. Airway resistance (Raw) results from frictional changes in the air that flows from the mouth to the alveoli. It is commonly measured using a body plethysmograph and has the advantage in that lung volume (i.e., thoracic gas volume [TGV]) is measured at the same time.

This chapter will focus on the measurement of Raw using a body plethysmograph. This measurement and method are widely used but frequently misunderstood. Additionally, because...
the body plethysmograph allows lung volumes to be determined (see Chapter 2), the measurement of Raw can be corrected for the lung volume at which the measurement was made. The resulting calculations, specific resistance and specific conductance, will also be discussed.

**Physiology**

During quiet spontaneous breathing the respiratory muscles generate pressure differences between the alveoli and the airway opening (i.e., the mouth). The pressure differences, or pressure gradients, result in airflow from the airway opening into the alveoli. This gradient depends on the amount of flow, characteristics of the flow (e.g., laminar and turbulent), gas viscosity, and airway contour.

Because airflow ($V$) is related to the pressure gradient ($\Delta P$), Raw can be expressed in the following manner:

$$\text{Raw} = \frac{\text{Pressure difference between alveoli and mouth}}{\text{Flow}}$$

or

$$\text{Raw} = \frac{\Delta P}{V}$$

(Eq. 4.1)

Raw depends on several factors, including: (a) size of airways, (b) number of airways, and (c) elastic recoil. The smaller the airway size (e.g., bronchoconstriction), the greater the Raw. When the number of airways is decreased (e.g., pneumonectomy), the reduced cross-sectional area results in an increased Raw. The greater the elastic recoil, the lower the Raw (e.g., in idiopathic pulmonary fibrosis), and conversely, Raw is increased when there is a loss of elastic recoil pressure (e.g., in emphysema).

In healthy individuals, the decreasing size of airways distal to the trachea is more than compensated for by the increased number of airways. In fact, the total cross-sectional area is increased toward the lung periphery. Hence, during quiet breathing the majority of Raw is in the trachea and large airways.

The relationship between Raw and lung volume is hyperbolic (Figure 4.1). As you inhale and lung volume increases, the airways increase in diameter and Raw decreases. As you exhale and lung volume decreases, the airways decrease in diameter and Raw increases. Hence, the Raw value will vary depending on the lung volume at which the measurement is made, and thus knowing the actual lung volume when the Raw measurement was made is important.

The reciprocal of Raw is called airway conductance (Gaw). The relationship between Gaw and lung volume is linear (Figure 4.2). The slope of the Gaw and lung volume
relationship is called the specific conductance of the airway (sGaw), which corrects the conductance for the volume at which it was measured. These relationships can be written mathematically as

\[
\text{Gaw} = \frac{1}{\text{Raw}} \quad \text{(Eq. 4.2)}
\]

and

\[
\text{sGaw} = \frac{\text{Gaw}}{\text{TGV}} \quad \text{(Eq. 4.3)}
\]

where

TGV = Thoracic gas volume at which Raw was measured

Similarly, specific resistance of the airway (sRaw) is calculated by correcting the Raw for the volume at which it was measured.

\[
\text{sRaw} = \frac{\text{Raw} \times \text{TGV}}{\text{TGV}} \quad \text{(Eq. 4.4)}
\]

where

TGV = Thoracic gas volume at which Raw was measured

**Figure 4.1**

The relationship between lung volume and airway resistance (Raw) is hyperbolic. Higher lung volumes have lower Raw because the airways have a larger diameter. Lower lung volumes have higher Raw because the airways have a smaller diameter.
CHAPTER 4 Airway Resistance by Body Plethysmography

Technique

Three types of body plethysmographs (body boxes) were described in Chapter 2: (a) variable-pressure box (constant-volume box), (b) flow box, and (c) volume-displacement box. The principles are similar for each type, and all measure Raw.

As previously described, Raw is the ratio of the pressure gradient in the airway (ΔPₐ) to airflow (V) measured at the mouth. In the body box, airflow at the mouth can be measured readily with a flow-sensing device (e.g., pneumotachograph). However, determining the alveolar pressure gradient when there is airflow is more complicated.

The patient breathes on a mouthpiece-shutter system inside the airtight body box. Because the body box is airtight, the total amount of gas in the body box–lung system remains constant. Hence, gas will flow only from a point of higher pressure to a point of lower pressure. Thus, during inspiration gas will flow into the lungs only if the alveolar pressure (Pₐ) is less than the body box pressure. Similarly, during expiration gas will flow out of the lungs only if Pₐ exceeds the body box pressure. At the beginning of inspiration, the respiratory muscles enlarge the thoracic cage, causing a lower Pₐ compared with atmospheric pressure. The enlargement of the thoracic cage also results in an increase in the body box pressure because the box is airtight. Hence, the change in Pₐ can be detected by the change in body box pressure, which is measured by a sensitive pressure transducer.

The relationship between lung volume and airway conductance (Gaw) is linear. Thus, Gaw increases linearly with lung volume. The slope of this relationship (i.e., ΔGaw/ΔV) is known as specific conductance (sGaw).

![Figure 4.2](image-url)

The relationship between lung volume and airway conductance (Gaw) is linear. Thus, Gaw increases linearly with lung volume. The slope of this relationship (i.e., ΔGaw/ΔV) is known as specific conductance (sGaw).

<table>
<thead>
<tr>
<th>Lung volume (L)</th>
<th>Conductance (L/sec/cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© Jones & Bartlett Learning, LLC. NOT FOR SALE OR DISTRIBUTION.
With the ability to measure airflow and $P_A$ changes, the measurement of $Raw$ in the body box can be described as requiring two maneuvers: (a) open-shutter panting and (b) closed-shutter panting.

The patient breathes on the mouthpiece inside the body box and performs the gentle open-shutter panting maneuver. A breathing or panting rate of approximately two to three breaths/sec (2 to 3 Hz) is recommended. This gentle panting eliminates volume variations related to gas temperature and humidity.

With the shutter system open, the patient performs a number of gentle pants (e.g., two to six). The relationship between body box pressure changes ($\Delta P_{bb}$), which are proportional to $P_A$ changes, and airflow ($V$) are recorded. This relationship is expressed as $V/\Delta P_{bb}$. If this relationship is plotted graphically it produces an S-shaped curve (Figure 4.3). A line is constructed through the center portion (i.e., between $\pm 0.5$ liter/sec) of the S-shaped curve. The slope or tangent of this line (i.e., $\Delta V/\Delta P_{bb}$) is then determined and used in the calculations.

Immediately after the open-shutter pants, the shutter system is closed (thus there is zero flow) and the patient continues panting at a slower rate (i.e., about one breath/sec). The relationship between body box pressure changes ($\Delta P_{bb}$) and mouth pressure changes ($\Delta P_m$) are recorded. Mouth pressure changes are assumed to equal $P_A$ changes when the glottis is open.

**Figure 4.3**

The S-shaped curve created during open-shutter panting for Raw showing the relationship between flow and body box pressure.
If this is plotted graphically it produces a series of superimposed straight lines (Figure 4.4).

As was described in Chapter 2, looping or bending can occur with glottis closure or box leaks. A measurement line parallel to the superimposed panting straight lines is constructed through the series of straight lines. The tangent or slope of this line is then determined and used, along with the tangent from the open-shutter step, to calculate Raw and TGV.

The purpose of the closed-shutter step is to calibrate the changes in $P_A$ to changes in $P_{BB}$ determined with the open-shutter step. This maneuver also permits measurement of TGV, which is needed to calculate $sGaw$ or $sRaw$.

Obtain at least four or five sets of acceptable open- and closed-shutter panting maneuvers. Between each set of panting maneuvers, assure the patient returns to tidal breathing and rests, if necessary. Praise the patient’s performance during each attempt (“that was a great job”) and offer suggestions on how to improve subsequent maneuvers, if necessary (e.g., “slow the panting frequency,” “pant using smaller volumes”). Visually inspect each maneuver to ensure there was no evidence of thermal drift (i.e., closed S-shaped curve) and to ensure the panting frequencies were similar. The Raw values in some individuals increases at higher panting frequencies, possibly because of uneven time constants within the airways. If serial measurements are to be performed, the panting frequency should be kept the same to aid in the interpretation. Manually adjust computer measured open- and closed-shutter slopes, if necessary.

The Raw and $sGaw$ for each open- and closed-shutter set should be determined. The average of three to five acceptable maneuver sets should then be reported. A reasonable
The repeatability goal is to have the Raw and sGaw values agree within 10% of the mean. For example, if Raw values of 2.6, 2.8, 2.9, 2.8, 2.7, and 3.4 cm H₂O/liter/sec were obtained on a patient, the mean value of 2.76 cm H₂O/liter/sec would likely be reported, with the 3.4 value excluded as an outlier. The technologist should comment on the variability of these measures.

**Calculations**

In practice, the technologist observes a computer screen on which the open- and closed-shutter maneuvers are displayed. During the open-shutter maneuver, flow is displayed on the vertical (y) axis, and body box pressure or volume is displayed on the horizontal (x) axis (Figure 4.5). During the closed-shutter maneuver, mouth pressure is displayed on the y axis, and body box pressure or volume is displayed on the x axis (Figure 4.4).

The relationship between flow and body box pressure can be described by line A in Figure 4.5. The tangent of angle A (as measured from the horizontal axis) is used to estimate $\Delta V/\Delta P_{BB}$. Similarly, the relationship between mouth pressure and body box pressure can be described by line B in Figure 4.6. The tangent of angle B (as measured from the horizontal axis) is used to estimate $\Delta P_M/\Delta P_{BB}$.

**Figure 4.5**

The S-shaped curve during open-shutter panting showing the relationship between flow and body box pressure. Line A is the fit for this example. The tangent of angle A (indicated by arrows) is used to estimate changes in flow and changes in body box pressure. The shaded area (i.e., ±0.5 liter/sec) is the area commonly used to obtain the fit line.
Equation 4.1 can be rewritten as:

\[
\text{Raw} = \frac{\text{Closed-shutter maneuver}}{\text{Open-shutter maneuver}} \times \frac{P_A/P_{BB}}{V/P_{BB}} \times \frac{P_{cal}/P_{BB,cal}}{V_{cal}/P_{BB,cal}} \quad \text{(Eq. 4.5)}
\]

The following example uses some hypothetical numbers for a single open- and closed-shutter set. The open-shutter panting maneuver produced the display shown in Figure 4.5. Angle A is measured to be 55 degrees, and the tangent of 55 degrees is 1.428. The closed-shutter panting produced the display shown in Figure 4.6. Angle B is measured to be
45 degrees, and the tangent of 45 degrees is 1.000. The flow (\(V\)), mouth pressure (\(P_M\)), and body box pressure (\(P_{BB}\)) calibration factors for this example are 1 liter/sec/cm, 2.5 cm H\(_2\)O/cm, and 10 mL/cm, respectively. The resistance of the body box breathing system (\(R_{sys}\)) must be subtracted and is 0.2 cm H\(_2\)O/liter/sec. Using Equation 4.5:

\[
\text{Raw} = \frac{2.4 \text{ cm } H_2O/cm}{1.428 \times \frac{10 \text{ mL/cm}}{1 \text{ liter/sec/cm}}} - R_{sys} \times \frac{10 \text{ mL/cm}}{1 \text{ liter/sec/cm}}
\]

\[
\text{Raw} = 0.700 \times 2.5 \text{ cm } H_2O/\text{liter/sec} - 0.2
\]

\[
\text{Raw} = 1.55 \text{ cm } H_2O/\text{liter/sec}
\]

Using these numbers and the rewritten equation in Chapter 2, the TGV during the Raw maneuvers can be calculated as follows:

\[
\begin{align*}
\text{TGV} & = P \times \frac{1}{\tan \angle B} \times \frac{P_{cal \text{ factor}}}{P_{cal \text{ factor}}} \times \frac{10 \text{ mL/cm}}{1 \text{ liter/sec/cm}} \\
\text{TGV} & = 970 \text{ cm } H_2O \times \frac{1}{1.000} \times \frac{10 \text{ mL/cm}}{2.5 \text{ cm } H_2O/cm} \\
\text{TGV} & = 970 \text{ cm } H_2O \times 4 \text{ mL/cm } H_2O \\
\text{TGV} & = 3,880 \text{ mL, or } 3.88 \text{ liters}
\end{align*}
\]

Using Equations 4.2 and 4.3, the conductance (\(Gaw\)) and specific conductance (\(sGaw\)) can be obtained as follows:

\[
\begin{align*}
\text{Gaw} & = \frac{1}{\text{Raw}} = \frac{1}{1.55} = 0.65 \\
\text{sGaw} & = \frac{\text{Gaw}}{\text{TGV}} = \frac{0.65}{3.88} = 0.17 \text{ cm } H_2O/\text{liter/sec/liter}
\end{align*}
\]

Raw and \(sGaw\) are also frequently expressed in SI units. For Raw, the SI units are kPa/liter/sec and the conversion factor from the conventional cm H\(_2\)O/liter/sec to SI units of kPa/liter/sec is 0.09806. The SI units for \(sGaw\) are kPa/liter/sec/liter.

**Technical Considerations**

Because of distortion, determining the position of line A (Figure 4.5) presents a challenge. Several factors have been described as affecting the appearance of the open-shutter S-shaped \(V/P_{BB}\) relationship. These can be separated into instrumental and biological factors. The instrumental factors include: (a) the flow sensing device, (b) the sensitivity and frequency response of the pressure...
transducer, and (c) air leaks in the body box. The biological factors include: (a) temperature and humidity, (b) expiratory looping, (c) turbulence, and (d) changes in the respiratory exchange ratio.

Even when an individual performs the panting maneuver perfectly, a certain amount of distortion is observed, and it increases when the person does not perform the maneuver correctly. A common problem results when panting is too slow or too fast. If the individual pants too slowly, body box temperature changes cause the S-shaped curve to open up (Figure 4.7). If the subject pants too quickly, the S-shaped curve takes on a figure-8 appearance (Figure 4.8). Increasing or reducing the patient’s panting speed, as needed, will help solve these problems. Additionally, the volume of air breathed in and out during the panting can be increased or decreased to aid in getting to the proper speed and the clean S-shaped curve.

In individuals with significant airflow obstruction, airway collapse occurs during expiration, resulting in increased expiratory resistance. This dynamic closure of the airways results in a characteristic looping pattern—a bending of the expiratory portion (Figure 4.9). This bending of the expiratory portion can create measurement problems, especially if it occurs within the ± 0.5 liter/sec measurement range.

It is very difficult to use one line to estimate the Raw when this expiratory looping or bending is present. A line drawn through the long axis of the loop (line C, Figure 4.9) will estimate an average expiratory Raw. A line drawn through the ± 0.5 liter/sec range (line D, Figure 4.9) will estimate the late inspiratory and early expiratory Raw. The angle of line C is considerably greater than line D (Figure 4.9), producing a much higher Raw. Some researchers have estimated that the difference may be threefold or fourfold.13,14

Figure 4.7
An example of an open-shutter panting pattern during the Raw maneuver in the body box when the panting is too slow. Note the open appearance of the S-shaped curve.
Figure 4.8
An example of an open-shutter panting pattern during the Raw maneuver in the body box when the panting is too fast. Note the figure-8 appearance.

Figure 4.9
An example of an open-shutter panting pattern during the Raw maneuver in the body box in a patient with significant airflow obstruction. Note the bending or looping of the expiratory portion. Line D is the recommended fit.
So how do you measure the Raw when this looping or bending is present? Probably the best strategy is to fit the line between the \( \pm 0.5 \) liter/sec range without including the looping, as is done with line D (Figure 4.9). This will generally produce lower but less variable Raw values.

Computerization of this measurement has improved speed and has somewhat reduced subjectivity. Before the use of the computer, the technologist typically would align a rotating cursor parallel with the data lines displayed on an oscilloscope screen or paper record and read the slope from a circular scale. Lord and coworkers found substantial variation of Raw values by different observers using this manual method.

In a comparison study between the manual and computerized methods, it was determined that wide variability in Raw values existed in each method. However, no significant differences were found between the two methods. Today, computerization of this measurement process has become the standard, and it allows the user to examine the computer fit and make adjustments if necessary. This may or may not help standardize the results obtained by different observers.

**Reference Values and Basic Interpretation**

Reference (predicted) values for Raw measurements in the body box have been described. In DuBois and colleagues’ original study, 21 healthy adult subjects had a mean Raw of 1.5 cm H\(_2\)O/liter/sec \( \pm 0.49 \) (1 standard deviation). The range was 0.6 to 2.4 cm H\(_2\)O/liter/sec. Viljanen and coworkers found a mean Raw in men of 1.37 \( \pm 0.53 \) and in women of 1.80 \( \pm 0.7 \) cm H\(_2\)O/liter/sec.

Reference values for sGaw in the body box have also been described. Pelzer and Thomson found that for 23 male nonsmokers the mean sGaw was 0.251 \( \pm 0.079 \), and for 24 female nonsmokers it was 0.224 \( \pm 0.075 \) liter/sec/cm H\(_2\)O/liter. Viljanen and coworkers found that the mean sGaw was 0.21 \( \pm 0.09 \) for men and 0.20 \( \pm 0.07 \) for women.

From these studies it seems reasonable to suggest that in adults, Raw values that exceed 2.5 cm H\(_2\)O/liter/sec would be greater than the normal range. Also, sGaw values that are lower than 0.12 liter/sec/cm H\(_2\)O/liter would fall below the normal range.

In children the airways are smaller and thus exhibit a higher Raw and lower sGaw. One study found the range for Raw to be 1.5 to 4.0 cm H\(_2\)O/liter/sec in boys and girls aged 4 to 19 years. Other studies have shown Raw values as high as 6 to 10 cm H\(_2\)O/liter/sec, depending on height.

Raw and sGaw typically fall in the normal range in individuals with mild airflow obstruction. Raw values increase as airflow obstruction worsens. However, because approximately 80% of Raw is created by the upper airway, trachea, and larger bronchi, individuals with airflow obstruction located mainly in the smaller airways may have Raw values near normal. Upper and large airway obstructions, such as tumors, can cause Raw values to be increased and sGaw values to be decreased.

Because Raw varies according to lung volume (Figure 4.1), it is important to know the lung volume at which the panting maneuvers were performed. Thus, sGaw, which corrects the Raw for lung volume, is a crucial measurement in interpreting Raw.
Calibrate the body box system every day it is used. Along with daily calibration, the use of (a) biological controls and (b) known resistances will help ensure quality.

For biological controls, choose two or three laboratory or department workers who are healthy nonsmokers. Gather Raw and sGaw data (e.g., five maneuvers that are averaged) on each individual and record the results using a computer or quality control notebook. Repeat this procedure at least monthly or biweekly, keeping a mean and standard deviation for both Raw and sGaw. If at the monthly test, or at any other time when the Raw and sGaw data are suspect, a biological control’s mean values for Raw and sGaw deviate from the past mean values by more than ±2 standard deviations, have the body box examined or serviced.

The second suggestion for quality control is to apply a known resistance to the body box system. Resistors can be made in the laboratory by using screens to create various amounts of resistance, or they can be purchased commercially. One product, the Hans Rudolph 7100 R5 (Figure 4.10), provides a resistance of 5 cm H2O/liter/sec (±20%) in a flow range of 0 to 2 liters/sec.

Figure 4.10
The Hans Rudolph 7100 R5 resistance device. It provides a known resistance of 5 cm H2O/liter/sec (± 20%) in the flow range of 0 to 2 liters/sec. It can be used for quality control applications of Raw in the body box.
Source: Printed with permission from: Hans Rudolph, Inc.
When a known resistance device is obtained, gather Raw values on a biological control (e.g., five maneuvers that are averaged). Next, place the known resistance device between the biological control’s mouth and the body box mouthpiece and repeat the Raw maneuvers. The difference between the average Raw values (i.e., before and after applying the known resistance) should approximate the known resistance.

**Self-Assessment Questions**

1. The measurement of resistance as applied to the respiratory system includes the resistance of all the following except:
   a. Chest wall
   b. Airway
   c. Diaphragm
   d. Lung tissue

2. The resistance to airflow depends on all the following except:
   a. Size of airways
   b. Breathing technique
   c. Number of airways
   d. Elastic recoil

3. The relationship between Raw and lung volume is:
   a. Linear
   b. Hyperbolic
   c. Constant
   d. Increased in emphysema

4. Airway conductance can be described as:
   a. The reciprocal of Raw
   b. The reciprocal of flow
   c. $1/\text{Raw}$
   d. The difference between Raw and TGV
   e. a and c

5. Specific conductance can be described as:
   a. Conductance divided by TGV
   b. The reciprocal of conductance
   c. The conductance divided by flow
   d. A sensitive measurement of volume

6. If the Raw is 3.7 cm H$_2$O/liter/sec, the flow is ± 1.5 liters/sec, and TGV is 3.5 liters, what is the specific conductance?
   a. 0.274
   b. 0.08
   c. 0.29
   d. 0.18
   e. 0.11
7. The S-shaped appearance of the flow and body box pressure relationship that appears as a person performs the panting maneuver can become distorted because:
   a. Of errors in the flow sensing device
   b. Patient pants too quickly
   c. Patient pants too slowly
   d. Of air leaks in the body box
   e. b, c, and d

8. The relationship of resistance to airflow is:
   a. Change in volume/change in flow
   b. Change in volume/change in pressure
   c. Change in pressure/change in volume
   d. Change in pressure/change in flow
   e. Change in flow/change in pressure

9. When Gaw is corrected for the volume at which it is measured, it is called:
   a. Raw
   b. Specific conductance
   c. Specific resistance
   d. Upstream resistance
   e. Absolute conductance

10. The reference range for Raw in adults is:
    a. Less than 0.25
    b. Less than 2.5
    c. More than 2.5
    d. Less than 0.12
    e. More than 1.25

References


Cardiopulmonary Exercise Test

Introduction

Dyspnea on exertion is one of the most common complaints in individuals with respiratory disease. The pulmonary function tests described in the previous chapters may be normal in some of these patients because clinical manifestations sometimes occur only when the heart and lungs are stressed (e.g., during exercise). Hence, the exercise test becomes a valuable tool in stressing the organs involved and determining what abnormalities exist.

There are a number of exercise tests that are performed in the pulmonary function laboratory, including: (a) the cardiopulmonary exercise test (CPET), (b) the 6-minute walk test, and (c) the exercise test for exercise-induced bronchoconstriction (EIB). This chapter will present the CPET. The 6-minute walk and EIB tests are presented in Chapters 6 and 7, respectively.

The CPET evaluates a patient’s exercise tolerance while exercising on a cycle ergometer or treadmill using incremental-work or constant-work protocols. Typically patients are monitored to assess the electrocardiograph (ECG), respiratory rate, blood pressure, oxygen saturation (pulse oximetry), and in some cases arterial blood gases. In addition, measurements of
exhaled gas concentrations and volumes are made, and in some cases exercise flow–volume curves are generated.

There are many indications for the CPET, including the following:

- Evaluation of exercise tolerance or limitation (e.g., determination of functional impairment and exercise-limiting factors)
- Evaluation of undiagnosed exercise intolerance (e.g., symptoms are disproportionate to cardiac and pulmonary function tests)
- Evaluation of patients with cardiovascular disease (e.g., heart failure, transplantation, and cardiac rehabilitation prescription and monitoring)
- Evaluation of patients with respiratory disease (e.g., pulmonary rehabilitation prescription and monitoring, O₂ prescription)
- Evaluation of patients prior to surgery (e.g., lung volume reduction surgery)

This chapter will discuss the physiologic responses to exercise, CPET protocols, instrumentation, techniques, calculations, and the basic elements of interpretation using case presentations.

**Terms and Normal Responses to Exercise**

To understand the responses of patients with respiratory disease, you must first understand the normal or healthy responses to exercise. However, a complete discussion of the normal responses with all the interactions of the many physiological and biochemical mechanisms involved would require an entire chapter, if not an entire book. Given the space constraints, only a brief and practical discussion will be presented.

The responses to exercise can be divided into several broad categories: (a) pulmonary or ventilatory response, (b) transfer of oxygen (O₂) into the pulmonary circulation, (c) cardiovascular response, and (d) supply of energy to meet the demands of the exercising muscles.

**Ventilatory Response**

The most basic pulmonary response to exercise is an increase in ventilation. In the laboratory, the amount of ventilation is usually determined by measuring the total volume of exhaled air in liters per minute, or minute ventilation (VE).

Ventilation increases with the amount of work and O₂ consumption (Figures 5.1 and 5.2). At low and moderate levels of exercise, ventilation increases linearly with both work and O₂ consumption up to the anaerobic threshold (AT), discussed later, after which ventilation rises more abruptly.

The maximum amount of VE (i.e., the ventilatory ceiling) that can be reached during exercise can be estimated by measuring the maximum voluntary ventilation (MVV). The MVV can be measured directly by having the patient breathe deeply in and out as fast as possible for 12 to 15 seconds (see Chapter 1). The total amount of air exhaled during the 12- to 15-second period is then extrapolated to liters/min. An alternative to the direct measurement is to estimate the MVV from the forced expiratory volume in 1 second (FEV₁) obtained during
Figure 5.1
In healthy individuals ventilation (\(V_E\)) increases with exercise workload in a linear manner up to the point when metabolism becomes anaerobic, after which ventilation increases more abruptly.

Figure 5.2
O\(_2\) consumption (\(\dot{V}_{O_2}\)) increases linearly with ventilation up to anaerobic metabolism, at which point ventilation increases faster than \(\dot{V}_{O_2}\).
forced spirometry. For the estimation of MVV, Jones recommends using $\text{MVV} = 35 \times \text{FEV}_1$; however, notable experts Weisman and Zeballos prefer $\text{MVV} = 40 \times \text{FEV}_1$.

In healthy individuals, exercise is not limited by ventilation because there is adequate breathing reserve. The breathing reserve is the difference between the maximum minute ventilation (i.e., $\dot{V}e$) achieved during exercise and the ventilatory ceiling (i.e., MVV). In healthy individuals the maximum $\dot{V}e$/MVV is approximately 0.60 to 0.70. In patients with respiratory disease (airflow obstruction and restriction), the breathing reserve (i.e., maximum $\dot{V}e$/MVV) is reduced to the extent that $\dot{V}e$ approaches, equals, or even exceeds MVV. In patients with cardiovascular disease, the breathing reserve is commonly increased at maximal exercise. In patients with pulmonary vascular disease, the breathing reserve is commonly normal.

The early increase in ventilation is accomplished primarily by an increase in tidal volume ($VT$ or $TV$) with a smaller increase in respiratory frequency ($f$). VT continues to increase up to approximately 50% to 70% of the vital capacity (VC), after which VT remains nearly constant and $f$ becomes the primary factor for increased ventilation (Figure 5.3).

**Figure 5.3**

Increases in ventilation due to exercise are accomplished by increases in tidal volume ($VT$) and respiratory frequency ($f$). In healthy individuals, the early increases in ventilation are primarily achieved by increases in VT. The VT increases up to approximately 60% of the patient’s VC and levels off, while $f$ increases up to 50 to 60 breaths/min. In patients with restrictive processes the relationship between $f$ and VT is shifted upward and to the left (dashed line). This is a result of their rapid shallow breathing pattern.
Newer indices have emerged to more thoroughly assess ventilatory response during exercise. One technique involves plotting the exercise tidal volume flow-volume curve within the maximal flow-volume curve (Figure 5.4). This provides an examination of the ventilatory demand versus ventilatory capacity. The correct use of this technique depends heavily on the accurate placement of the exercise tidal volume curve within the maximal flow-volume curve. The flow-volume maneuvers are commonly performed at rest (and possibly during unloaded pedaling of cycle ergometer) and at the end of exercise.

**Gas Exchange**

With each tidal breath, some of the inspired air reaches the alveoli and takes part in gas exchange, while the rest remains in the conducting airways and is called physiological dead.
164   CHAPTER 5  Cardiopulmonary Exercise Test

**Figure 5.5**

The relationship of physiologic dead space (Vd) to VT is commonly called the Vd/VT ratio. In healthy individuals this ratio is approximately 0.35 (or 35%) at rest and falls to between 0.05 and 0.25 (or 5% and 25%) during exercise.

---

space (Vd). The amount of Vd at rest in healthy individuals is usually less than 35% of the VT. At rest, the normal Vd to VT ratio is about 30% to 40%. During exercise, this Vd to VT ratio normally falls to between 5% and 25% (Figure 5.5) because of the increase in VT and reduction of blood flow.

As work increases, the exercising muscles demand more O₂ and eliminate more carbon dioxide (CO₂). The relationship between O₂ consumption (VO2) and work is linear (Figure 5.6). The point when VO₂ fails to rise with further work is called the maximal O₂ consumption (VO₂ max). The relationship between VO₂ and VE (which is also referred to as the ventilatory equivalent for O₂) is also linear up to the AT, after which ventilation increases faster than VO₂ because lactic acid is produced.

The relationship between CO₂ production (VCO₂) and work is linear up to approximately the AT, after which there is increased CO₂ production from buffering of lactic acid (Figure 5.7). This is also true of the relationship between VCO₂ and VE (which is also called the ventilatory equivalent for CO₂).

In healthy individuals, the arterial oxygen level (Pao₂) remains relatively constant even up to high work rates. The arterial carbon dioxide level (Paco₂) also remains relatively constant up to about 60% of VO₂ max. Near this work level the metabolic acidosis resulting from lactic acid production causes further increases in ventilation. This increase in ventilation is more than is needed to maintain a constant Paco₂. Thus, there is a progressive decrease in Paco₂. The alveolar-arterial oxygen gradient (Pao₂-PaO₂) remains relatively constant up to heavy exercise, where it can increase slightly (Figure 5.8).
**Figure 5.6**

O₂ consumption (\( \dot{V}O_2 \)) increases linearly with work up to maximal O₂ consumption (\( \dot{V}O_{2\text{max}} \)).

**Figure 5.7**

\( \dot{V}CO_2 \) production increases linearly with work up to approximately the point anaerobic metabolism begins, after which there is increased \( \dot{V}CO_2 \) production from buffering lactic acid.
Cardiovascular Response

To increase blood flow to the exercising muscles, the body’s main cardiovascular response is an increase in *cardiac output*. The cardiac output is the amount of blood pumped by the ventricles/min and is the product of stroke volume and heart rate. Initially, both the stroke volume and heart rate increase, but the relative increases depend on the nature of the exercise and the individual’s physical condition. At a heart rate of approximately 110 to 130 beats/min, further increases in cardiac output are achieved mostly by increases in heart rate. The relationship between $V\dot{O}_2$ and heart rate (sometimes called *O$_2$ pulse*) normally increases in a linear fashion with incremental exercise (*Figure. 5.9*).

The maximum heart rate is dependent on the age of the patient. A simple formula to approximate maximum heart rate is: Maximum heart rate = 220 – age.

Systemic blood pressure also increases during exercise in healthy individuals. The *systolic blood pressure* generally increases 80 to 150 mmHg above the resting level. The *diastolic blood pressure* rises very little and generally remains near resting levels (*Figure 5.10*).

Energy Delivery and Utilization

The onset of $O_2$ debt in the exercising muscle is often called the *anaerobic threshold* (AT), also known as the lactate acid threshold, gas exchange threshold, or ventilatory threshold. It is considered an estimate of the onset of metabolic acidosis caused mostly by the increased rise...
The relationship of heart rate (HR) to oxygen consumption ($\dot{V}O_2$) is linear with incremental exercise.

Figure 5.9

Systolic blood pressure increases 80 to 150 mmHg during exercise in healthy individuals. The diastolic blood pressure generally remains near resting levels.

Figure 5.10
CHAPTER 5  Cardiopulmonary Exercise Test

of arterial blood lactate during exercise. The clinical application of the AT is controversial, but it is nevertheless widely used to identify the work rate or \( \dot{O}_2 \) consumption threshold when lactate accumulates. This has been interpreted to mean that anaerobic metabolism has occurred. When assessing endurance, the AT is believed to indicate performance.\(^7\)

Two methods are generally used to determine the AT in the CPET. The invasive approach is to withdraw arterial blood and analyze it for lactate. The relationship between blood lactate and work (\( \dot{V}O_2 \)) can then be examined to determine the threshold when lactate levels sharply increase. When lactate levels cannot be measured, the use of arterial bicarbonate is an acceptable alternative.\(^1\)

The noninvasive approach includes examination of the change in \( \dot{V}CO_2 \) and \( \dot{V}E \) relative to \( \dot{V}O_2 \). One examination method is called the v-slope method. It uses computerized regression analysis of the slopes of \( \dot{V}CO_2 \) and \( \dot{V}O_2 \) in a graphic plot.\(^8\) Before the AT occurs, there is a linear relationship between \( \dot{V}CO_2 \) and \( \dot{V}O_2 \). At and after the AT, \( \dot{V}CO_2 \) increases faster than \( \dot{V}O_2 \) because of lactate production. Thus, the slope of \( \dot{V}CO_2 \) to \( \dot{V}O_2 \) becomes steeper. This point of deflection is thought to correspond to the AT. You can manually perform this v-slope technique simply by drawing a line along the linear portion of the \( \dot{V}O_2 \) versus \( \dot{V}CO_2 \) plot and eyeballing when the plot departs from the drawn line.\(^9\)

A second noninvasive approach for determining the AT is to use the ventilatory equivalents. The AT is defined as the \( \dot{V}O_2 \) at which \( \dot{V}E/\dot{V}O_2 \) and end-tidal \( O_2 \) reach a maximum and thereafter begin to rise consistently, coinciding with an unchanged \( \dot{V}E/\dot{V}CO_2 \) and end-tidal \( CO_2 \).\(^1\)

The respiratory exchange ratio (R or RER) is the ratio of \( \dot{V}CO_2 \) to \( \dot{V}O_2 \). The R rises slowly with exercise up to the AT, after which it rises more quickly.

**Work and Power**

The relationships among force, work, and power can sometimes be confusing, and they are summarized as follows:

- **Force** = Mass \( \times \) Acceleration
- **Work** = Force \( \times \) Distance
- **Power** = Work per unit of time

The unit of force is called a newton. The unit of work is called a joule or kilopond-meter (kpm). The units of power are joule/sec, kilopond-meter/min (kpm/min), or watt. The conversion between watts and kpm/min is 1 watt = 6.12 kpm/min.

The term **metabolic equivalent of task (MET)** is sometimes used and is a way to express the energy cost of physical activities. It is an index number rather than an energy unit. One MET is equal to 3.5 mL \( O_2 \)/min/kg of body weight. MET values range from less than 1 (sleeping) to 18 (extremely heavy exercise). Someone walking slowly, for example, with an MET of 2, would require two times the energy level that the same person would at rest.

**Patient Safety**

Patient safety must be considered during any exercise test. An examination by the attending physician, with a complete review of the patient’s history, should precede the ordering of any exercise test.
When the patient arrives in the laboratory, perform a pretest evaluation to identify any contraindications. The pretest evaluation should include a preexercise questionnaire, and, in most hospitals, a signed consent form describing the risks and possible discomforts. Additionally, laboratory staff should carefully explain the procedure to the patient.

The pretest evaluation should also include a 12-lead ECG, resting blood pressure, and in some cases a resting arterial blood gas sample to verify oxygenation status. A doctor should review the questionnaire and the results of these tests to determine if any contraindications to exercise are present (Table 5.1).

A physician trained and certified in advanced cardiovascular life support who is knowledgeable about the physiologic changes that occur during exercise should be present or nearby regardless of the patient’s age.

The technologists should be trained in a field related to cardiopulmonary exercise testing (e.g., exercise physiology, respiratory therapy, or pulmonary function testing). The technologists must have basic knowledge of exercise responses and be certified in basic cardiac life support.

The testing room should be large enough to accommodate the exercise and emergency equipment and allow adequate access to the patient in emergency situations. The testing room should be well lit and maintained at a comfortable temperature and humidity. Emergency equipment, including defibrillator, O₂, and drugs should be readily available.

### Table 5.1

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction in past 3–5 days</td>
<td>Left main coronary stenosis or its equivalent</td>
</tr>
<tr>
<td>Uncontrolled angina, arrhythmias, heart failure, or asthma</td>
<td>Moderate stenotic valvular disease</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Untreated hypertension (resting blood pressure &gt; 200 mmHg systolic, &gt; 120 mmHg diastolic)</td>
</tr>
<tr>
<td>Syncope</td>
<td>High-degree AV block</td>
</tr>
<tr>
<td>Active endocarditis, myocarditis, or pericarditis</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Symptomatic severe aortic stenosis</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Acute pulmonary embolus or pulmonary infarction</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>O₂ saturation ≤ 85% on room air (exercise with supplemental O₂)</td>
<td>Orthopedic impairment</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Mental impairment or other noncardiopulmonary disorder that may affect exercise performance</td>
</tr>
</tbody>
</table>

*Source: Adapted from the American Thoracic Society/American College of Chest Physicians.*
During the exercise period, blood pressure and breath sounds should be assessed periodically, \( O_2 \) saturation should be monitored by oximetry, and the ECG should be examined continuously to determine if any indications to terminate exercise are present (Table 5.2).

### Instrumentation

There are a number of devices and instruments used during the CPET including: (a) treadmill, (b) cycle ergometer, (c) ECG, (d) pulse oximeter, (e) gas analyzers, (f) breathing valves, and (g) flow-measuring devices.

### Treadmill and Cycle Ergometer

A motor-driven treadmill and cycle ergometer are commonly used to exercise the patient in the CPET. A motor-driven treadmill allows walking or running (natural activities familiar to both old and young patients). Treadmills have been shown to produce a slightly higher \( \dot{V}O_2 \max \) compared to cycle ergometers. The drawbacks of using a treadmill include a greater risk of injury should the patient fall, difficulty in obtaining blood samples and blood pressure measurements, ECG noise, and inability to measure power accurately.

A cycle ergometer is, in my opinion, a more practical device. It is smaller and somewhat quieter, it allows for easier blood pressure measurements and arterial blood sampling, and it is less likely that the patient will fall. Additionally, power can be measured directly. However, a cycle ergometer produces a slightly lower \( \dot{V}O_2 \max \), it is not a natural form of exercise, and it is more difficult to calibrate than a treadmill.

Cycle ergometers can be braked either mechanically or electronically. The mechanical-braked cycles regulate work by adjustable frictional devices, but pedaling rate changes can...
alter the power (i.e., amount of work). Electronically braked cycles provide a much more accurate measurement of power because of their automatic adjustment of resistance. This means that if a patient reduces the pedaling rate from 60 to 50 rpm, the electronically braked cycle increases the resistance to pedaling so the power remains constant.

**ECG and Blood Pressure**

A suitable ECG system that meets the current American Heart Association specifications is essential. The system should have continuous monitoring capabilities and a minimum of three leads, with the ability to print a 12-lead ECG. The Mason-Likar adaption of the 12-lead ECG is commonly used, with the limb leads placed on the torso to reduce motion artifact. The minimization of motion artifact is important, and strong attention should be given to skin preparation and the use of appropriate electrodes (e.g., silver-silver chloride with sweat-resistant adhesive). Other suggestions for reducing motion artifact noise include lightweight shielded cables and flexible knit tube shirts.

A manual blood pressure measuring device (sphygmomanometer) is necessary and should be available even if the laboratory uses an automatic blood pressure measuring device (automatic devices are more expensive and may perform erratically at high exercise levels). If an automated device is used, periodically check the readings against those made by auscultation. A variety of blood pressure cuff sizes should be available (e.g., pediatric, adult, and large adult) because inappropriate cuff sizes can alter blood pressure readings. Appropriate cleaning of the cuffs between patients is recommended.

It may be possible to include intra-arterial blood pressure if an arterial catheter has been inserted. The pressures obtained from this method are slightly higher than those made by auscultation. Careful attention must be given to the zeroing of the pressure transducer and should be done at the left atrium level.

**Pulse Oximeter**

A pulse oximeter should be used as a monitor and trending, but it is not reliable for determining the absolute magnitude of change. In general, pulse oximeters have reasonable accuracy compared to directly measured arterial \( O_2 \) saturation, provided there is a good pulse signal. However, accuracy declines as the \( O_2 \) saturation falls below 88%. In addition, dark skin color can interfere with signal detection, and most oximeters cannot detect carboxyhemoglobin. See Chapter 11 for a more detailed description of pulse oximeters.

**Gas Analyzers**

For the CPET, different types of instruments are available for analyzing \( O_2 \) and \( CO_2 \). The mass spectrometer is considered the gold standard. It uses small amounts of gas, is linear and stable, and can measure all the necessary gases used in the laboratory. The basic principle of operation is the separation of gases based on the mass-to-charge ratio. However, because mass spectrometers are so expensive, commercial CPET systems use discrete \( O_2 \) and \( CO_2 \) analyzers.
Paramagnetic, polargraphic, or electrochemical fuel cell principles can also be used to analyze O₂. Most commercial CPET systems use an electrochemical fuel cell (e.g., zirconium oxide) because it is reliable, accurate, and relatively inexpensive. Electrochemical fuel cell analyzers measure the difference in electrical potential across a semipermeable membrane produced by the presence of O₂. Because of the high temperatures of operation, the life of the sensor can be shortened by operation, and the fuel cells need to be replaced periodically.

For CO₂ analysis, an infrared analyzer is used in most CPET systems. The principle of operation is based on the fact that CO₂ absorbs infrared radiation. The instrument has a source of infrared radiation, a reference cell, and a detector. As in the CO infrared analyzer (see Chapter 3), linearization is necessary, and water vapor must be removed.

**Breathing Valves**

Two-way breathing valves are often used to separate inspired gas from expired gas. The valve shown in Figure 5.11 is a commonly used type, and the figure shows it connected to a mask. These valves must have low resistance and dead space, and they must be easy to clean. Some manufacturers of CPET systems have eliminated the valve and use a flow-sensing device, such as a pneumotachograph, at the patient's mouth. The advantage of eliminating the valve is that resistance and system dead space are reduced. However, to test patients who require increased inspired O₂ concentrations when they exercise, a two-way valve to separate the inspired gas and expired gas is required.

**Figure 5.11**

A commonly used two-way breathing valve used in exercise testing systems.

*Source:* Printed with permission from: Hans Rudolph, Inc.
Measurement of Minute Ventilation and Gas Exchange

CPET systems incorporate various types of flow-measuring devices to determine minute ventilation (volume), including pneumotachographs, mass flow sensors, Pitot-type sensors, and turbines. If the flow-measuring device is situated near the patient’s mouth, then ideally it should be lightweight, have low dead space and resistance, and not be affected by moisture or saliva that may accumulate during testing. Whichever device is used, accurate calibration before every test is critical.

The advances of computer hardware and software have greatly reduced the total time required for analysis, calculations, and technologist time. However, the new computerized systems have not always compared favorably to the old manual systems, and results from different computerized systems sometimes agree and sometimes do not agree with one another. Some of the differences between systems are probably caused by various time intervals used to sample data. The variability increases as the sampling interval decreases. Sampling intervals of 30 and 60 seconds on the automated systems compare best with nonautomated systems. The measurement of $V\dot{E}$, $V\dot{O}_2$, and $V\dot{CO}_2$ can be accomplished using two approaches or methods: (a) breath by breath and (b) mixing chamber.

Breath by Breath

The breath-by-breath method measures data continuously during each breath. The flow, $O_2$, and $CO_2$ signals are integrated to obtain $V\dot{O}_2$ and $V\dot{CO}_2$ for each breath. The gas analyzers must be rapid, and the response times of both the analyzers and the flow measuring device must be synchronized. Basically, each breath is broken down into a large number of parts, and the $V\dot{O}_2$ and $V\dot{CO}_2$ are calculated for each part. These measurements are then summed for the entire expiration, which is then extrapolated to the minute. The large amount of breath-by-breath data can be handled in a variety of ways. For example, the CPET system can be programmed to provide a running average of a certain number of breaths (e.g., five breaths), or it can be programmed to average the data during a time window or interval (e.g., 15, 30, or 60 seconds). As of 2010, the recommendation is to use 30- to 60-second intervals for averaging data.

Mixing Chamber

The mixing chamber method uses a small chamber (commonly 2 to 5 liters) on the exhaled side of the breathing valve. As the exhaled gas enters the chamber, it is mixed by a series of baffles or struts. The mixing of the exhaled gas causes it to become homogeneous by the time it exits at the outlet of the chamber, where it is sampled and analyzed continuously by the $O_2$ and $CO_2$ analyzers. This method does not require the high-speed $O_2$ analyzers and the adjustment for time delays used in the breath-by-breath method. The main disadvantage of the mixing chamber method results from the limitations of the commercially available systems (i.e., the inability to sample and analyze both end-tidal air and the air in the mixing chamber simultaneously).

Testing Methodology

The testing methodology section includes discussion of the different exercise protocols, patient preparation, and arterial blood sampling.
Protocols

Many different exercise protocols can be used to evaluate a patient’s exercise tolerance. For simplicity, two main types will be presented: (a) the maximal symptom-limited incremental protocol and (b) the constant-work steady-state protocol.

Maximal Symptom-Limited Incremental Cycle Ergometer Protocol

The maximal symptom-limited incremental protocol using a cycle ergometer is widely used and is the most common protocol. Typically it starts with a 3-minute resting baseline period with the patient sitting on the cycle ergometer. This is followed by a 3-minute baseline with no work (i.e., zero watts, unloaded pedaling on the cycle ergometer). Then work is increased incrementally each minute in 5- to 25-watt increments, so that the patient reaches a maximum exertion level (exhaustion) in 8 to 12 minutes.

The increment size is determined after considering the physical examination, amount and intensity of the patient’s daily activities, and pulmonary function parameters. Wasserman (a recognized expert) and colleagues note that it is better to overestimate than underestimate the work increments.

Most commercial automated (computer-controlled) exercise systems that use an electronically braked cycle ergometer can increase the work in either a steplike method or a ramp method. When a new workload is applied in a steplike method, the whole increment is immediately applied. When a new workload is applied in the ramp method, the increment is applied continuously in small amounts, usually every second until the entire increment has been applied. There is no significant difference in the results obtained using the two methods.

Maximal Symptom-Limited Incremental Treadmill Protocol

A treadmill is commonly used to administer the symptom-limited incremental protocol. The lowest treadmill speed with no grade can be used for the exercise baseline. Work can be increased incrementally at regular intervals by increasing the speed and/or grade. There are a number of approaches to increasing the work, including the Bruce and Naughton protocols, but these approaches have some drawbacks (i.e., long increment duration). Another approach that might be more appropriate is the modified Balke protocol, in which the treadmill speed is fixed (e.g., 2.5 mph) and the grade is increased by a constant amount each minute.

Constant-Work Steady-State Protocol

The constant work rate protocol (sometimes called the steady-state exercise protocol) is based on the fact that an individual can exercise at a fixed submaximal workload for a long time without exhaustion. The submaximal workload permits the physiologic responses to become adapted to the exercise level and remain constant from minute to minute. Generally, it takes about 3 minutes for this equilibration (i.e., steady state) to occur, and measurements are taken between the fourth and sixth minutes.

This protocol has gained considerable popularity in the monitoring of responses to therapeutic interventions (e.g., medications, lung-volume reduction surgery, and pulmonary...
rehabilitation). A common approach is to first perform a maximal symptom-limited incremental protocol to determine the maximum work rate, then after approximately an hour of rest, the patient performs the constant work rate protocol at a work rate of approximately 50% to 75% of the maximal workload. The same workload can be used in future constant work rate protocol tests for that patient to compare the responses over time.

Protocol Comparison
Both protocols are useful. The incremental exercise protocol, which requires the patient to work harder and harder until exhaustion, is used to determine whether a patient has a normal exercise capacity. If not, the data can help identify possible reasons for the limitations. The measurement of $\dot{V}O_2\text{max}$ is the key measurement when determining exercise capacity. A reduced $\dot{V}O_2\text{max}$, at exhaustion, when compared to healthy individuals, reflects $O_2$ transport problems or muscle utilization problems.

The constant work rate protocol allows for precise measurements at a given $O_2$ consumption level. However, the real value of this protocol is that a patient can be exercised at various points in time (e.g., every 6 months, or before and after a therapeutic intervention) at the same workload. Then the many parameters (e.g., $\dot{V}O_2$, $Vd/VT$, $PaO_2$) can be compared and changes can be evaluated.

Patient Preparation
A brief medical history should be taken (e.g., current therapy, smoking history, chest pain, hypertension). In almost all cases, it is not necessary to withhold medications. In fact, you should ensure that a patient has taken all prescribed medications. Because ECG electrodes must be applied and arterial blood sampling may be necessary, the patient should dress appropriately and wear shoes appropriate for pedaling or walking. On the day of the test, the patient should avoid exercise and have a light breakfast or lunch no less than 2 hours before the test.

Arterial Blood Sampling
In many laboratories, arterial blood gas samples are obtained at rest and during exercise. The number of blood samples obtained varies among laboratories, but a recommended strategy is to sample at rest, end of unloaded pedaling, every other minute during the incremental exercise period, and after 2 minutes of recovery. The method of trying to obtain a blood sample from a single arterial puncture at peak exercise or immediately after exercise can be problematic. The best method to obtain numerous samples, especially during exercise, is to use an arterial catheter.

Data from several studies have shown that the frequency of major complications from arterial catheter insertion is small, and infections related to arterial catheters and the incidence of radial artery occlusions are low. Thousands of arterial catheters have been inserted by well-trained respiratory care and pulmonary function laboratory personnel with extremely low rates of major complications, infection, or thrombosis.
CHAPTER 5 Cardiopulmonary Exercise Test

The radial artery is the preferred site for catheter insertion because it is accessible and adequate collateral circulation is usually present and easily checked. Use the brachial artery only if the radial sites are unavailable or attempts have been unsuccessful.

The two methods of inserting a catheter into an artery are: (a) transfixing the artery (deliberately puncturing the posterior wall of the artery) and (b) direct threading (not puncturing the posterior wall). There is no significant difference in the incidence of thrombosis or serious complications between the two methods, and the choice of method is arbitrary.

Two methods are used to keep the arterial catheter open and free of clots. The first is the continuous-flow technique using a pressure bag, transfer pack with heparinized solution, intravenous tubing, intraflow device, stopcocks, and tubing. A pressure transducer can also be incorporated to measure arterial blood pressure. The second method is the noncontinuous technique, which requires the injection of a small amount of heparinized saline into the catheter and tubing after each blood sample has been withdrawn.

Always flush or prime the catheter and attached tubing before obtaining the actual blood sample to ensure that there is no heparin solution contamination. Typically, this means withdrawing 1 to 3 mL of the blood–heparin solution mixture before obtaining the blood sample.

Measurements and Calculations

Rest Measurements

The measurement of resting physiologic parameters is relatively simple compared to the measurements during exercise. However, some important points need to be emphasized.

The patient must be in a steady state or equilibrium, and it takes a few minutes for the patient to get familiar with wearing a nose clip, breathing on a mouthpiece and valve, having an arterial catheter, and hearing technicians and doctors moving around. After equilibration is reached, collect the physiologic data. Allowing 2 or 3 minutes to collect resting data after the patient is accustomed to the system usually provides a good baseline assessment. Review the resting data to ensure repeatability and reasonability. Also examine the ECG and blood pressure data at rest to ensure they do not contraindicate exercise. Examine the blood gas data, if available, for reasonability and for hypoxemia. Laboratories commonly test patients who have a resting oxyhemoglobin saturation of less than 90%. In these cases, rest and exercise tests may be desired on both room air and supplemental O2.

For tests on increased levels of O2, remember that the fractional concentration of inspired O2 (FiO2) must remain constant. A simple and inexpensive approach is to fill a large reservoir bag (e.g., 120-liter meteorologic balloon) with the desired gas mixture and attach it to the inspired side of the one-way valve. Compressed gas cylinders with various O2 concentrations can be kept on hand, or a blender can be employed to keep the reservoir bag filled with a constant FiO2.

Exercise Measurements

After satisfactory resting data have been obtained, the patient can remain on the mouthpiece and go directly into the exercise protocol. However, another approach that may work better is
measurements and calculations

177
to allow the patient to come off the mouthpiece for a short time to cough or swallow. Give or repeat the exercise instructions at this time.

As mentioned earlier, there are two major exercise protocol strategies: (a) a constant work rate exercise protocol and (b) a symptom-limited incremental protocol. In a constant work rate protocol, one workload is used for a specific time (e.g., 6 minutes). However, if maximum O₂ consumption is desired, the symptom-limited incremental protocol must be used, in which the workload is initially low and is increased at intervals until the patient is exhausted.

The symptom-limited incremental exercise protocol using the cycle ergometer is the most widely used in clinical practice. It starts with a baseline of unloaded pedaling (i.e., 0 watts) for 3 minutes, after which work is increased in 5 to 25 watt increments every minute until the patient reaches exhaustion or the test is terminated by the medical monitor.

The symptom-limited incremental exercise protocol using the treadmill is similar to that of the cycle ergometer. The baseline is usually the lowest speed on the treadmill with no grade. Work is increased using combinations of speed and grade.

Calculations

Although most laboratories are equipped with computers that calculate all or some of the reported parameters, the student and practitioner can better understand how these data are analyzed by studying more commonly used formulas and related information.

\( V̇_E \) is the volume of air a patient exhales in 1 minute, expressed in liters/min, at body temperature and pressure saturated with water vapor (BTPS). The VT is also reported in BTPS and is calculated as follows:

\[
VT \text{ (liters at BTPS)} = \frac{V̇_E \text{ in liters/min at BTPS}}{\text{Respiratory frequency in breaths/min}} \quad (\text{Eq. 5.1})
\]

\( V̇_O₂ \) is the amount of O₂ the body consumes each minute. It is calculated from the \( V̇_E \) at standard temperature and pressure dry (STPD) and the difference between the inspired and expired O₂ concentrations. The calculation of \( V̇_O₂ \) is complicated by a correction for nitrogen (N₂) and water vapor. In its simplest form it can be calculated as follows:

\[
V̇_O₂ \text{ (liters/min @ STPD)} = (F_{O₂} \times V̇_{STPD} - (F_{O₂} \times V̇_{STPD})) \quad (\text{Eq. 5.2})
\]

where:

\( F_{O₂} \) = Fractional concentration of dry O₂ inspired

\( F_{O₂} \) = Fractional concentration of dry oxygen exhaled

\( V̇_{STPD} \) = Volume of inspired air/min at STPD

\( V̇_{STPD} \) = Volume of exhaled air/min at STPD

The conversion of volumes from ambient conditions (ATPS) to standard conditions (STPD) is described in Appendix B.
\( \dot{V}_{\text{CO}_2} \) is the amount of CO\(_2\) produced by the body each minute. It is calculated from the \( \dot{V}_E \) at STPD and the difference between the inspired and expired CO\(_2\) concentrations. The formula for calculating it is as follows:

\[
\dot{V}_{\text{CO}_2} \quad \text{(liters/min @ STPD)} = \dot{V}_{E_{\text{STPD}}} \times (F_{\text{CO}_2} - F_{\text{ICO}_2})
\]

(Eq. 5.3)

where:

- \( \dot{V}_{E_{\text{STPD}}} \) = Volume of exhaled air/min at STPD
- \( F_{\text{CO}_2} \) = Fractional concentration of dry exhaled CO\(_2\)
- \( F_{\text{ICO}_2} \) = Fractional concentration of dry inhaled CO\(_2\) (usually 0.04%)

The respiratory exchange ratio (R) measures the relationship of CO\(_2\) production to O\(_2\) consumption and is calculated as follows:

\[
R = \frac{\dot{V}_{\text{CO}_2}}{\dot{V}_{\text{O}_2}}
\]

(Eq. 5.4)

O\(_2\) pulse (\( \dot{V}_{\text{O}_2}/\text{HR} \)) determines the amount of O\(_2\) consumption per heart beat and is calculated as follows:

\[
\dot{V}_{\text{O}_2}/\text{HR} = \frac{\dot{V}_{\text{O}_2} \times 1000}{\text{HR}}
\]

(Eq. 5.5)

where:

- \( \dot{V}_{\text{O}_2} \) = O\(_2\) consumption in liters/min
- HR = Heart rate in beats/min
- 1000 = Conversion from liters to milliliters

The ventilatory equivalent for oxygen (\( \dot{V}_E/\dot{V}_{\text{O}_2} \)) measures the ventilation requirement for a given O\(_2\) consumption. Likewise, the ventilatory equivalent for carbon dioxide (\( \dot{V}_E/\dot{V}_{\text{CO}_2} \)) measures the ventilation requirement for a given amount of CO\(_2\) production. These two measurements are calculated as follows:

\[
\dot{V}_E/\dot{V}_{\text{O}_2} = \frac{\dot{V}_E - (f \times VDM)}{\dot{V}_{\text{O}_2}} \quad \text{and}
\]

(Eq. 5.6)

\[
\dot{V}_E/\dot{V}_{\text{CO}_2} = \frac{\dot{V}_E - (f \times VDM)}{\dot{V}_{\text{CO}_2}}
\]

(Eq. 5.7)

where:

- \( \dot{V}_E/\dot{V}_{\text{O}_2} \) = O\(_2\) ventilatory equivalent
- \( \dot{V}_E/\dot{V}_{\text{CO}_2} \) = CO\(_2\) ventilatory equivalent
Measurements and Calculations

\[ V_E = \text{Volume of exhaled air at BTPS in liters/min} \]
\[ f = \text{Respiratory frequency/min} \]
\[ VDM = \text{Valve dead space/breath in liters} \]
\[ V_{O_2} = \text{O}_2 \text{ consumption at STPD in liters/min} \]
\[ V_{CO_2} = \text{CO}_2 \text{ production at STPD in liters/min} \]

The physiologic dead space (VD) is the portion of each tidal breath that does not take part in gas exchange. It includes the volume of the anatomic dead space and those respiratory units that are ventilated but not perfused. The calculation of VD is as follows:

\[
VD = VT \times \frac{P_{ACO_2} - P_{EFCO_2}}{P_{ACO_2}} - VDM \quad \text{(Eq. 5.8)}
\]

where:
\[
VD = \text{Physiologic dead space in liters} \\
VT = \text{Tidal volume in liters at BTPS} \\
P_{ACO_2} = \text{Arterial CO}_2 \text{ tension in mmHg} \\
P_{EFCO_2} = \text{Mixed expired CO}_2 \text{ concentration in mmHg} \\
VDM = \text{Valve dead space}
\]

The ratio of VD/VT is calculated as follows:

\[
VD/VT = \frac{VD}{VT} \quad \text{(Eq. 5.9)}
\]

where:
\[
VD = \text{Physiologic dead space in liters} \\
VT = \text{Tidal volume in liters}
\]

The use of these complex equations is best illustrated by the following example of a healthy man. The room air exercise test was conducted on a cycle ergometer with a constant workload of 120 watts for 6 minutes. The following information is given:

- Minute ventilation (V̇E) at BTPS = 75 liters/min
- Minute ventilation (V̇E) at STPD = 54 liters/min
- Respiratory frequency (f) = 35 breaths/min
- Assume V̇I = V̇E (i.e., inspired volume = expired volume)
- Inspired O₂ concentration (ḞO₂) = 0.2093
- Expired O₂ concentration (ḞE O₂) = 0.1650
- Inspired CO₂ concentration (ḞCO₂) = 0.0004
- Expired CO₂ concentration (ḞE CO₂) = 0.0450
- Heart rate (HR) = 150 beats/min
- Valve dead space (VDM) = 0.040 liters
- Arterial blood CO₂ tension (ṖACO₂) = 35 mmHg
- Mixed expired CO₂ tension (ṖEFCO₂) = 29 mmHg
CHAPTER 5 Cardiopulmonary Exercise Test

Calculate the following parameters: VT, VO₂, VCO₂, R, O₂ pulse, ventilatory equivalent for O₂ and CO₂, V̄D, and V̄D/VT.

1. Using Eq. 5.1:
   \[ \text{VT} = \frac{\text{VE}}{f} = \frac{75 \text{ liters/min}}{35} = 2.14 \text{ liters} \]

2. Using Eq. 5.2:
   \[ \dot{V}_O = (F_iO_2 \times \dot{V}_{STPD}) - (F_eO_2 \times \dot{V}_{E} \times STPD) \]
   \[ \dot{V}_O = 0.2093 \times (54) - 0.1650 \times (54) \]
   \[ \dot{V}_O = 11.30 - 8.91 = 2.39 \text{ liters/min} \]

3. Using Eq. 5.3:
   \[ \dot{V}_C = \dot{V}_{E} \times \frac{F_{CO_2} - F_{ICO_2}}{P_{CO_2} - P_{ICO_2}} \]
   \[ \dot{V}_C = 54 \times \frac{0.0450 - 0.0004}{24 - 3} \]
   \[ \dot{V}_C = 2.41 \text{ liters/min} \]

4. Using Eq. 5.4:
   \[ R = \frac{\dot{V}_C}{\dot{V}_O} = \frac{2.41}{2.39} = 1.01 \]

5. Using Eq. 5.5:
   \[ \text{O}_2 \text{ pulse} = \frac{\dot{V}_O \times 1000}{HR} = \frac{2.39 \times 1000}{150} = 15.93 \]

6. Using Eq. 5.6 the O₂ ventilatory equivalent is:
   \[ \frac{\dot{V}_E}{\dot{V}_O} = \frac{\dot{V}_E - (f \times V̄D)}{\dot{V}_O} = \frac{75 - (35 \times 0.040)}{2.39} = 30.8 \]

7. Using Eq. 5.7 the CO₂ ventilatory equivalent is:
   \[ \frac{\dot{V}_E}{\dot{V}_C} = \frac{\dot{V}_E - (f \times V̄D)}{\dot{V}_C} = \frac{75 - (35 \times 0.040)}{2.41} = 30.5 \]
8. Using Eq. 5.8:

\[
V_D = VT \times \frac{P_{CO_2} - P_{E,CO_2}}{P_{CO_2}} - V_{DM}
\]

\[
V_D = 2.14 \times \frac{35 - 29}{35} = 0.040 = 0.327 \text{ liters}
\]

9. Using Eq. 5.9:

\[
\frac{V_D}{VT} = \frac{0.327}{2.14} = 0.153
\]

Quantifying Symptoms

Most patients report breathlessness as a major symptom during the CPET. The Visual Analog Scale (VAS), Borg scale, or modified Borg scale are commonly used to quantify these symptoms.

The VAS is a vertical or horizontal line, usually 100 mm in length, with descriptors at each end of the line (e.g., minimum or none at one end and maximal at the other end). It is displayed on a poster or piece of paper in front of the patient, and the patient indicates the level of breathlessness on the line.

The Borg or modified Borg scales have also been used to quantify symptoms. The Borg scale usually consists of a vertical line labeled 0 to 10, with verbal descriptors at fixed points on the scale (e.g., nothing at all; very, very slight; slight; moderate; severe; very severe; and maximal). A good correlation between the VAS and Borg scales has been reported.21

An example of the 10-point Borg scale is as follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing at all</td>
</tr>
<tr>
<td>0.5</td>
<td>Very, very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight (light)</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe (heavy)</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very severe</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Very, very severe (maximal)</td>
</tr>
</tbody>
</table>

Quality Control

The CPET system should be calibrated before testing every patient. Validation of the flow measuring device can be performed using a 3-liter calibration syringe. A range of flows should
be used to assure linearity. Gas analyzers should have a two-point verification with precisionanalyzed gas mixtures.

Mechanical simulators are available but have not been well validated and do not always simulate the variations typically seen during the actual testing of a patient.

The use of biological controls to assess the CPET system is an important consideration. The instrumentation is complex and consists of many components, and therefore assessment of the integrated unit is the best approach. Revill and Morgan\textsuperscript{22} have described a method in which five tests are performed over 8 days to establish an average baseline for each biological control. Keeping variables such as time of day and diet as constant as possible, additional tests were conducted periodically (e.g., weekly) and compared to the baseline average. Variations in $V\dot{E}$, $V\dot{O}_2$ and $V\dot{CO}_2$ can be graphed to display the change in each of the key variables. Values outside the 95% confidence interval for a specific biological control should prompt a complete check of the system.

Reference or Normal Values

To interpret CPET data properly, the reference or normal values used are very important. Although several normal studies have been compiled, the most commonly used reference values for maximal exercise testing as of 2010 are Jones and coworkers\textsuperscript{23} and Hansen and coworkers.\textsuperscript{24} Another commonly used reference study was published by Blackie and coworkers.\textsuperscript{25}

When selecting reference values for your laboratory, try to obtain a copy of the original article. After examining the study’s methods and patient population, test a tentative selection by performing exercise tests on 5 to 10 healthy men and 5 to 10 healthy women who are similar in age and other characteristics to your patient population. Compare their data with the study data to see if your selection is appropriate (that is, the healthy test subjects are classified as normal).

Case Presentations

The basic elements of interpretation are presented through a series of cases. Each case briefly describes the patient and the exercise protocol. Each case also displays a table of rest and exercise data and two panels of four graphs each. The data in the tables are limited, and more graphs could be presented, but I have elected to keep things simple.

It is a difficult task to interpret the large amount of data obtained from the CPET. In comparing the observed data with reference values, it is also difficult to decide what is normal. Weisman and Zeballos\textsuperscript{3} have provided a nice set of recommendations for assessing the responses to exercise in adults. They are as follows:

\[
\begin{align*}
V\dot{O}_2\text{max} & > 84\% \text{ predicted} \\
AT & > 40\% \text{ of predicted } V\dot{O}_2\text{max}
\end{align*}
\]
Case Presentations

Case 5.1

Background
A healthy 21-year-old college student and cross-country runner was tested in the pulmonary function laboratory. He complained of recent viral upper respiratory infections that were causing a “lung problem” and affecting his running. His coach was concerned about his recent level of dyspnea and performance. His pulmonary function tests were normal with no improvement after administration of a bronchodilator. A maximal symptom-limited exercise test was ordered to determine whether a disease was causing his dyspnea and poor performance.

An arterial catheter was placed in the radial artery to obtain blood gas samples. A 12-lead ECG, blood pressure, V˙E, and expired gas concentrations were obtained. The resting parameters were obtained after the patient had breathed quietly on the mouthpiece for approximately 5 minutes. The exercise was performed on a cycle ergometer starting at 50 watts, with 50-watt increments/min until exhaustion. The results of the rest and exercise test are shown in Table 5.3 and Figures 5.12 and 5.13.

Interpretation

The interpretation of exercise results is best approached by comparing the patient’s rest and exercise response with a predicted response; however, regard the predicted value as an estimate or approximation.

The resting data for this patient show no abnormalities. The exercise response is broken into two sets of graph panels. The ventilatory response is displayed in Figure 5.12. The ventilatory response as measured by comparing V˙E to O2 consumption (Figure 5.12A) is linear until about 90% of the maximum V˙O2 and then it approaches the ventilatory ceiling. The relationship of V˙O2 to work rate is linear (i.e., increase in work causes corresponding increase in V˙O2), and Figure 5.12B shows a normal response by this patient. The increase in ventilation was obtained by increasing the f and VT until the higher workloads, when only increases in f were observed (Figure 5.12C). The Vd/VT ratio was 30% at rest and fell to 26% at maximal exercise. As Figure 5.12D shows, a normal response is a fall in the Vd/VT ratio.

The second panel of graphs (Figure 5.13) shows the cardiovascular and gas exchange responses. The blood pressure response (Figure 5.13A) is normal, with an increase in the systolic pressure and no change in the diastolic pressure. However, the systolic blood pressure...
### Table 5.3
Ventilatory, Cardiovascular, and Gas Exchange Measurements from the Final Minutes of Rest and Maximal Exercise in Case 5.1

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Max exercise*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload (watts on cycle)</td>
<td>0</td>
<td>350 (95)</td>
</tr>
<tr>
<td>( \dot{V}E ) (liters/min)</td>
<td>13.8</td>
<td>170.8 (134)</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) (liters/min)</td>
<td>0.300</td>
<td>4.20 (95)</td>
</tr>
<tr>
<td>( \dot{V}CO_2 ) (liters/min)</td>
<td>0.250</td>
<td>4.31</td>
</tr>
<tr>
<td>( R )</td>
<td>0.83</td>
<td>1.03</td>
</tr>
<tr>
<td>( f ) (breaths/min)</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>VT (L)</td>
<td>0.986</td>
<td>4.270</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>0.291</td>
<td>1.110</td>
</tr>
<tr>
<td>Vd/VT (%)</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>pH</td>
<td>7.43</td>
<td>7.31</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>75(^\dagger)</td>
<td>74(^\dagger)</td>
</tr>
<tr>
<td>HbO2 (%)</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>PaO2-PaO2 (mmHg)</td>
<td>5.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68</td>
<td>193 (98)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>118</td>
<td>161</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79</td>
<td>81</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent of predicted maximum

At 5,000 feet, normal PaO2 range is approximately 65 to 75 mmHg. The PaO2 was normal at rest (altitude 5,000 feet) and remained unchanged during exercise (Figure 5.13C). The PaO2-PaO2 gradient in Table 5.3 was 5.7 at rest and increased to 17.7 at maximal exercise, a likely normal response.

The AT, the point representing the failure of the acid-base buffering system to prevent metabolic acidosis, can be estimated in several ways. One method is to determine the inflection in the \( \dot{V}O_2 \) versus \( \dot{V}CO_2 \) graph (Figure 5.13D) that corresponds to the increase in ventilation.
seen in Figure 5.12A. It occurs in this patient at approximately 70% of maximum, which is appropriate for a fit runner.

There were no abnormalities in the ECG, and the overall impression is of a normal exercise response with the possible exception of the systolic blood pressure. However, the fact that only 95% of the maximum predicted workload was achieved before the patient quit exercising is suspect in a well-trained athlete.
CHAPTER 5  Cardiopulmonary Exercise Test

Case 5.2

Background

A 50-year-old man complaining of dyspnea was seen by the occupational medicine clinic as an outpatient. He had worked with beryllium for approximately 20 years and was a 40-pack-year smoker. His pulmonary function tests showed airflow limitation (FEV₁ = 2.33 liters or

Figure 5.13

The cardiovascular and gas exchange responses of the 21-year-old man in Case 5.1. A. Systolic (●) and diastolic (○) blood pressure versus O₂ consumption (V˙O₂ as a percent of predicted maximum) with normal response lines (dashed). B. Heart rate (HR) versus O₂ consumption (V˙O₂ as a percent of predicted maximum) with normal response line (dashed). C. PaO₂ versus O₂ consumption (V˙O₂ as a percentage of predicted maximum) with normal response line (dashed). D. CO₂ production (V˙CO₂) versus O₂ consumption (V˙O₂) with normal response line (dashed) and estimated AT point.
Case Presentations

61% predicted, and FEV₁/FVC = 0.52) with no improvement after a bronchodilator and a reduced single-breath CO diffusing capacity (Dl,CO = 18.3 or 51% predicted and Dl,CO/VA = 2.9 or 57% predicted). A maximal symptom-limited multistage exercise test was ordered.

An arterial catheter was placed in the radial artery, and a 12-lead ECG and resting data were obtained. The exercise was performed on a cycle ergometer starting at 20 watts with 30-watt increments/min until exhaustion. The patient quit after approximately 6 minutes, complaining of leg fatigue, shortness of breath, and chest tightness. The results of the rest and exercise test are shown in Table 5.4 and Figures 5.14 and 5.15.

### Table 5.4

Ventilatory, Cardiovascular, and Gas Exchange Measurements from the Final Minutes of Rest and Maximal Exercise in Case 5.2

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Max exercise*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload (watts on cycle)</td>
<td>0</td>
<td>170 (76)</td>
</tr>
<tr>
<td>V˙E (liters/min)</td>
<td>12.7</td>
<td>91.7 (105)</td>
</tr>
<tr>
<td>V˙O₂ (liters/min)</td>
<td>0.388</td>
<td>1.693 (60)</td>
</tr>
<tr>
<td>V˙CO₂ (liters/min)</td>
<td>0.298</td>
<td>1.928</td>
</tr>
<tr>
<td>R</td>
<td>0.77</td>
<td>1.14</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>VT (L)</td>
<td>1.058</td>
<td>1.910</td>
</tr>
<tr>
<td>VD (L)</td>
<td>0.382</td>
<td>0.779</td>
</tr>
<tr>
<td>VD/VT (%)</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>FIO₂</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>pH</td>
<td>7.42</td>
<td>7.39</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>52¹</td>
<td>45¹</td>
</tr>
<tr>
<td>HbO₂ (%)</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>PAO₂-PaO₂ (mmHg)</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78</td>
<td>167 (94)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124</td>
<td>150</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85</td>
<td>105</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent of predicted maximum

At 5,000 feet, normal PaO₂ range is 65 to 75 mmHg
Interpretation

At rest, the data reveal a low PaO₂ and O₂ saturation (HbO₂) with a correspondingly widened PAO₂-PaO₂.

Figure 5.14A shows a normal linear ventilation response up to about 45% of the ventilatory ceiling, after which there is a sharp increase. The O₂ consumption should increase linearly with work, and as Figure 5.14B shows, this patient’s response was essentially linear; however, he fell short of predicted maximums. The increases in ventilation were accomplished with appropriate recruitment of VT, but frequency was excessive at maximum exercise (Figure 5.14C).
The VD/VT was slightly elevated at rest, and it inappropriately increased during exercise (Figure 5.14D).

The blood pressure response (Figure 5.15A) shows a slight diastolic hypertensive response and a decreased systolic response. The heart rate response is excessive (Figure 5.15B). The PaO2 is low at rest, and it drops during exercise (Figure 5.15C). The PaO2-PaO2 gradient was elevated at rest and increased throughout exercise. Although widening of the PaO2-PaO2 gradient is seen in healthy individuals, it is abnormally widened at rest in this patient, and it widens even more with exercise. The AT can be estimated from the inflection in the VO2 versus VCO2. 

Case Presentations
graph (Figure 5.15D). Although it is only an approximation, this point represents the failure of the acid-base buffering system to prevent metabolic acidosis, and it occurs in this patient at approximately 40% to 45% of maximum.

No abnormalities were seen in the ECG, and the overall impression is one of exercise limitation due to abnormal gas exchange and ventilatory abnormalities. Additionally, the cardiovascular response was excessive given the level of work achieved.

Case 5.3

Background

A 62-year-old woman was referred to the pulmonary rehabilitation program. She was a 90-pack-year smoker with an FEV₁ of 1.12 liters (44% predicted) and an FEV₁/FVC of 37%, with no response to a bronchodilator. The DLCO was 12.7 mL/min/mmHg (51% predicted). Before beginning the program she underwent a maximal symptom-limited multistage exercise test.

An arterial catheter was placed in the radial artery, and a 12-lead ECG was applied. A room-air arterial blood sample revealed a PaO₂ of 53 mmHg and an Hb O₂ of 88%. Both the rest and exercise testing were performed with the patient breathing supplemental O₂. A blender was used to produce 28% oxygen, which flowed to a large reservoir bag. The bag was connected to the inspired side of the two-way patient valve. The exercise was performed on a cycle ergometer starting at 5 watts and using 10-watt increments/min until exhaustion. The patient quit after 6 minutes of exercise, complaining of shortness of breath and leg fatigue. The results of the exercise test are shown in Table 5.5 and Figures 5.16 and 5.17.

Interpretation

The resting data reveal a low PaO₂ at rest on room air, which was normalized on supplemental oxygen (28%). The PAO₂-PaO₂ is correspondingly widened, and the blood pressure is elevated.

The patient achieved a workload of 57% of the predicted maximum workload and a maximum VO₂ of 52% of predicted maximum. Figure 5.16A shows that the VE increased excessively, reaching the ventilatory ceiling (which is low in this patient because of her airflow limitation) and probably limiting further exercise. The O₂ consumption increased linearly with work (a normal response), although only 52% of predicted maximum was achieved (Figure 5.16B). The excessive increase in ventilation was accomplished mostly with excessive increases in respiratory rate (Figure 5.16C). The Vd/VT increased inappropriately during exercise (Figure 5.16D).

Figure 5.17A shows the hypertensive response to exercise, although the heart rate response is normal (Figure. 5.17B). The PAO₂-PaO₂ was elevated at rest and remained elevated during exercise (Figure. 5.17C). No fall in the PaO₂ occurred with exercise. The AT approximation is seen at the inflection of the VO₂ and VCO₂ graph (Figure. 5.17D) and is approximately 45% of maximum.

The ECG appeared normal, and the overall impression is one of exercise limitation due to ventilatory and cardiovascular abnormalities.
Case 5.4

Background

A 64-year-old man arrived in the pulmonary function laboratory for an exercise test. Pulmonary function tests on the previous day revealed the following:

- Total lung capacity (TLC) = 58% of predicted
- Forced vital capacity (FVC) = 47% of predicted
- FEV₁/FVC = 85%
- DLCO = 44% of predicted
- DLCO/VA = 92% of predicted

Table 5.5: Ventilatory, Cardiovascular, and Gas Exchange Measurements from the Final Minutes of Rest and Maximal Exercise in Case 5.3

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Max Exercise*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload (watts on cycle)</td>
<td>0</td>
<td>55 (57)</td>
</tr>
<tr>
<td>VE (liters/min)</td>
<td>14.3</td>
<td>42.0 (82)</td>
</tr>
<tr>
<td>VO₂ (liters/min)</td>
<td>0.316</td>
<td>0.707 (52)</td>
</tr>
<tr>
<td>VCO₂ (liters/min)</td>
<td>0.248</td>
<td>0.685</td>
</tr>
<tr>
<td>R</td>
<td>0.78</td>
<td>0.97</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>VT (L)</td>
<td>1.021</td>
<td>1.556</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>0.379</td>
<td>0.709</td>
</tr>
<tr>
<td>Vd/VT (%)</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>Fio₂ (%)</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td>pH</td>
<td>7.41</td>
<td>7.34</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>80⁰</td>
<td>85¹</td>
</tr>
<tr>
<td>HbO₂ (%)</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>PaO₂-PaO₂ (mmHg)</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>96</td>
<td>141 (84)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>175</td>
<td>249</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>97</td>
<td>105</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent of predicted maximum

¹On supplemental oxygen (28%)
CHAPTER 5 Cardiopulmonary Exercise Test

No response to a bronchodilator was seen, and the patient claimed he had never smoked. These results are consistent with a restrictive process.

An arterial catheter was placed in the radial artery, and a 12-lead ECG was applied. The analysis of a room-air arterial blood sample revealed a pH of 7.45, PaCO₂ of 35 mmHg, PaO₂ of 60 mmHg, and SaO₂ of 90.5%. The PaO₂ is slightly low for 5,000-feet altitude, but it was decided to exercise the patient on room air.

Figure 5.16

The ventilatory responses of the 62-year-old woman in Case 5.3. A. Expired Vₑ versus O₂ consumption (Vₒ₂ as a percent of predicted maximum) with predicted line (dashed) and ventilatory ceiling calculated from FEV₁ × 40. B. Workload versus O₂ consumption (Vₒ₂) with predicted line (dashed). C. VT versus f with a vertical dashed line representing the patient’s vital capacity. D. Vo/VT versus O₂ consumption (Vₒ₂ as a percent of predicted maximum) with predicted response line (dashed).
The exercise was performed on a cycle ergometer starting at 10 watts, and the workload was increased 10 watts/min until exhaustion. The patient quit after 6 minutes of exercise despite hard coaching by the technologists. His complaint was shortness of breath and dizziness. The results of this test are shown in Table 5.6 and Figures 5.18 and 5.19.

Figure 5.17

The cardiovascular and gas exchange responses of the 62-year-old woman in Case 5.3. A. Systolic (•) and diastolic (○) blood pressure versus \( \dot{V}O_2 \) consumption (\( \dot{V}O_2 \) as a percent of predicted maximum) with normal response lines (dashed). B. Heart rate (HR) versus \( \dot{V}O_2 \) consumption (\( \dot{V}O_2 \) as a percent of predicted maximum) with normal response line (dashed). C. \( \text{PAO}_2-\text{PaO}_2 \) versus \( \dot{V}O_2 \) consumption (\( \dot{V}O_2 \) as a percentage of predicted maximum) with normal response line (dashed). D. \( \dot{V}CO_2 \) production (\( \dot{V}CO_2 \)) versus \( \dot{V}O_2 \) consumption (\( \dot{V}O_2 \)) with normal response line (dashed) and estimated AT point.
CHAPTER 5  Cardiopulmonary Exercise Test

Interpretation

The resting data reveal a normal resting heart rate, slightly elevated \( \dot{V}E \), increased Vd/VT, a slightly low PaO\(_2\), and a widened P A\(_2\)-PaO\(_2\).

Figure 5.18A shows that \( \dot{V}E \) is slightly high at rest and increases excessively for the level of O\(_2\) consumption achieved. The ventilatory ceiling was not reached. The excessive increase in \( \dot{V}E \) was achieved primarily with the increase in respiratory rate, with VT remaining low (Figure 5.18C).

The \( O_2 \) consumption increased linearly with work (a normal response) up to approximately 25% of maximum (Figure 5.18B). The Vd/VT was increased at rest and inappropriately increased further during exercise (Figure 5.18D).

Table 5.6
Ventilatory, Cardiovascular, and Gas Exchange Measurements from the Final Minute of Rest and Maximal Exercise in Case 5.4

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Max exercise*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload (watts on cycle)</td>
<td>0</td>
<td>60 (25)</td>
</tr>
<tr>
<td>( \dot{V}E ) (liters/min)</td>
<td>16.3</td>
<td>48.2 (55)</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) (liters/min)</td>
<td>0.357</td>
<td>0.737 (24)</td>
</tr>
<tr>
<td>( \dot{V}CO_2 ) (liters/min)</td>
<td>0.296</td>
<td>0.578</td>
</tr>
<tr>
<td>R</td>
<td>0.83</td>
<td>0.78</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>VT (L)</td>
<td>1.019</td>
<td>1.236</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>0.440</td>
<td>0.699</td>
</tr>
<tr>
<td>Vd/VT (%)</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Fio(_2)</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>pH</td>
<td>7.45</td>
<td>7.45</td>
</tr>
<tr>
<td>PaCO(_2) (mmHg)</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>PaO(_2) (mmHg)</td>
<td>60(^\dagger)</td>
<td>55(^\dagger)</td>
</tr>
<tr>
<td>HbO(_2) (%)</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>P A(_2)-PaO(_2) (mmHg)</td>
<td>19.6</td>
<td>27.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87</td>
<td>129</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>108</td>
<td>147</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68</td>
<td>93</td>
</tr>
</tbody>
</table>

*Values in parentheses are percent of predicted maximum

At 5,000 feet, normal PaO\(_2\) range is 65 to 75 mmHg
Figure 5.18

The ventilatory responses of the 64-year-old man in Case 5.4. A. Expired Ve versus O₂ consumption (V̇O₂ as a percentage of predicted maximum) with predicted line (dashed) and ventilatory ceiling calculated from FEV₁ × 40. B. Workload versus O₂ consumption (V̇O₂) with predicted line (dashed). C VT versus f with a vertical dashed line representing the patient’s vital capacity. D. V̇V/O₂ versus O₂ consumption (V̇O₂ as a percentage of predicted maximum) with predicted response line (dashed).

Figure 5.19A shows a normal resting blood pressure, but with exercise diastolic hypertension developed. The heart rate response (Figure 5.19B) is excessive for the level of O₂ consumption achieved. The resting PaO₂ of 60 mmHg breathing room air is slightly below the normal range at 5,000-feet altitude. During exercise, the PaO₂ decreased slightly (Figure 5.19C), which corresponds with the abnormal widening of the PAO₂-PaO₂. The pH remained unchanged during exercise, and the PaCO₂ fell slightly. The AT approximation can be identified by the inflection of the V̇O₂ and V̇CO₂ graph (Figure 5.19D), but in this patient...
no inflection upward is seen; therefore, either the AT was not reached or this method of determination was not sensitive enough. Most likely the AT was not reached.

The ECG appeared normal, and the overall impression is that exercise tolerance was severely reduced. Although marked abnormalities of ventilation and gas exchange were present, the patient was not limited by these abnormalities. Additionally, the fact that the AT was not achieved suggests deconditioning.

Figure 5.19

The cardiovascular and gas exchange responses of the 64-year-old man in Case 5.4. A. Systolic (●) and diastolic (○) blood pressure versus \( V_{O2} \) consumption (\( V_{O2} \) as a percentage of predicted maximum) with normal response lines (dashed). B. Heart rate (HR) versus \( V_{O2} \) consumption (\( V_{O2} \) as a percentage of predicted maximum) with normal response line (dashed). C. \( \text{PaO}_2 \) versus \( V_{O2} \) consumption (\( V_{O2} \) as a percentage of predicted maximum) with normal response line (dashed). D. \( \text{CO}_2 \) production (\( V_{CO2} \)) versus \( V_{O2} \) consumption (\( V_{O2} \)) with normal response line (dashed).
Self-Assessment Questions

1. Which of the following is true regarding the cycle ergometer and exercise testing?
   a. A slightly higher VO₂ max can be achieved versus the treadmill
   b. Can be mechanically or electronically braked
   c. Does not provide an accurate measurement of power
   d. Patient’s height and weight impact work performed
   e. None of above

2. During a symptom-limited incremental exercise test, VE in a normal individual:
   a. Increases in a non-linear fashion
   b. Increases in a linear fashion up to approximately 50% of maximum VO₂
   c. Increases up to the ventilatory ceiling
   d. a and c
   e. b and c

3. The main cardiovascular response to exercise is:
   a. Increase in ventilation
   b. Increase in cardiac output
   c. Increase in blood pressure
   d. Decrease in arterial O₂ content

4. Which of the following is/are most correct about minute ventilation during exercise?
   a. Increases linearly with work up to the anaerobic threshold
   b. Increases linearly with O₂ consumption up to the anaerobic threshold
   c. Increases linearly with Vd/VT
   d. a and b
   e. a and c

5. A normal amount of physiologic dead space at rest in healthy individuals is usually less than:
   a. 10% of inspiratory capacity
   b. 35% of tidal volume
   c. 50% of tidal volume
   d. 35% of vital capacity
   e. 50% of vital capacity

6. All the following are characteristics of the breath-by-breath exercise systems except:
   a. Rapid response gas analyzers
   b. Computerization
   c. 3-liter mixing chamber
   d. Synchronization of gas analyzer and volume signals

7. During exercise, the O₂ consumption increases with work:
   a. In a linear fashion
   b. In a non-linear fashion
   c. Does not increase with work
   d. Only when PaO₂ increases
8. The respiratory exchange ratio (R) measures the relationship of:
   a. CO₂ production to CO₂ consumption
   b. CO₂ production to O₂ production
   c. CO₂ production to O₂ consumption
   d. CO₂ production to V̇E

9. A patient’s resting blood pressure is 120/65. After 4 minutes of exercise, the blood pressure is 190/70. This is:
   a. A normal response
   b. A hypotensive response
   c. A hypertensive response
   d. An indication to stop the exercise test

10. What is the response of PaO₂ during exercise in healthy individuals?
    a. Remains relatively constant even up to high work rates
    b. Remains relatively constant but falls at high work rates
    c. Increases linearly with work
    d. Decreases from increases in lactic acid
    e. Increases each minute of exercise until ventilatory ceiling is reached

11. While performing a CPET on a patient, the technologist observes that the patient’s blood pressure has gone from a resting level of 135/75 to 185/75. Which of the following is the correct action?
    a. Continue the exercise test, but reduce the workload
    b. Continue the exercise test because the blood pressure response is appropriate
    c. Stop the exercise test
    d. Stop the exercise test, let patient rest for a few minutes, then resume exercise

12. In the maximal symptom-limited incremental cycle ergometer exercise protocol, the work is increased:
    a. Up to 80% of target
    b. Until patient reaches maximum exertion level (exhaustion)
    c. Every 3 minutes until heart rate reaches maximum
    d. Every 6 minutes
    e. None of the above

13. A patient has the following values measured during a maximal symptom-limited exercise test:
    \[
    \begin{align*}
    &F_{\text{O}_2} = 0.21 \\
    &F_{\text{E}_2} = 0.17 \\
    &F_{\text{E}_2} = 0.045 \\
    &V_{\text{E}_{\text{STPD}}} = 54 \text{ liters} \\
    &V_{\text{L}_{\text{STPD}}} = 54 \text{ liters}
    \end{align*}
    \]
    What is this patient’s \( \dot{V}_O_2 \) (liters/min STPD)?
    a. 1.93
    b. 2.13
    c. 3.27
    d. 2.93
During the CPET, exercise should be stopped if there is:

a. Severe chest pain (angina)
b. Dizziness
c. Systolic blood pressure over 250 mmHg
d. Fall in diastolic blood pressure of more than 20 mmHg
e. All of above

The anaerobic threshold can be identified by which of the following?

a. Increase in dead space to tidal volume ratio
b. Increase in blood pH
c. Change in rate of \( \dot{V}_{CO_2} \) relative to \( V_O_2 \)
d. Decrease in blood lactate
e. Decrease in \( VO_2 \)

References


Six-Minute Walk Test

Introduction

Chapter 5 presented the cardiopulmonary exercise test (CPET), which is the best method to measure aerobic capacity, provide a global assessment of exercise response, and determine the factors limiting exercise. It is a progressive incremental test that increases work on a cycle ergometer or treadmill until the patient reaches exhaustion or a symptom-limited end. However, the CPET is a complex test that requires sophisticated and costly instrumentation operated by well-trained staff. Simpler exercise tests to evaluate functional exercise capacity have emerged, and the least complex and most popular is the 6-minute walk test (6MWT).

The 6MWT is a submaximal test conducted on a hard flat surface (e.g., hallway) and measures the distance walked in a period of 6 minutes. Patients choose their own intensity and are allowed to stop and rest during the test. The distance walked is called the 6-minute walk distance (6MWD). The 6MWT does not determine peak oxygen consumption or determine the cause or mechanisms of exercise limitations like the CPET. It does, however, provide useful information about the patient’s ability to perform activities of daily living, and changes in 6MWD have been shown to correlate with subjective improvements in dyspnea.

The shuttle-walk test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a short course. The walking speed is increased every minute until the patient cannot reach the turnaround point within the
required time. The shuttle-walk test is less standardized and less used, and some patients don’t hear the audio prompts well enough.

Historically, the development of objective measures of functional exercise capacity started in the 1960s and 1970s. Cooper described a 12-minute test to evaluate physical fitness in healthy individuals.

McGavin and coworkers described a 12-minute walk test in a hospital corridor for assessing disability in chronic bronchiitis. Each patient was asked to cover as much distance while walking as fast as possible. A doctor accompanied the patient, acting as a timekeeper and giving encouragement.

Mungall and Hainsworth found the distance covered in a 12-minute hospital corridor walking test in patients with chronic obstructive airway disease to be a useful measure of disability.

Butland and coworkers noted that the 12-minute walk test is a useful and reproducible measure of exercise tolerance, but it is time consuming and exhausting for the patient. They explored the use of shorter-duration walking tests and compared the 2-, 6-, and 12-minute tests. They found a high correlation among the three tests and concluded that shorter times are easier for both patients and physicians, and they determined that the 6-minute walk test may be the best compromise.

Solway and coworkers reviewed the literature on the most commonly utilized functional walk tests, including the time-based tests (e.g., 6MWT), fixed-distance tests, and velocity-based walk tests (e.g., shuttle-walk test). They found the 6MWT was the most commonly used, easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests.

This chapter will discuss the indications, contraindications, safety issues, testing technique, quality assurance, and interpretation of the 6MWT.

Indications

The list of indications for the 6MWT is long and includes the following general categories: (a) assess functional status (single measurement), (b) measure the response to medical interventions, and (c) predict mortality and morbidity.

Contraindications

The absolute and relative contraindications for the 6MWT are shown in Table 6.1.

Patient Safety

The 6MWT should be performed by a nurse, respiratory therapist, pulmonary function technologist, physical therapist, or other medically trained individual certified in cardiopulmonary resuscitation. The 6MWT should be conducted in a location that is easily accessible in case of an emergency. An emergency cart (crash cart) should be available nearby. A telephone or other
means of calling for help should be available. The presence of a physician is not required, but this may vary depending on the situation and facility policy.

Patients on oxygen therapy can be tested, and oxygen should be administered at the patient’s prescribed flow rate or as directed by the ordering physician.

The 6MWT can be stopped because of chest pain, intolerable dyspnea, leg cramps, walking instability, or other signs of severe distress. If a test is stopped for any reason, the patient should sit or lie down, vital signs and oxygen saturation should be obtained, and a physician should be summoned to evaluate the patient. Oxygen should be administered as appropriate.6

### Testing Technique

#### Walking Course

The 6MWT should be performed in a long, flat, unobstructed, and straight hallway or corridor with a hard surface that is free from a lot of traffic. In some climates it is possible to conduct the test outdoors as long as patient safety requirements can be met.

The course should be at least 100 feet (30 meters) in length and marked with a starting line and increments of approximately 10 feet (3 meters) with tape. The turnaround points should be marked with a traffic cone, chair, or other marker (e.g., tape).

Although shorter courses could be used, the patient would have to turn around more often, and that would potentially reduce the distance walked. However, if the same course is going to be used serially before and after an intervention, a shorter course would work. The use of a treadmill for the 6MWT is not recommended.6

Sciurba and coworkers7 reported that greater distances were achieved on a continuous (circular) course compared to a straight (back and forth) course. They also found that the course length did not have a significant effect on walking distance.

---

**Table 6.1: Absolute and Relative Contraindications for 6MWT**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction in the previous month</td>
<td>Resting heart rate &gt; 120 beats/min</td>
</tr>
<tr>
<td>Unstable coronary artery disease or angina in the previous month</td>
<td>Systolic blood pressure &gt; 180 mmHg, and diastolic blood pressure &gt; 100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Exercise-related syncope</td>
</tr>
<tr>
<td></td>
<td>Arthritis or neuromuscular disease that limits walking ability</td>
</tr>
</tbody>
</table>

CHAPTER 6  Six-Minute Walk Test

Equipment/Materials
The equipment and materials needed for the 6MWT are as follows:

- Stopwatch
- Measuring tape
- Chair
- Work sheet
- Portable oxygen delivery setup with nasal cannula
- Sphygmomanometer
- Borg scale

Patient Preparation
The patient should be instructed to wear comfortable clothing, including walking shoes. If the patient requires a walking aid (e.g., cane), it should be brought and used during the test. The patient should be instructed to take all usual medications and have a light meal 2 to 4 hours before the test.

Procedure
The procedure for the 6MWT is as follows:

1. The patient should be seated in a chair near the starting line for at least 10 minutes. During this time it is recommended to obtain the patient’s pulse rate, blood pressure, and pulse oximetry oxygen saturation (SpO₂). Check for contraindications.

2. Have the patient stand at the starting line. Rate the patient’s baseline breathlessness and leg fatigue using the Borg scale (Figure 6.1).

3. Use the following standardized instructions from the ATS guideline⁵:

   The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.

4. Demonstrate by walking one lap on the course.

5. Provide the following additional standardized instructions from the ATS guideline⁵:

   Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk as far as possible for 6 minutes, but don’t run or jog.

   Start now, or whenever you are ready.
6. Start the timer as soon as the patient starts walking. Do not walk with the patient.

7. Do not talk to anyone during the walk. Use only the following standardized phrases of encouragement from the ATS guideline:

End of minute 1: You are doing well. You have 5 minutes to go.
End of minute 2: Keep up the good work. You have 4 minutes to go.
End of minute 3: You are doing well. You are halfway done.
End of minute 4: Keep up the good work. You have only 2 minutes left.
End of minute 5: You are doing well. You have only 1 minute to go.

At 5 minutes and 45 seconds: In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.

End of minute 6: Stop!

8. If the patient stops walking during the 6 minutes and needs to rest, allow the pause and have the patient lean against the wall or sit on a chair, if necessary. Tell the patient to continue walking whenever he or she can. Do not stop the timer. If the patient refuses to continue or should not continue, provide a chair for the patient to sit on, note the distance walked, and provide a comment about the reason the patient stopped walking and the time the patient stopped.

9. At the end of 6 minutes, tell the patient to stop. Walk to the patient and take a chair for the patient to sit on, if appropriate. Mark the spot where the patient stopped.

---

**Figure 6.1** The 10-point Borg scale.

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing at all</td>
</tr>
<tr>
<td>0.5</td>
<td>Very, very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight (light)</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe (heavy)</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very severe</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Very, very severe (maximal)</td>
</tr>
</tbody>
</table>

---
10. Have the patient rate his or her postwalk breathlessness and leg fatigue using the Borg scale. It is okay to remind the patient of the number he or she selected before the exercise period started.

11. If using a pulse oximeter, measure the \( \text{SpO}_2 \) and pulse rate.

12. Record the number of laps and additional distance covered using the markers on the course. Calculate the total distance walked, rounding to the nearest foot or meter, and record the distance on the work sheet.

**Quality Assurance and Other Issues**

Testing variability can be reduced by following the guidelines provided by the ATS\(^6\) as summarized in the previous section. It is ideal to have the same individual conduct the patient testing each time.

The use of a practice test is controversial. Sciurba and coworkers\(^7\) reported a definite learning effect and found that patients walk approximately 66 more feet in the second test. A practice test helps make sure the patient understands what is expected and helps establish a good baseline if pre- and postintervention testing is planned. Patients seem to learn to pace themselves with practice and can achieve a greater distance with a practice walk.

If supplemental oxygen is needed during walks and pre- and postintervention serial testing is planned, the oxygen should be administered the same way with the same flow rate each time. If the flow rate must be increased at other visits, this should be noted on the work sheet and considered in the interpretation of the data. It is not recommended to walk with the patient and carry the oxygen source (e.g., oxygen tank).

**Reporting Results**

The following information should be reported for the 6MWT:

- Demographic data
- Date of test
- Medications taken on day of test
- Supplemental oxygen use during the test, including flow rate and type (e.g., pulsed)
- Baseline data
  - Time
  - \( \text{SpO}_2 \) and pulse rate
  - Blood pressure
  - Borg scale rating for breathlessness
  - Borg scale rating for leg fatigue
- End of 6MWT data
  - Time
  - \( \text{SpO}_2 \) and pulse rate
  - Borg scale rating for breathlessness
Interpretation

The evaluation of results that are obtained before and after an intervention requires the assessment of change. It is not clear whether it is best to express change as an absolute value or as a percentage. The ATS guideline\(^6\) suggests that change in 6MWD be expressed as an absolute value. Redelmeier and coworkers\(^8\) reported that a 54-meter difference in 6MWD (95% confidence interval of 37 to 71 meters) in patients with chronic lung disease was meaningful compared to subjective ratings of walking ability. Thus, when using this study as a basis, one can be 95% confident that a significant improvement occurred if the change was greater than 70 meters.

A review by Wise and Brown\(^9\) suggested that the minimal clinically important difference in patients with severe COPD is 54 to 80 meters. Using reported data they calculated a coefficient of repeatability of 86 meters and suggested that changes less than 86 meters are probably not meaningful.

Single measurements of 6MWD have been shown to be useful prognostic indicators in patients with primary pulmonary hypertension (PPH). Miyamoto and coworkers\(^10\) reported the 6MWD was significantly shorter in patients with PPH than in age- and gender-matched healthy subjects (297 ± 188 versus 655 ± 91 meters).

There are few data on the 6MWD in healthy individuals using standardized methods. Enright and Sherrill\(^11\) published data on 255 male and 253 female subjects who were an average of 59.5 and 62.0 years old, respectively. Troosters and coworkers\(^12\) published data on 51 healthy patients between the ages of 50 and 85 years. It is clear that age, height, weight, and gender independently affect the 6MWD and should be taken into account when interpreting 6MWD data.

Self-Assessment Questions

1. All of the following are true about the 6MWT except:
   a. It is a submaximal test.
   b. It measures the distance walked in a period of 6 minutes.
   c. It measures peak oxygen consumption.
   d. Patients choose their own intensity.
   e. Standardized encouragement wording is used.

2. The presence of a physician during the 6MWT is not required according to professional society guidelines.
   a. True
   b. False
3. Which of the following is not true about the 6MWT course:
   a. The course should be a long hallway or corridor.
   b. The course should have a hard surface.
   c. The course should be free of a lot of traffic.
   d. The course should be approximately 100 feet in length.
   e. None of the above.

4. During a 6MWT the patient complains of leg fatigue and stops walking. Which of the following is the most correct action:
   a. Stop the clock and have the patient sit on a chair.
   b. Have the patient lean against the wall or sit on a chair, but do not stop the clock.
   c. Stop the test and measure the distance walked.
   d. Administer oxygen and measure SpO₂.

5. A treadmill can be used for the 6MWT.
   a. True
   b. False

6. A patient on 2 L/min of oxygen and pulling a small wheeled oxygen cylinder completes three lengths of a 30-meter walking course and stops 10 meters short of completing the fourth length after 5 minutes. He states that he needs to rest and is provided with a chair. At 6 minutes he is still unable to continue. What would you report for the 6MWD?
   a. 110 meters
   b. 90 meters
   c. Test was invalid because patient did not complete 6 minutes of walking
   d. 120 meters

References


Exercise-Induced Bronchoconstriction Test

Introduction

It has been recognized for many years that exercise can have adverse effects on asthmatic patients. As many as 75% to 90% of all asthmatics have exercise-induced bronchoconstriction (EIB), also called exercise-induced asthma (EIA). Although EIB is especially prevalent in children and adolescents, it affects all age groups.\(^1,2\)

In the pulmonary function laboratory, this exercise test can be used as a provocation tool (i.e., challenge) to detect airway hyperresponsiveness. However, unlike other bronchial challenges, such as methacholine and mannitol, it is difficult to study EIB in a dose–response manner because of the physiologic effects of exercise. More commonly, exercise is used to confirm a clinical suspicion of EIB or to evaluate pharmacotherapy.

This section will acquaint the reader with the physiology of exercise in asthmatics, preparation of patients for performing the EIB test, pulmonary function tests, testing technique, and basic interpretation.

Physiology

The investigations by Jones and colleagues in the 1960s pioneered the study of EIB.\(^3\) Although EIB had been recognized previously, Jones and colleagues demonstrated that in asthmatic children: (a) exercise of 1 to 2 minutes produces an increase in the FEV\(_1\), (b) prolonged exercise...
(8 to 12 minutes) produces a decrease in the FEV₁, with the FEV₁ reaching its lowest value 1 to 5 minutes after exercise, and (c) both the increase and decrease can be minimized by pretreatment with a beta sympathomimetic medication.

Since then, EIB has been studied extensively. In addition to showing the relationship between the severity of EIB and the type, intensity, and duration of exercise, studies have shown that during an exercise period of 6 to 8 minutes (a standardized time for this test), both asthmatic and normal patients have a rise in peak expiratory flow rate (PEFR) and FEV₁. Increased catecholamine release most likely causes this bronchodilatation. Near the end of or after the exercise period, an asthmatic patient with EIB has a marked fall in these ventilatory function parameters, with the values reaching their lowest level 3 to 15 minutes after exercise (Figure 7.1). However, no one theory or hypothesis has completely explained this reaction to exercise. The most popular hypotheses focus on the effect of heat and moisture loss from the respiratory tract. Investigators also believe that other mechanisms may play a role. These mechanisms include: (a) mechanical stimulation of breathing at a high minute ventilation (Ve), (b) lower CO₂ tension, which narrows the airway, and (c) release of lactic acid by exercising muscles.

**Figure 7.1**

Typical ventilatory response (as measured by PEFR) of an asthmatic child for 6 minutes of running.

Although the initiating stimulus remains controversial, other observations have shown that in some patients an immediate and a delayed response is seen. The delayed or late response occurs 3 to 5 hours after the exercise period. The delayed response is uncommon, does not appear to depend on the existence of an immediate response, and is not specifically related to exercise.

A refractory period of 3 to 4 hours has also been reported. During this refractory period, a second exercise period shortly after recovery from the initial exercise will produce an episode of EIB that is less severe than the first. Some athletes can take advantage of this phenomenon by engaging in some form of strenuous exercise before an event.

Running has been reported as the most asthmogenic form of exercise, with treadmill running being a little less potent than free running. Cycling is the next most asthmogenic form of exercise, followed by walking, swimming, and kayaking (Figure 7.2).

The severity of EIB depends on the intensity of the exercise. The maximum effect occurs when the work rate is approximately 75% to 90% of maximum workload. It is interesting that further increases in intensity beyond this level do not produce more severe EIB.

Oxygen (O₂) saturation in patients with EIB follows the pattern of the ventilatory function. During the first few minutes of exercise, there is usually an increase in arterial O₂ tension.

**Figure 7.2**

Ventilatory response, expressed as the percent fall from baseline PEFR, to different types of exercise in groups of asthmatic and normal subjects. The numbers (n) indicate the number of subjects. The error bars indicate ± 1 standard error of the mean (SEM), and no normal subjects were studied for swimming or treadmill walking.

As the flow rates decrease toward the end of or following exercise, O₂ tension and saturation usually fall.²¹

Testing Technique

Patient Preparation and Contraindications

Drugs that can prevent EIB should not be administered for various periods before the test. Inhaled beta sympathomimetic agents (e.g., isoproterenol, metaproterenol, albuterol, terbutaline, salmeterol, and fenoterol), disodium cromoglycate, atropine, antihistamines, and oral and inhaled steroids have been shown to lessen or prevent EIB. Oral beta sympathomimetics and theophylline do not prevent EIB.²² However, they do produce significant bronchodilatation, and it may be reasonable to withhold them.

It is frequently impossible or inadvisable for patients with difficult-to-control asthma to have some or all of these drugs withheld for long periods. In some cases, a patient may be able to avoid bronchodilators for no more than 4 to 6 hours. These patients (because of the severity of their asthma) usually develop EIB despite taking medication. Thus, a practical yet effective approach is to withhold the medications shown in Table 7.1 before the test for the noted time.

In addition to withholding medications, the patient should also avoid heavy exercise for at least 4 hours before the test. The patient should dress appropriately for walking or running and wear sneakers or running or walking shoes. Comfortable pants or shorts and a shirt that allows for easy ECG electrode application are also recommended.

Before exercise, every patient should be examined by a physician who has obtained a thorough history and has judged the patient’s cardiovascular status. Contraindications for

Table 7.1

Medications That Should Be Withheld for at Least the Amount of Time Shown Prior to the EIB Test

<table>
<thead>
<tr>
<th>Drug</th>
<th>Withhold (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled beta sympathomimetics</td>
<td></td>
</tr>
<tr>
<td>Short acting (e.g., albuterol)</td>
<td>4–8</td>
</tr>
<tr>
<td>Long acting (e.g., salmeterol)</td>
<td>24–48</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>48</td>
</tr>
<tr>
<td>Anticholinergics (e.g., ipratropium)</td>
<td>8–24</td>
</tr>
<tr>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td>24</td>
</tr>
<tr>
<td>Long acting</td>
<td>72</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>8</td>
</tr>
</tbody>
</table>
Testing Technique

Pulmonary Function Tests

The most common pulmonary function test (PFT) used with EIB procedures is forced spirometry. It should be performed according to the most current recommendations by the American Thoracic Society (ATS) and European Respiratory Society (ERS) as described in Chapter 1. Alternatively, the use of peak flow meters can be a good tool for assessing EIB in children who are too young to perform consistently acceptable spirometry.

The use of the body plethysmograph to measure airway resistance (Raw) and specific conductance (sGaw) is sometimes preferred because it does not require a deep breath or a forced expiration and is less dependent on effort. However, the body plethysmograph is a more costly tool, and it may not be available in some laboratories.

Electrocardiograph (ECG)

The patient’s heart rate should be monitored before, during, and after exercise, with a three-lead ECG as a minimum. A pulse oximeter or other reliable device could also be used as an alternative. A 12-lead ECG is appropriate for older patients and those at risk for heart disease.

Inhalate

The test is commonly conducted with the patient breathing ambient air. The importance of the inspired air temperature and humidity has been discussed. The test should be conducted in an air-conditioned room at approximately 20°C to 25°C and low relative humidity (i.e., less than 50%).

### Table 7.2

**Absolute and Relative Contraindications for EIB Testing**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ &lt; 50% predicted, or &lt; 1.0 L</td>
<td>FEV₁ &lt; 60% predicted, or &lt; 1.5 L</td>
</tr>
<tr>
<td>Heart attack or stroke in previous 3 months</td>
<td>Inability to perform acceptable and repeatable spirometry</td>
</tr>
<tr>
<td>Uncontrolled hypertension (i.e., resting systolic blood pressure &gt; 200 mmHg, resting diastolic blood pressure &gt; 120 mmHg)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Chest pain or ECG abnormality that contraindicates exercise</td>
<td></td>
</tr>
</tbody>
</table>


Exercise challenges (Table 7.2) include a history of myocardial infarction (MI) or angina-like chest pain, hypertension, or ECG abnormalities.
CHAPTER 7 Exercise-Induced Bronchoconstriction Test

If it is not possible to achieve these conditions for ambient air breathing, an alternative is to have the patient inspire dry air through a valve and mouthpiece connected to a large (e.g., 100 liter) talc-free reservoir bag. The bag is filled with medical-grade compressed air. An alternative to using the large reservoir bag is to use a demand valve connected to a compressed air source.

When the patient is breathing from a reservoir bag or demand valve, a face mask could be used instead of a valve and mouthpiece. If this option is used, assure that no nose breathing takes place by using special face masks that have a separate nose compartment.

It may be necessary or desirable to have some patients breathe cold, dry air during the exercise period. A commercially available heat exchanger (TurboAire Challenger from VacuMed, Ventura, Calif.), which requires a compressed air source, will deliver very cold, dry air to the mouth.

Exercise

A treadmill is the recommended mode of exercise. Although free running is more asthmogenic, it has obvious shortcomings as an EIB-testing method, including: (a) inability to measure and control temperature, environmental pollutants, or allergens; (b) inability to measure and control work; and (c) inability to monitor ECG, O₂ saturation, and blood pressure. An electronically braked cycle ergometer can be used as an alternative method of exercise.

Testing Protocol

Measure lung function, most commonly spirometry, before the patient exercises, and repeat the measurements until acceptable repeatability is obtained. Evaluate the results to ensure that no contraindications exist, as previously noted.

A nose clip should be worn to ensure mouth breathing. If possible, measure the ambient temperature and humidity and note them on the report.

Set the treadmill with little or no grade and start it at a slow speed. Increase the grade and speed in several steps during the first 2 to 4 minutes to allow careful observation of ECG, O₂ saturation, and blood pressure.

A target heart rate of 80% to 90% of the patient’s maximum heart rate (approximately 220 – age) should be achieved by the fourth minute of exercise. After the patient reaches the target heart rate, an additional 4 to 6 minutes of exercise should be maintained, keeping the heart rate at the target level. Adjusting the speed and/or grade may be necessary to maintain the heart rate at the target level.

As noted earlier, measure PFTs before exercise. The recommended postexercise testing schedule is to measure PFTs 5, 10, 15, 20, and 30 minutes after the cessation of exercise. Some laboratories also include PFT measurements immediately after exercise ends. Many patients start wheezing and coughing near the end of the exercise period, and early recognition and subsequent treatment can be beneficial.

If EIB is documented by PFTs (e.g., fall in FEV₁ > 10% from baseline), administer an inhaled bronchodilator. The laboratory may want to remeasure PFTs after the bronchodilator to ensure that the patient has recovered before leaving the laboratory. Occasionally, the EIB is
so severe that PFTs cannot be obtained and treatment is required immediately. Document this in the report, and perform postbronchodilator PFTs before the patient leaves the laboratory.

When the purpose of the EIB test is to evaluate pharmacotherapy, the drug(s) being evaluated should be administered long enough before exercise to have time to take effect. PFTs can be measured before and after the administration of the pretreatment drug, although the essential measurement is after administration. PFTs would be measured again at least once after exercise, as previously described.

**Patient Safety**

Patient safety must be considered during any exercise test. An examination by the attending physician, with a complete review of the patient’s history, should precede the ordering of any exercise test.

When the patient arrives at the laboratory, perform a pretest evaluation to identify any contraindications. The pretest evaluation should include a preexercise questionnaire, and, in most hospitals, a signed consent form describing the risks and possible discomforts. Additionally, laboratory staff should carefully explain the procedure to the patient.

The pretest evaluation should also include a 12-lead ECG, resting blood pressure, pulse oximetry, and in some cases a resting arterial blood gas sample to verify oxygenation status. A doctor should review the questionnaire and the results of these tests to determine if any contraindications to exercise (Table 7.2) are present.

A physician trained and certified in advanced cardiovascular life support who is knowledgeable about the physiologic changes that occur during exercise should observe the patient during exercise and recovery.

The technologists should be trained in a field related to cardiopulmonary exercise testing (e.g., exercise physiology, respiratory therapy, or pulmonary function testing). The technologists must have basic knowledge of exercise responses; be able to recognize indicators of respiratory distress and, ideally, the presence of significant arrhythmias; and be certified in basic cardiac life support.

The testing room should be large enough to accommodate the exercise and emergency equipment and to allow adequate access to the patient in emergency situations. The testing room should be well lit and maintained at a comfortable temperature and humidity. Emergency equipment, including defibrillator, O2, and drugs should be readily available.

During the exercise period, blood pressure and breath sounds should be assessed periodically, O2 saturation should be monitored by oximetry, and the ECG should be examined continuously to determine if any indications to terminate exercise (Table 7.3) are present.

**Assessment of Response**

The most common way to quantify EIB is to use the percent fall index. This is calculated using a measurement of pulmonary function (e.g., FEV1, PEFR, sGaw) measured immediately before exercise and its lowest value after exercise, expressed as a percentage of the preexercise value.

\[
\text{Preexercise value} - \text{Postexercise value} \times 100/ \text{Preexercise value}
\]
CHAPTER 7 Exercise-Induced Bronchoconstriction Test

Generally, a fall in FEV₁ of at least 10% from preexercise levels is considered an abnormal or positive response.¹ In addition to the percent fall index, it is useful to report the preexercise FEV₁ value and the lowest value after exercise.²

Case Presentation

Case 7.1

A 20-year-old man was admitted to the hospital because of increasing problems with his asthma. The major complaint was that his asthma attacks were restricting his sports activities, especially in the winter months. He enjoyed basketball, soccer, and cycling but had adopted a sedentary lifestyle because of increased problems with asthma. He often pretreated himself with aerosolized bronchodilators before exercise but claimed that such pretreatment had not been effective.

His admission spirometry is shown in Table 7.4. These results are consistent with airflow limitation, with good response to a bronchodilator.

The next day, spirometry was done before and after treadmill exercise, and the results are shown in Table 7.5. These results suggest the patient does not have EIB.

The bronchospastic response to exercise is accentuated when asthmatics breathe cold, dry air (compared to the response when they breathe air at standard room conditions).²³⁻²⁵ Strauss and colleagues further note that environmental conditions influence the magnitude of the response.²⁴ Thus, variations in environmental temperature and humidity are significant interactive variables that must be controlled.

Table 7.3
Common Indications for Terminating Exercise Testing

| Severe chest pain with or without ST changes |
| Complex ectopy |
| Severe dyspnea |
| Dizziness |
| Second- or third-degree heart block |
| Sudden pallor |
| Loss of coordination or mental confusion |
| Systolic blood pressure above 250 mmHg, or diastolic blood pressure above 120 mmHg |
| Systolic or diastolic blood pressure fall of more than 20 mmHg from the highest value during the test |
| Signs of respiratory failure |

Case Presentation

The patient was rescheduled for treadmill exercise while breathing cold, dry air. The speed, grade, and exercise time were kept close to those used in the first test. The results (Table 7.6 and Figure 7.3) clearly demonstrate EIB. The issue of appropriate pharmacological treatment was addressed on a third exercise day. The patient was again exercised on the treadmill while breathing cold, dry air, but this time he

Table 7.4

Spirometry on 20-Year-Old Asthmatic Man in Case 7.1, Before and After Two Puffs of Albuterol from a Metered Dose Inhaler

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Before Rx*</th>
<th>After Rx</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>6.02</td>
<td>5.24 (87)</td>
<td>5.49</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>4.81</td>
<td>3.80 (79)</td>
<td>4.56</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>80</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/sec)</td>
<td>5.76</td>
<td>2.59 (45)</td>
<td>3.48</td>
</tr>
</tbody>
</table>
*Values in parentheses are percent predicted

Table 7.5

Spirometry on 20-Year-Old Asthmatic Man in Case 7.1, Before and After Treadmill Exercise

<table>
<thead>
<tr>
<th>Before</th>
<th>5 minutes after</th>
<th>20 minutes after</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.33</td>
<td>5.29</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.99</td>
<td>3.83</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/sec)</td>
<td>2.78</td>
<td>2.61</td>
</tr>
</tbody>
</table>

Table 7.6

Spirometry on 20-Year-Old Asthmatic Man in Case 7.1, Before and After Treadmill Exercise While Breathing Cold, Dry Air

<table>
<thead>
<tr>
<th>Before</th>
<th>5 minutes after</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.29</td>
<td>4.51</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.89</td>
<td>2.93</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>74</td>
<td>65</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/sec)</td>
<td>2.61</td>
<td>1.82</td>
</tr>
</tbody>
</table>
was pretreated with albuterol (two puffs from a metered-dose inhaler). The results (shown in Table 7.7) reveal the effectiveness of this treatment before exercise. Despite a positive history, this patient did not demonstrate EIB in the laboratory until cold, dry air was added. Additionally, medication was shown to be effective in blocking the reaction to exercise and thus will be helpful in managing this patient’s asthma.
Self-Assessment Questions

1. During the first minute of exercise, ventilatory function as measured by PEFR usually:
   a. Increases
   b. Decreases
   c. Cannot be measured
   d. None of the above

2. A standardized time for an exercise period when evaluating a patient for EIB is:
   a. 1–2 minutes
   b. 6–8 minutes
   c. 13–15 minutes
   d. 20–22 minutes

3. Which of the following forms of exercise is considered the most asthmogenic?
   a. Running
   b. Swimming
   c. Walking
   d. Cycling

4. All the following are considered factors in producing EIB except:
   a. Age
   b. Heat and moisture loss
   c. Intensity of exercise
   d. Mechanical stimulation of breathing at high V˙E

5. Generally, what percentage fall in FEV₁ from preexercise levels defines an abnormal or positive response to exercise?
   a. 0% to 3%
   b. 4% to 8%
   c. 10%
   d. 12% and 0.200 liter

References


Bronchial Challenge Testing with Pharmacological Agents

Introduction

The evaluation of twitchy or hyperresponsive airways is an increasingly popular but difficult task for the pulmonary function laboratory. The evaluation process is frequently called a bronchial challenge or bronchial provocative breathing test, and it uses a stimulant to provoke airway changes. A number of stimuli are used and have been divided into two groups: direct and indirect agents.

Direct stimulants provoke airway constriction by acting directly on the receptors on bronchial smooth muscle, bronchial vascular endothelial cells, and mucus-producing cells. Direct stimulants include methacholine, histamine, carbachol, and acetylcholine.

Indirect stimulants provoke airway constriction indirectly by releasing a number of mediators from inflammatory cells within the airway. These mediators then stimulate specific receptors on bronchial smooth muscle. Indirect stimulants include mannitol, adenosine, specific allergens, exercise, and hypertonic and hypotonic aerosols.

This chapter focuses on the use of aerosolized methacholine because it is the most commonly used direct agent, has standardized procedures, is relatively easy to perform, and is believed to be useful and safe. In addition, there is a discussion on the use of the indirect agent dry-powder mannitol because it has become more widely used and reasonably well standardized. This chapter provides a practical reference guide for those performing or setting up inhaled bronchial provocation tests and for those learning these procedures for the first time.
CHAPTER 8 Bronchial Challenge Testing with Pharmacological Agents

Methacholine Challenge Test

Indications for Methacholine Challenge Test

The most common indication for performing methacholine bronchial challenges is to diagnose hyperresponsive airways when other methods, such as spirometry before and after bronchodilator, have not been helpful. Spirometry is not always a good predictor of hyperresponsiveness because some patients demonstrate normal baseline pulmonary function despite complaints of tightness, wheezing, cough, and little or no response to a bronchodilator.2-4

Other patients demonstrate spirometric improvement after use of a bronchodilator or have diurnal variation in peak expiratory flow rate. In this group, methacholine challenges are used to confirm a diagnosis of asthma. However, these challenges will not discriminate between asthma and chronic obstructive pulmonary disease (COPD) (i.e., irreversible obstructive lung disease such as emphysema) because COPD patients can also demonstrate hyperresponsiveness.5,6

Methacholine challenges are also useful in evaluating the effects of occupational and environmental exposures, assessing the severity of asthma, and assessing the response to therapy.7 The use of serial methacholine challenges can be useful in monitoring patients and in research trials.8

Contraindications

There are some contraindications that should be evaluated because of patient safety or because they may compromise the quality and interpretation of the test.7,8 These include the following:

- Severe airflow obstruction (FEV₁ less than 50% predicted or 1.0 liter)
- Recent myocardial infarction or stroke within 3 months
- Known aortic aneurysm
- Inability to perform the procedures
- Uncontrolled hypertension
- Upper respiratory tract infection within 2 weeks

The patient must be able to perform acceptable and repeatable forced spirometry if FEV₁ is the primary outcome measure. In some cases, the FEV₁ values decrease just from performing the spirometric maneuvers (i.e., spirometry-induced bronchoconstriction). This issue may warrant cancellation or postponement. Patients who cannot perform acceptable spirometry in the prechallenge testing should be cancelled or tested using another method of assessment (e.g., airway resistance). Check with the ordering physician before cancelling the challenge.

Methacholine is sold as Provocholine (Methapharm Inc., Brantford, Ontario, Canada), and the product information sheet states: “administration of methacholine to patients with epilepsy, cardiovascular disease accompanied by bradycardia, vagotonia, peptic ulcer disease, thyroid disease, urinary tract obstruction, or other conditions that could be adversely affected by a cholinergic agent should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.” There have been no studies to evaluate fetal harm, carcinogenic or mutagenic potential, or its effect on fertility. In addition, the safety and efficacy of Provocholine has not been established in children younger than age 5 years.
**Methacholine Challenge Test**

**Methacholine Chloride**

Methacholine chloride is an analogue of acetylcholine. Bronchial smooth muscle, which contains a considerable amount of parasympathetic (cholinergic) innervation, constricts when the vagus nerve is stimulated, and acetylcholine is released from nerve endings. When methacholine chloride solutions are inhaled, patients with asthma develop bronchoconstriction with lower concentrations than nonasthmatics.

The Provocoline brand of methacholine, which is approved for human use by the Food and Drug Administration (FDA), is supplied in sealed 20 mL amber vials containing 100 mg of methacholine chloride. Provocoline should be reconstituted using a diluent of sterile 0.9% sodium chloride solution containing 0.4% phenol as a preservative. Provocoline powder should be stored at room temperature before being reconstituted, and the solutions should be refrigerated after being reconstituted.

According to the manufacturer, Provocoline powder is stable for 2 years when stored at 59° F to 80° F (15° C to 30° C), and after it is reconstituted, the solutions are stable for up to 2 weeks when stored at 36° F to 46° F (2° C to 8° C). The manufacturer recommends discarding low concentrations of Provocoline (i.e., ≤ 0.025 mg/mL) after dilution and use. Freezing the solutions does not affect their stability. A shelf life for methacholine solutions of at least 4 months has been reported, although these reports were published prior to FDA approval of Provocoline.

**Preparing the Solutions**

Although the preparation of Provocoline solutions is relatively easy, it should be done by a pharmacist or well-trained individual. The dry powder is reconstituted to solution using various amounts of diluent to achieve varying concentrations in a series of small vials. Each vial of solution should be clearly labeled with the concentration of the solution, date prepared, date of expiration, and identification of the individual who prepared the solutions. It is helpful to arrange all the labeled vials in a tray in order of increasing concentration.

There are three different recommended dosing schedules, and the dilution scheme varies depending on which one you use. The three dosing schedules and dilution schemes are: (a) Provocoline package insert (Table 8.1), (b) ATS guideline twofold scheme (Table 8.2), and (c) ATS Guideline fourfold scheme (Table 8.3).

**Table 8.1**

<table>
<thead>
<tr>
<th>Take</th>
<th>Add diluent</th>
<th>To get</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg Provocoline</td>
<td>4 mL</td>
<td>25 mg/mL</td>
</tr>
<tr>
<td>1 mL of 25 mg/mL</td>
<td>1.5 mL</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>1 mL of 10 mg/mL</td>
<td>9 mL</td>
<td>2.5 mg/mL</td>
</tr>
<tr>
<td>1 mL of 2.5 mg/mL</td>
<td>9 mL</td>
<td>0.25 mg/mL</td>
</tr>
<tr>
<td>1 mL of 0.25 mg/mL</td>
<td>9 mL</td>
<td>0.025 mg/mL</td>
</tr>
</tbody>
</table>
Table 8.2

Method for Preparing Provocholine Dilutions Based on Twofold ATS Guideline Scheme

<table>
<thead>
<tr>
<th>Take</th>
<th>Add diluent</th>
<th>To get</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg Provocholine</td>
<td>6.25 mL</td>
<td>16 mg/mL</td>
</tr>
<tr>
<td>3 mL of 16 mg/mL</td>
<td>9 mL</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>3 mL of 4 mg/mL</td>
<td>9 mL</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>3 mL of 1 mg/mL</td>
<td>9 mL</td>
<td>0.25 mg/mL</td>
</tr>
<tr>
<td>3 mL of 0.25 mg/mL</td>
<td>9 mL</td>
<td>0.0625 mg/mL</td>
</tr>
</tbody>
</table>


Table 8.3

Method for Preparing Provocholine Dilutions Based on Fourfold ATS Guideline Scheme

<table>
<thead>
<tr>
<th>Take</th>
<th>Add diluent</th>
<th>To get</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg Provocholine</td>
<td>6.25 mL</td>
<td>16 mg/mL</td>
</tr>
<tr>
<td>3 mL of 16 mg/mL</td>
<td>3 mL</td>
<td>8 mg/mL</td>
</tr>
<tr>
<td>3 mL of 8 mg/mL</td>
<td>3 mL</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>3 mL of 4 mg/mL</td>
<td>3 mL</td>
<td>2 mg/mL</td>
</tr>
<tr>
<td>3 mL of 2 mg/mL</td>
<td>3 mL</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>3 mL of 1 mg/mL</td>
<td>3 mL</td>
<td>0.5 mg/mL</td>
</tr>
<tr>
<td>3 mL of 0.5 mg/mL</td>
<td>3 mL</td>
<td>0.25 mg/mL</td>
</tr>
<tr>
<td>3 mL of 0.25 mg/mL</td>
<td>3 mL</td>
<td>0.125 mg/mL</td>
</tr>
<tr>
<td>3 mL of 0.125 mg/mL</td>
<td>3 mL</td>
<td>0.0625 mg/mL</td>
</tr>
<tr>
<td>3 mL of 0.0625 mg/mL</td>
<td>3 mL</td>
<td>0.031 mg/mL</td>
</tr>
</tbody>
</table>


After the solutions have been prepared they should be stored in a refrigerator. The solutions should be allowed to warm to room temperature before testing begins.

Aerosol Delivery Variables

Transferring the methacholine solution from the nebulizer to the airway is an important and deceptively complex step. A number of factors and variables affect the amount of challenge material that reaches the mouth and the airway’s smooth muscles.
The amount reaching the mouth from the nebulizer depends on the following:

- Nebulizer output
- Particle size
- Amount and type of tubing between nebulizer and mouth
- Continuous versus intermittent aerosol
- Amount of liquid in nebulizer

The amount reaching the smooth muscles of the airway from the mouth depends on the previously listed factors and on the following:

- Inspiratory flow rate
- Lung volume at beginning of inspiration
- Breathing pattern
- Volume inhaled
- Breath-hold time

This chapter will not discuss the issues surrounding all these factors; however, one of the most important factors, nebulizer output, deserves some discussion. Various brands of nebulizers have a wide range of output at the same flow rate, and the output of a particular nebulizer varies directly with the powering flow rate (Figure 8.1). A study of the reproducibility of nebulizer output has shown the coefficient of variation to be 24% for numerous nebulizers of the same brand and 10% for repeated measurements of the same nebulizer.

Select a high-quality nebulizer with a consistent output that can generate aerosols with a particle mass median diameter (MMD) between 1.0 and 3.6 µm. Use the same nebulizer throughout any one challenge, throwing out excess agent between doses. Perform repeated measurements (i.e., on different days) on the same patient using the same nebulizer, if possible. If you use more than one nebulizer to test the same patient, measure the nebulizer output to ensure consistency.

The simplest way to measure the nebulizer output is to measure weight loss from the nebulizer at various flow levels. To do so, fill the nebulizer with a specific volume of saline or distilled water (e.g., 3 mL) and weigh it to an accuracy of 1.0 mg. Apply a known level of airflow to the filled nebulizer using a calibrated pressure-compensated flow meter. Continue the nebulization for a specific interval (e.g., 2 or 3 minutes). Then reweigh the nebulizer and divide the change in weight by the number of minutes. You can repeat this process at various flow rates and create a graph of nebulizer output (i.e., weight loss) in mL/min versus airflow (assume that 1 mL of water or saline equals 1,000 mg).

You will use a slightly different approach if you are using a dosimeter to power the nebulizer. The dosimeter should be properly powered (e.g., 20 psi) and set (e.g., opening time of 0.6 seconds). First, prime the nebulizer by actuating the dosimeter two or three times. Then weigh the filled nebulizer to an accuracy of 0.5 mg. Actuate the nebulizer a specific number of times (e.g., 20) manually or by applying negative pressure through a syringe (e.g., 3-liter calibration syringe) attached to the mouthpiece. Then reweigh the nebulizer, and divide by the number of actuations to determine the output per dosimeter actuation (e.g., 0.009 mL/breath).
In summary, remember that nebulizer output varies among different brands of nebulizers and even among different nebulizers of the same brand. Measure the output regularly, and clean reusable nebulizers properly after each use. It is probably best to use disposable nebulizers and thus not have to deal with the cleaning issue, but with proper cleaning and care the output for reusable nebulizers can remain relatively constant over many years.14

Aerosol Delivery Techniques

The two most widely used and accepted methods of delivery are: (a) the 2-minute tidal breathing method (continuous aerosol generation), and (b) the 5-breath method (intermittent aerosol generation). Whether these two methods produce similar results is controversial. A number of older publications examined comparability using methacholine and/or histamine and found no
significant differences between the two methods. More recently, Wubbel and coworkers found no significant difference in results in 12 asthmatic subjects. However, Cockcroft, Allen, and coworkers reported that the 2-minute tidal breathing method exposes the patient to twice as much aerosol at each concentration and produces twice the response. Thus, there could be a large number of false-negative results when using the 5-breath dosimeter method.

Prieto and coworkers also reported that the tidal breathing method produces PC_{20} values significantly lower than the 5-breath dosimeter method.

While this controversy continues, new guidelines will hopefully provide more definitive recommendations. Until such time, these two methods are the mainstay, and both will be presented here.

Two-Minute Tidal Breathing Method
In 1977, Cockcroft and coworkers described a 2-minute tidal breathing technique that used a Wright nebulizer (a low-output nebulizer) for continuous aerosol generation. Breathing quietly, the patient breathes the aerosol from a face mask held over the mouth and nose (with a nose clip) for 2 minutes. A mouthpiece can be used instead of a face mask.

The output of the Wright nebulizer was reported in the 1970s to be approximately 0.13 to 0.16 mL/min when powered at a flow rate of 7 to 8 liters/min. By contrast, the DeVilbiss 646 nebulizer (DeVilbiss Healthcare Inc., Somerset, Pa.) has an output of approximately 0.4 to 0.5 mL/min when powered at the same flow rate. Because the Wright nebulizer is obsolete and difficult to obtain, one can use any good-quality nebulizer (i.e., one with appropriate particle size and reproducible and measurable output) for this 2-minute tidal breathing technique, but the powering flow rate would likely be lower (e.g., 4 to 5 liters/min) than needed for the Wright nebulizer to produce the desired 0.13 to 0.16 mL/min output.

Five-Breath Method
The other widely used delivery technique (5-breath method), recommended by Chai and coworkers, has the patient take five consecutive deep breaths from functional residual capacity (FRC) to total lung capacity (TLC) using a dosimeter (described later and shown in Figure 8.2). Inspiration should be prolonged (i.e., 1 to 5 seconds) with a short breath hold of approximately 2 to 5 seconds.

One concern of the 5-breath method is the bronchodilating and bronchoprotecting phenomena of maximum inhalations to TLC. Todd and coworkers reported lower PC_{20} values when using submaximal inhalations (50% to 60% below TLC) from the dosimeter. Thus, it is possible that deep inhalations to TLC during the inhalation of methacholine may reduce the diagnostic sensitivity of the challenge, and taking submaximal breaths may be a better approach.

A dosimeter is a device used to produce aerosolized solutions. It is essentially an electrical valve system that either uses a sensor to determine inspiratory effort or can be manually activated. When it senses an inspiratory effort or when the user manually activates the device, a solenoid is triggered and compressed air is admitted into the nebulizer for a selected time. Typically, this time is 0.6 seconds, although most dosimeters allow the user to choose other times. Additionally, dosimeters available as of 2010 have such features as breath counters and delay periods (i.e., a time that can be inserted between the beginning of an inspiratory effort and when the nebulization actually begins).
Chapter 8 Bronchial Challenge Testing with Pharmacological Agents

Not all nebulizers can be used with a dosimeter. Dosimeters that are breath actuated must have a port to attach the sensor. The DeVilbiss 646 nebulizer, for example, has two large openings: one for the patient to inhale from and the second to house the sensor.

A variation of the 5-breath method is to inhale the methacholine aerosol in the same manner as previously described but without the dosimeter. Many laboratories cannot justify the cost of a dosimeter (typically $1,500 to $2,000) if challenges are done infrequently. I have used this 5-breath no-dosimeter technique, compared the results with the 5-breath dosimeter technique, and found the two to be similar (i.e., the concentration causing a significant fall in ventilatory function in the same patient is within two doubling doses). When using this method, one recommendation is to use a thumb valve that allows aerosolization only when desired. This avoids wasting solution and continuously nebulizing the challenge agent.

Dosing Schemes

Dosing

As previously mentioned, there are three dosing protocols for methacholine challenges at the time of this writing: (a) Provocholine package insert, (b) ATS guideline twofold scheme, and (c) ATS guideline fourfold scheme. Each has advantages and disadvantages.

The dilution scheme recommended in the Provocholine package insert includes methacholine concentrations of 0.025, 0.25, 2.5, 10, and 25 mg/mL. There is a tenfold increase between the lowest (0.025) and next-lowest concentration (0.25) and a tenfold increase in concentration between the next two concentrations (0.25 and 2.5 mg/mL). Then there is a fivefold increase followed by a 2.5-fold increase in methacholine concentrations. This nonlinear escalation in concentration and the large tenfold increases have raised concerns regarding safety and interpretation.
The ATS guideline recommends a twofold dilution scheme, which is also recommended by the Canadian Thoracic Society. This scheme includes 0.031, 0.0625, 0.125, 0.25, 0.50, 1, 2, 4, 8, and 16 mg/mL. As you can see, the dosing steps are linear. However, there are twice as many steps compared to the Provocholine label recommendation, so it requires much more time to complete the challenge. Consequently, the ATS guideline also included a faster fourfold dilution scheme that includes fewer steps: 0.0625, 0.25, 1, 4, and 16 mg/mL (Table 8.4).

Starting Dose
Regardless of the aerosol generation or delivery method, use a very low starting dose (e.g., 0.03 to 0.15 mg/mL) when testing patients suspected of being hyperresponsive. After the initial dose, increase the concentrations in small steps until the test is positive or the highest dose is reached.

Methods that employ a higher starting dose or use large increments to shorten the length of the test have been reported. However, these methods are not recommended because of safety and interpretation concerns.

One safe, valid, and useful time-shortening method was reported by Hargreave and colleagues. If the patient’s baseline FEV₁ is more than 80% of predicted and does not fall by more than 10% after inhalation of the diluent, and if the patient does not take pulmonary medication, the starting dose can be as high as 1 or 2 mg/mL. If the patient takes bronchodilators, the starting dose should be 0.25 mg/mL, and if the patient takes steroids, the starting dose should be 0.125 mg/mL. In all other instances, the starting concentration should be 0.03 mg/mL.

Table 8.4

| Dosing Schemes Recommended by the ATS and Provocholine package insert |
|-------------------------------------------------|----------------|----------------|
| **ATS twofold** | **ATS fourfold** | **Provocholine package insert** |
| 0.031 | 0.625 | 0.025 |
| 0.0625 | 0.25 | 0.25 |
| 0.125 | 1 | 2.5 |
| 0.25 | 4 | 10 |
| 0.5 | 16 | 25 |
| 1 | | |
| 2 | | |
| 4 | | |
| 8 | | |
| 16 | | |

*Doses are mg/mL.
Use of Diluent Step
As previously noted, the diluent used to reconstitute the methacholine powder is a sterile 0.9% 
sodium chloride solution containing 0.4% phenol as a preservative. Some patients respond to the 
inhalation of the diluent alone with increases or decreases in FEV₁. In some cases these changes 
can be very large.25 Thus, it is best to have the patient inhale the diluent alone as a first step prior 
to inhaling the first dose of methacholine. Although the use of a diluent step is considered unnec-
essary by some, it is recommended and useful for both safety and interpretation concerns.

Patient Preparation
Bronchial challenges require special attention to patient preparation. The more important 
patient preparation factors include withholding medications, recent viral infections, smoking, 
antigen exposures, and suggestion. In addition to patient preparation issues, each laboratory 
should establish other contraindication criteria (e.g., reduced ventilatory function) to determine 
if a challenge should be carried out, cancelled, or postponed.

Medications
Patients should not take drugs that affect airway caliber (e.g., bronchodilators) and are considered 
antagonists to the challenge agents (e.g., anticholinergics) for an interval that equals or exceeds 
their duration of action. Table 8.5 lists drugs that should be withheld for the noted time interval.

Table 8.5
Medications That Should Be Withheld for at Least the Amount of Time Shown Prior to the 
Challenge

<table>
<thead>
<tr>
<th>Drug</th>
<th>Withhold time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled bronchodilators</td>
<td></td>
</tr>
<tr>
<td>Short acting (e.g., albuterol, terbutaline)</td>
<td>8 hours</td>
</tr>
<tr>
<td>Medium acting (e.g., ipratropium bromide)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Long acting (e.g., salmeterol, formoterol)</td>
<td>48 hours</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>1 week</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>48 hours</td>
</tr>
<tr>
<td>Oral bronchodilators</td>
<td></td>
</tr>
<tr>
<td>Short-acting theophylline preparations</td>
<td>12–18 hours</td>
</tr>
<tr>
<td>Long-acting theophylline preparations</td>
<td>24–48 hours</td>
</tr>
<tr>
<td>Leukotriene modifiers (e.g., montelukast [Singulair], zafirlukast [Accolate])</td>
<td>24 hours</td>
</tr>
<tr>
<td>Inhaled steroids (e.g., beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, flunisolide)</td>
<td>Usually not withheld</td>
</tr>
<tr>
<td>Inhaled corticosteroids plus long-acting beta agonists (e.g., Advair)</td>
<td>48 hours</td>
</tr>
</tbody>
</table>
Methacholine Challenge Test

If the medications cannot be withheld for the interval shown, consult with the ordering doctor to determine whether to perform or reschedule the test.

Cola Drinks, Coffee, Tea, Chocolate, and Smoking
The ATS recommends that patients avoid cola drinks, coffee, tea, chocolate, and smoking for at least 2 hours before the challenge.7

Viral Infections
Viral infections can increase airway hyperresponsiveness for as long as 3 weeks and therefore should be considered criteria for postponing the challenge.

Antigen and Occupational Exposures
Antigen and occupational exposures can also increase airway hyperresponsiveness and should be avoided for at least 24 hours.

Suggestion
Both bronchoconstriction and bronchodilatation can be induced by suggestion.26-28 One study found that bronchodilatation or bronchoconstriction can be achieved in 47.5% of asthmatic subjects with appropriate suggestion.28 Because most patients want to know what is involved and some explanation is standard procedure, you can tell them they will be inhaling a mist that could make them feel worse, feel better, or cause no change. However, avoid giving them too much information. Be sure to give anxious patients assurances that they are not going to have an asthma attack and the test is safe and not uncomfortable.

Safety
Methacholine challenge testing has been performed safely and without serious side effects for many years. I am not aware of any reports and have not seen any severe adverse effects in performing or overseeing thousands of these tests. The main adverse effect is acute bronchoconstriction, which can be considerable sometimes; however, the effect is short-lived and is easily reversed by administering an inhaled beta agonist to the patient. Each laboratory or institution should determine the need for written informed consent. An example of a consent form can be found in the 1999 ATS “Guidelines for Methacholine and Exercise Challenge Testing.”7

A physician who is knowledgeable and experienced in the emergency treatment of acute airflow obstruction should be nearby and readily available, but the physician does not need to be present in the laboratory during the test. The technologist performing the test should know therapeutic procedures for severe acute airflow obstruction (e.g., bronchodilator administration and oxygen therapy) and should have current basic cardiopulmonary resuscitation (CPR) certification. Additionally, technologists with asthma or other respiratory problems are at increased risk of developing bronchospasm during testing and should take extra precautions to minimize their exposure to the aerosolized methacholine.7
The room in which the challenge is performed should be well ventilated. Technologists who administer the methacholine challenge should minimize their exposure to the aerosol and stand or sit away from the nebulizer.

**Procedure**
The basic procedure for performing a methacholine challenge is as follows:

1. Assure the equipment and/or instrumentation is working properly and that calibration checks have been performed.
2. Remove the methacholine solutions from the refrigerator at least 30 minutes before testing.
3. Ensure correct patient preparation as described.
4. Explain the procedure to the patient, but avoid giving too much information. Obtain a signed consent form if appropriate.
5. Obtain prechallenge PFTs, including at least the FEV$_1$, and check for any contraindications (i.e., reduced ventilatory function or patient unable to perform acceptable and repeatable spirometry).
6. Aerosolize the diluent (saline) in the same manner that the challenge material will be aerosolized. For example, if using the 5-breath dosimeter technique, five breaths of the diluent should be inhaled through the dosimeter/nebulizer setup.
7. Obtain PFTs approximately 1 to 2 minutes after diluent administration (keep this time constant throughout the test). The diluent must not cause significant bronchoconstriction or bronchodilatation. Therefore, if the FEV$_1$ increases or decreases by 10% to 20%, repeat administration of the diluent and remeasure the PFTs. If after the second diluent the FEV$_1$ decreases so that the total decrease from the prechallenge FEV$_1$ value is more than 20%, the challenge should be stopped. Otherwise, proceed to the next step using the second diluent FEV$_1$ value as the control.
8. Have the patient inhale the lowest or first concentration of methacholine according to the laboratory’s dosing schedule. Wait approximately 1 to 2 minutes and measure the PFTs in the same manner as was done after administration of the diluent. If the change in the FEV$_1$ from the postdiluent PFTs is less than 20%, administer the next strongest concentration. Use the same nebulizer throughout the challenge, and throw out excess agent between concentrations.
9. Continue the challenge until the FEV$_1$ has fallen by at least 20% or until the highest concentration has been inhaled. One recommendation is to confirm the 20% fall in FEV$_1$ by having at least two separate FVC maneuvers to confirm a 20% fall in FEV$_1$.
10. When a 20% or greater fall in FEV$_1$ is confirmed, stop the challenge and administer an aerosolized bronchodilator. Perform spirometry after a short waiting period (e.g., 5–10 minutes) after administering the bronchodilator to ensure that the patient has fully recovered (i.e., FEV$_1$ is at least 90% of the prechallenge value) before leaving the laboratory.
Responses to methacholine challenges can be quantified using several PFTs. Simple spirometry provides measurements of FVC, FEV₁, and FEF₂₅₋₇₅, and the body box provides measurements of airway resistance (Raw) and specific conductance (sGaw). But what measurements are best? How much change in the various parameters is considered meaningful? When are the measurements made? How is change calculated?

**What to Measure**

To recognize hyperresponsive airways, spirometry is usually sufficient and the measurement of FEV₁ is the most reliable. The ATS recommends that the FEV₁ be included in all bronchial challenge test results, even if other values are measured and reported. However, FEV₁ is an effort-dependent parameter, requires a deep breath, and may not be the most sensitive.

In some cases, spirometry may be undesirable in bronchial challenges because the deep breath required can cause bronchoconstriction or bronchodilatation, and multiple spirometric efforts can cause bronchoconstriction. Hence, the measurements Raw and sGaw are sometimes used. Pulse oximetry, transcutaneous monitoring, and monitoring of breath sounds can also be employed, especially in small children who cannot perform spirometry.

**When Measurements are Made**

Knowing when to make measurements and which maneuver, in a group of maneuvers, to report is critical. Methacholine acts quickly. Responses usually reach maximal effect in 1 to 5 minutes, followed by a plateau period, and then the effect spontaneously disappears quickly. The duration of the plateau period is approximately 4 and 12 minutes. There may be increased variability in the PFTs because of this time course. The two most commonly used methods are to report either the lowest FEV₁ value or the highest FEV₁ value at each concentration level. The ATS guideline recommends using the highest FEV₁ value at each dose level because lower FEV₁ values can be easily obtained from poor patient technique (e.g., not taking a deep breath before blasting out hard and fast). It is not uncommon to see the first FEV₁ fall below the 20% threshold, but the second or third FEV₁ fall above the 20% threshold. When this happens, it is best to report the highest FEV₁ and administer the next strongest dose. Whichever method for reporting is used, be consistent throughout a test and from test to test in the same patient.

Typically, the FEV₁ is measured within 1 to 2 minutes after administration of each concentration. The amount of time required to get acceptable and repeatable PFTs varies among patients.

**How to Calculate the Percent Change**

Determine the percent change in the pulmonary function parameters from the diluent value. If more than one diluent is administered, the percent change should be calculated from the final diluent. The following two examples illustrate how to calculate the percent change. The first
example uses the lowest FEV$_1$ value. The second example uses the highest FEV$_1$ value. The FEV$_1$ values from a methacholine challenge for these examples are as follows:

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Maneuver</th>
<th>Maneuver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prechallenge FEV$_1$</td>
<td>Postdiluent FEV$_1$</td>
</tr>
<tr>
<td>1</td>
<td>3.20</td>
<td>3.27</td>
</tr>
<tr>
<td>2</td>
<td>3.24</td>
<td>3.24</td>
</tr>
<tr>
<td>3</td>
<td>3.30</td>
<td>3.29</td>
</tr>
</tbody>
</table>

**Example 1: Calculation of the percent change using lowest FEV$_1$ value**

$$\text{% change} = \frac{\text{Lowest postdiluent FEV$_1$} - \text{Lowest postmethacholine FEV$_1$}}{\text{Lowest postdiluent FEV$_1$}} \times 100$$

$$\text{% change} = \frac{3.24 - 2.94}{3.24} \times 100 \approx 9.3\%$$

**Example 2: Calculation of the percent change using highest FEV$_1$ value**

$$\text{% change} = \frac{\text{Highest postdiluent FEV$_1$} - \text{Highest postmethacholine FEV$_1$}}{\text{Highest postdiluent FEV$_1$}} \times 100$$

$$\text{% change} = \frac{3.29 - 3.03}{3.29} \times 100 \approx 8.0\%$$

If reporting sGaw, report the mean of several maneuvers for each concentration. Then calculate the percent change in the previous manner using the mean value.

**Expressing the Results**

As previously noted, the methacholine challenge test proceeds from the diluent with increasing concentrations of the agonist until there is at least a 20% fall in FEV$_1$ or the highest concentration has been administered. The dose or concentration that corresponded with the 20% fall in FEV$_1$ is referred to as the PC$_{20}$FEV$_1$ (i.e., provocative concentration that caused a 20% fall in FEV$_1$). Other amounts of change in various pulmonary function parameters can also be used. For example, the term PC$_{40}$sGaw refers to the provocative concentration that caused a 40% fall in specific conductance.
Data from a methacholine challenge test consisting of a tabular format and representative flow–volume curves. The tabular format contains the FVC, FEV₁, FEV₁/FVC%, and percent change in FEV₁ for baseline (prechallenge), diluent, and the concentrations of methacholine in mg/mL. The flow–volume curves are from the postdiluent and post-2.5 mg/mL methacholine steps.

<table>
<thead>
<tr>
<th></th>
<th>Prechallenge</th>
<th>Diluent</th>
<th>0.31</th>
<th>0.62</th>
<th>1.25</th>
<th>2.50</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.75</td>
<td>5.71</td>
<td>5.69</td>
<td>5.68</td>
<td>5.24</td>
<td>4.93</td>
<td>5.70</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>4.31</td>
<td>4.29</td>
<td>4.21</td>
<td>4.09</td>
<td>3.79</td>
<td>3.29</td>
<td>4.20</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>75</td>
<td>75</td>
<td>74</td>
<td>72</td>
<td>72</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>% change FEV₁*</td>
<td>–</td>
<td>–</td>
<td>–2</td>
<td>–5</td>
<td>–12</td>
<td>–23</td>
<td></td>
</tr>
</tbody>
</table>

* Percent change from diluent

Rx = postbronchodilator

Figures 8.3 and 8.4 present methacholine test information in tabular and graphic format. Figure 8.3 includes the pulmonary function values for each step in the test, including the postbronchodilator (reversal) step, in a tabular format as well as representative flow–volume curves for diluent and the dose that caused more than a 20% fall in FEV₁.

Figure 8.4 displays two ways of graphically displaying the challenge. Figure 8.4A plots the percent change in FEV₁ on the y axis and noncumulative log dose in mg/mL on the x axis. Figure 8.4B plots the percent change in FEV₁ on the y axis and the dose administered in mg/mL on the x axis.
Figure 8.4

Graphic representation of methacholine challenge data presented in Figure 8.3. A. The percent change in FEV₁ is plotted against the noncumulative log dose in mg/mL. B. The percent change in FEV₁ is plotted against the dose in mg/mL.
Methacholine Challenge Test

The calculation of the provocative concentration is done by linear interpolation. Many pulmonary function testing instruments have software that calculates this automatically. However, the process is relatively simple if done manually, as demonstrated using data in Table 8.6.

The calculation of PC_{20 FEV1} is as follows. Using the linear interpolation formula of:

\[
\frac{X - X_1}{Y - Y_1} = \frac{X_2 - X_1}{Y_2 - Y_1}
\]

where

- \( X = PC_{20 FEV1} \)
- \( X_1 = \) Concentration preceding the concentration that caused a greater than 20% fall
- \( X_2 = \) Concentration that caused a greater than 20% fall
- \( Y = 80\% \) of postdiluent FEV1
- \( Y_1 = \) FEV1 at concentration preceding the concentration that caused a greater than 20% fall
- \( Y_2 = \) FEV1 at concentration that caused a greater than 20% fall

The logarithm of the concentrations is used, thus simplifying:

\[
\log X = \log X_1 + \frac{(Y - Y_1) (\log X_2 - \log X_1)}{(Y_2 - Y_1)}
\]

\[
\log PC_{20 FEV1} = \log 1.25 + \frac{(3.43 - 3.79)(\log 2.5 - \log 1.25)}{(3.29 - 3.79)}
\]

\[
\log PC_{20 FEV1} = 0.097 + \frac{(-0.36)(0.398 - 0.097)}{-0.50}
\]

Table 8.6

Methacholine Challenge Test Example

<table>
<thead>
<tr>
<th></th>
<th>Prechallenge</th>
<th>0.31 mg/mL</th>
<th>0.62 mg/mL</th>
<th>1.25 mg/mL</th>
<th>2.50 mg/mL</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.75</td>
<td>5.71</td>
<td>5.69</td>
<td>5.68</td>
<td>5.24</td>
<td>4.93</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.31</td>
<td>4.29</td>
<td>4.21</td>
<td>4.09</td>
<td>3.79</td>
<td>3.29</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>75</td>
<td>75</td>
<td>74</td>
<td>72</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>% change</td>
<td>—</td>
<td>—</td>
<td>-2</td>
<td>-5</td>
<td>-12</td>
<td>-23</td>
</tr>
</tbody>
</table>

* Percent change from diluent

Rx = postbronchodilator
There is some discussion in the literature regarding a more detailed analysis of the dose–response curves. Essentially this discussion focuses on the position and slope of the dose–response curve in defining sensitivity and reactivity. However, expressing the results of bronchial challenge tests as the provocative concentration and displaying the dose-response curve (Figure 8.5) is usually adequate for clinical questions.

If the FEV₁ does not fall by at least 20% after the highest concentration of methacholine (e.g., 16 mg/mL), then the PC₂₀ should be reported as greater than 16 mg/mL. If the FEV₁ falls by more than 20% after diluent, a PC₂₀ value is not reported and comments on the outcome should be included (e.g., FEV₁ decreased by more than 20% after diluent administration and methacholine was not administered).

**Basic Elements of Interpretation**

The reaction of normal populations to methacholine is somewhat variable. This is due in part to the fact that uniform standardization of methodology has not been achieved. However,

---

**Figure 8.5**

Example of dose–response curve for FEV₁. A 20% or greater fall in FEV₁ is considered meaningful, and a dashed line extends from –20% on the y axis to the line connecting the change in FEV₁ and intersects it at point A, from which a vertical line (PC₂₀FEV₁) points to the exact concentration on the x axis.
in the most commonly used techniques, which were described earlier, the range for the lower limit of normal for $PC_{20FEV1}$ is 4 to 16 mg/mL. Commonly, the dividing line between hyperresponsive and nonhyperresponsive airways is 8 mg/mL, with a gray zone of 4 to 16 mg/mL.24

The ATS guideline7 provides an interpretation scheme and categorization of bronchial responsiveness as shown in Table 8.7.

Hargreave and colleagues used the guidelines shown in Table 8.8 for stratifying hyperresponsiveness and describing the severity of the reaction.38

**Table 8.7**

ATS Interpretation Scheme and Categorization of Bronchial Responsiveness

<table>
<thead>
<tr>
<th>$PC_{20FEV1}$ (mg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>Moderate to severe bronchial hyperresponsiveness</td>
</tr>
<tr>
<td>1.0 to 4.0</td>
<td>Mild bronchial hyperresponsiveness</td>
</tr>
<tr>
<td>4.0 to 16</td>
<td>Borderline</td>
</tr>
<tr>
<td>&gt; 16</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Table 8.8**

$PC_{20}$ FEV$_1$ Values and Severity Classifications

<table>
<thead>
<tr>
<th>$PC_{20}$FEV$_1$ (mg/mL)</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03–0.124</td>
<td>Severe</td>
</tr>
<tr>
<td>0.125–1.99</td>
<td>Moderate</td>
</tr>
<tr>
<td>2.00–7.99</td>
<td>Mild</td>
</tr>
<tr>
<td>Above 8.00</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Mannitol is a well-known substance that is regarded as safe to inhale. The use of a dry powder formulation of mannitol as a bronchial challenge agent was first described by Anderson and colleagues39 in the late 1990s. Although it is a relatively new agent, mannitol is quickly gaining popularity and standardization worldwide.

Mannitol challenges have been found useful in identifying asthmatic patients responsive to hypertonic saline, eucapnic hyperventilation, and exercise.40 Indirect agents, such as mannitol,
are very sensitive for clinically current asthma and correlate better with airway inflammation of asthma. Thus, mannitol is often used as a challenge agent in monitoring disease activity and the assessment of anti-inflammatory therapy clinically and in research trials.41

Contraindications

Mannitol challenges should not be performed in those with known hypersensitivity to mannitol. In addition, there are some contraindications and precautions that should be evaluated because of patient safety or because they may compromise the quality and interpretation of the test.7,8 The contraindications include the following:

• Myocardial infarction or stroke within 6 months
• Known aortic or cerebral aneurysm
• Inability to perform the procedures
• Uncontrolled hypertension

A list of precautions (or relative contraindications) to consider includes the following:

• Airflow obstruction; FEV₁ less than 70% predicted according to Aridol package insert
• Upper respiratory tract infection within 2 weeks
• Recent abdominal or thoracic surgery
• Spirometry-induced bronchoconstriction

Mannitol is sold as Aridol (Pharmaxis Ltd., Frenchs Forest, New South Wales, Australia). The product information sheet states that animal reproduction or carcinogenicity studies have not been carried out with inhaled mannitol, and it should not be given to pregnant woman. It is not known if mannitol is excreted in human milk; therefore, caution should be exercised when mannitol is administered to breastfeeding women. The effect of inhaled mannitol on fertility has not been investigated.

According to the product insert, Aridol should not be used in children younger than age 6 years, but only because of their possible inability to perform acceptable and repeatable spirometry. From a safety standpoint, adverse events in children are similar to those seen in adults.

Mannitol

Mannitol is a naturally occurring sugar hexahydric alcohol found in most vegetables. The formulation prepared for bronchial challenges is a white crystalline powder. It is the only ingredient in the contents of Aridol gelatin capsules. The capsules are color coded for each dose of 5, 10, 20, and 40 mg. Also included is a 0 mg clear capsule. Aridol is to be administered by inhalation only, and the product should be stored below 25° C.

Dosage and Administration

Aridol is supplied in a kit containing the necessary capsules to complete one challenge along with the inhaler. Up to nine doses (for a total of 635 mg) are used for a mannitol challenge.
and these are shown in Table 8.9. The first dose is a placebo and considered the control from which the percentage change is calculated. The 80 and 160 mg doses are administered in multiples of 40 mg capsules. There should be no time delay between administration of multiple capsules (i.e., one capsule should be followed immediately by the next until the total dose has been inhaled).

### Table 8.9

<table>
<thead>
<tr>
<th>Step number</th>
<th>Dose (mg)</th>
<th>Cumulative dose (mg)</th>
<th>Capsules/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>155</td>
<td>2 × 40 mg</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>315</td>
<td>4 × 40 mg</td>
</tr>
<tr>
<td>8</td>
<td>160</td>
<td>475</td>
<td>4 × 40 mg</td>
</tr>
<tr>
<td>9</td>
<td>160</td>
<td>635</td>
<td>4 × 40 mg</td>
</tr>
</tbody>
</table>

Patient Preparation

Like methacholine challenges, mannitol challenges require special attention to patient preparation. The more important patient preparation factors include withholding medications and caffeinated foods and drinks; having the patient refrain from exercise and smoking; and ruling out recent viral infections.

**Medications**

Patients should not take drugs that affect airway caliber (e.g., bronchodilators) and are anti-inflammatory agents. A list of medications and recommended periods for withholding medications before the mannitol challenge, according to the Aridol package insert, are shown in Table 8.10.

If the medications cannot be withheld for the interval shown, consult the ordering doctor to determine whether to perform or reschedule the test.

**Cola Drinks, Coffee, Tea, Chocolate**

The Aridol package insert states that patients should not ingest significant amounts of coffee, tea, cola drinks, chocolate, or other foods containing caffeine on the day of the test. Caffeine is a weak bronchodilator and may decrease bronchial hyperresponsiveness.
Patients should not smoke for at least 6 hours prior to the challenge test.

**Exercise**

Vigorous exercise should be avoided prior to testing on the day of the challenge test.

**Viral Infections**

Viral infections can increase airway hyperresponsiveness for as long as 3 weeks and therefore should be considered criteria for postponing the challenge.

**Safety**

The mannitol challenge should be conducted under the supervision of a physician or other appropriately trained individual who is familiar with all aspects of bronchial challenge testing and treatment of acute bronchoconstriction. However, a physician does not need to be present in the laboratory during the test, but the physician should be nearby and readily available.

Medications to treat bronchoconstriction (e.g., inhaled bronchodilators and oxygen) should be kept in the testing room. Many patients experience occasional coughing during a mannitol challenge. In some patients the coughing may be severe enough to cause a delay of the challenge, or in some cases it may cause the challenge to be discontinued.

**Table 8.10**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Withhold time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled nonsteroidal anti-inflammatory agents</td>
<td></td>
</tr>
<tr>
<td>Sodium cromoglycate, nedocromil</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Inhaled bronchodilators</td>
<td></td>
</tr>
<tr>
<td>Short-acting beta-agonist (e.g., albuterol)</td>
<td>8 hours</td>
</tr>
<tr>
<td>Long-acting beta-agonist (e.g., salmeterol, formoterol)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>72 hours</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>12 hours</td>
</tr>
<tr>
<td>Antihistamines (e.g., cetirizine, fexofenadine)</td>
<td>72 hours</td>
</tr>
<tr>
<td>Theophylline</td>
<td>24 hours</td>
</tr>
<tr>
<td>Leukotriene modifiers (e.g., montelukast, zafi rlukast)</td>
<td>4 days</td>
</tr>
<tr>
<td>Inhaled corticosteroids (e.g., beclomethasone, fl uticasone)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Inhaled corticosteroids plus long-acting beta-agonists (e.g., fluticasone plus salmeterol, beclomethasone plus formoterol)</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
Mannitol Challenge Test

**Procedure**

The general procedure for performing the mannitol challenge test is as follows:

1. Ensure correct patient preparation as described.
2. Explain the procedure but avoid giving too much information. Obtain a signed consent form if appropriate.
3. Obtain prechallenge spirometry and check for any contraindications (i.e., reduced ventilatory function or spirometry-induced worsening).
4. Insert the 0 mg capsule into the inhaler device, and puncture the capsule by slowly depressing the buttons on the side of the device. Pierce the capsule only once (depressing the buttons) because repiercing may cause the capsule to split. Note that the inhaler device is designed to be used for only one challenge and should not be cleaned or reused.
5. Have the patient attach a nose clip and slowly exhale as much as possible, insert the inhaler device into the patient’s mouth, then have the patient take a controlled deep inspiration, hold the breath for 5 seconds, and exhale through the mouth. The inspiration needs to be sufficient to hear the capsule rotate in the inhaler device chamber. Instruct the patient to exhale away from the inhaler to minimize humidity within the device. Some patients will cough from impaction of the powder on the back of the throat if the inspiratory rate is too fast. Thus, it is important that the patient not inhale too fast (i.e., > 90 L/min), and the patient should try to keep the inspiratory flow rate at about 60 L/min.
6. At the end of 60 seconds, perform spirometry. The highest FEV₁ from this step becomes the control value from which the percentage change is calculated.
7. Insert the 5 mg capsule into the inhalation device and repeat steps 5 and 6. Inhalation of Aridol may cause cough and/or dry throat, and the patient can take sips of water during the challenge.
8. Repeat steps 5 and 6 for the dose steps of 10, 20, 40, 80, 160, 160, and 160 mg (total of 635 mg) or until a positive response has been observed. The highest FEV₁ from each dose step should be reported. A positive response is defined as one of the following:
   a. a 15% fall in FEV₁ from the control (0 mg dose), or
   b. a 10% fall between consecutive doses

   The challenge test is time critical, and there should be minimal delay between FEV₁ measurement and the next dose so the osmotic effect in the airway is cumulative.
9. Administer an aerosolized bronchodilator after a positive response has been obtained. Perform spirometry after administering the bronchodilator to ensure that the patient has fully recovered (i.e., FEV₁ is at least 90% to 95% of the prechallenge value) before leaving the laboratory.

**Pulmonary Function Tests**

Responses to mannitol challenges are quantified using spirometry and the measurement of FEV₁. The highest FEV₁ value obtained at each dose step should be reported. Because the challenge is time critical, Raw and sGaw are not usually included.
CHAPTER 8 Bronchial Challenge Testing with Pharmacological Agents

How to Calculate the Percent Change

Positive responses are determined by a change in FEV₁ from the post 0 mg dose, or if there is a 10% incremental fall in FEV₁ between consecutive doses. The following example illustrates how to calculate the percent change for mannitol challenges. The FEV₁ values from a mannitol challenge are shown in Table 8.11.

The percent change for the 5 mg dose step is calculated as follows:

\[
\text{% change} = \frac{\text{Post 0 mg } \text{FEV}_1 - \text{Post 5 mg } \text{FEV}_1}{\text{Post 0 mg } \text{FEV}_1} \times 100
\]

\[
\text{% change} = \frac{3.29 - 3.03}{3.29} \times 100 = -7.9\%
\]

The percent change for the 20 mg dose step is calculated as follows:

\[
\text{% change} = \times \frac{\text{Post 0 mg } \text{FEV}_1 - \text{Post 20 mg } \text{FEV}_1}{\text{Post 0 mg } \text{FEV}_1} \times 100
\]

\[
\text{% change} = \frac{3.29 - 2.77}{3.29} \times 100 = -15.8\%
\]

What Is a Positive Response?

A positive response for the mannitol challenge occurs with either of the following: (a) a 15% fall in FEV₁ from the control step (0 mg dose) at a cumulative dose of 635 mg or less, or (b) a 10% incremental fall in FEV₁ between consecutive doses.
**What Is a Negative Response?**

A mannitol challenge is considered negative when a cumulative dose of 635 mg has been administered and the patient’s FEV₁ has not fallen by 15% or more from the control step.

**Expressing the Results**

As previously noted, the mannitol challenge test proceeds from the 0 mg dose step with increasing concentrations of mannitol until there is at least a 15% fall in FEV₁, an incremental fall in FEV₁ of at least 10% between consecutive doses, or the highest dose (third 160 mg dose or total cumulative dose of 635 mg) has been administered.

The response is expressed as the cumulative dose and a provocative dose causing a 15% reduction in FEV₁ (PD₁₅) value is reported, if measured. If a PD₁₅ is not measured, report the maximum fall in FEV₁ divided by the cumulative dose of mannitol response–dose ratio, expressed as percent change in FEV₁ per milligram.

The PD₁₅ is determined by linear interpolation in a similar manner as used to calculate PC₂₀ for the methacholine challenge. The following example calculates the PD₁₅ for a mannitol challenge in tabular and graphical format (Table 8.12 and Figure 8.6).

**Table 8.12**

<table>
<thead>
<tr>
<th>Step</th>
<th>FEV₁ (L)</th>
<th>% change from 0 mg</th>
<th>Total dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge</td>
<td>3.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post 0 mg</td>
<td>2.97</td>
<td>+1.0</td>
<td>0</td>
</tr>
<tr>
<td>Post 5 mg mannitol</td>
<td>3.00</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Post 10 mg mannitol</td>
<td>3.01</td>
<td>+1.4</td>
<td>15</td>
</tr>
<tr>
<td>Post 20 mg mannitol</td>
<td>2.84</td>
<td>−4.4</td>
<td>35</td>
</tr>
<tr>
<td>Post 40 mg mannitol</td>
<td>2.70</td>
<td>−9.1</td>
<td>75</td>
</tr>
<tr>
<td>Post 80 mg mannitol</td>
<td>2.65</td>
<td>−10.8</td>
<td>155</td>
</tr>
<tr>
<td>Post 160 mg mannitol</td>
<td>2.60</td>
<td>−12.5</td>
<td>315</td>
</tr>
<tr>
<td>Post 160 mg mannitol</td>
<td>2.55</td>
<td>−14.1</td>
<td>475</td>
</tr>
<tr>
<td>Post 160 mg mannitol</td>
<td>2.40</td>
<td>−19.2</td>
<td>635</td>
</tr>
<tr>
<td>Postbrnocholitator</td>
<td>2.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Target FEV₁ for 15% fall = 2.52
Using the linear interpolation formula of:

\[
\frac{X - X_1}{Y - Y_1} = \frac{X_2 - X_1}{Y_2 - Y_1}
\]

where

- \( X_1 \) = \( PD_{15} \) FEV\(_1\)
- \( X_2 \) = Total dose preceding the dose that caused a 15% fall
- \( Y \) = 85% of post 0 mg FEV\(_1\)
- \( Y_1 \) = FEV\(_1\) of dose preceding the dose that caused 15% fall
- \( Y_2 \) = FEV\(_1\) of dose that caused 15% fall

The logarithm of the doses is used, thus simplifying:

\[
\log X = \log X_1 + \frac{(Y - Y_1) (\log X_2 - \log X_1)}{Y_2 - Y_1}
\]
Case Presentation

Case 8.1

A 32-year-old woman who is an avid runner underwent a methacholine challenge because she noticed wheezing and shortness of breath after some recent runs. She was not taking any medication and had no history of pulmonary problems. After performing the prechallenge PFTs, the diluent saline was administered; the results are shown in Table 8.13 and Figure 8.7.

Table 8.13

Results of Spirometry and Specific Conductance (sGaw) from Methacholine Challenge Showing Percent Change from the Postdiluent Values

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>% Change*</th>
<th>sGaw</th>
<th>% Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge</td>
<td>3.21</td>
<td>0.25</td>
<td>0.25</td>
<td>0.24</td>
</tr>
<tr>
<td>Diluent</td>
<td>3.19</td>
<td>0.24</td>
<td>0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>0.03125 mg/mL</td>
<td>3.17</td>
<td>0</td>
<td>0.23</td>
<td>−4</td>
</tr>
<tr>
<td>0.0625 mg/mL</td>
<td>3.22</td>
<td>0</td>
<td>0.24</td>
<td>0</td>
</tr>
<tr>
<td>0.125 mg/mL</td>
<td>3.12</td>
<td>−2</td>
<td>0.23</td>
<td>−4</td>
</tr>
<tr>
<td>0.25 mg/mL</td>
<td>3.15</td>
<td>−1</td>
<td>0.24</td>
<td>0</td>
</tr>
<tr>
<td>0.5 mg/mL</td>
<td>3.10</td>
<td>−3</td>
<td>0.24</td>
<td>0</td>
</tr>
<tr>
<td>1 mg/mL</td>
<td>3.20</td>
<td>0</td>
<td>0.23</td>
<td>−4</td>
</tr>
<tr>
<td>2 mg/mL</td>
<td>3.13</td>
<td>−2</td>
<td>0.18</td>
<td>−25</td>
</tr>
<tr>
<td>4 mg/mL</td>
<td>2.90</td>
<td>−9</td>
<td>0.15</td>
<td>−38</td>
</tr>
<tr>
<td>8 mg/mL</td>
<td>2.43</td>
<td>−24</td>
<td>0.11</td>
<td>−54</td>
</tr>
<tr>
<td>Recovery</td>
<td>3.30</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percent change is calculated from postdiluent value.
Question

1. How does one interpret the methacholine challenge?

Answer and Discussion

To interpret the challenge one needs to calculate the provocative concentration that caused a 20% fall in FEV₁. The PC<sub>20</sub>FEV₁ is calculated as follows:

\[
\log X = \log X_1 + \frac{(Y - Y_1) (\log X_2 - \log X_1)}{(Y_2 - Y_1)}
\]

where:
- \(\log X\) = Logarithm of the PC<sub>20</sub>FEV₁
- \(\log X_1\) = Logarithm of the dose preceding the dose that caused a greater than 20% fall
- \(Y\) = 80% of postdiluent FEV₁
- \(Y_1\) = FEV₁ at concentration preceding the concentration that caused a greater than 20% fall
- \(Y_2\) = FEV₁ of concentration that caused a greater than 20% fall
- \(\log X_2\) = Logarithm of the dose that caused a greater than 20% fall
The FEV\textsubscript{1} fell by exactly 20% between the 4 mg/mL and 8 mg/mL concentrations of methacholine, and the exact PC\textsubscript{20}FEV\textsubscript{1} was 6.33 mg/mL, as calculated in the previous question. This result would most likely be interpreted as borderline and/or mild bronchial hyperresponsiveness. The usual cutoff to separate patients with asthma from healthy individuals is 8 mg/mL, although some use 16 mg/mL. The patient in this case was clearly below either of these cutoff points and thus has a good probability of having some bronchial hyperresponsiveness.

The sGaw fell by more than 50%, and this is consistent with the fall in FEV\textsubscript{1}. The PC\textsubscript{40}sGaw was also below these cutoff points. However, no guidelines exist on a good cutoff point for determining bronchial hyperresponsiveness when using sGaw. It may be best to use both the change in FEV\textsubscript{1} and change in sGaw as a more sensitive indicator of bronchial responsiveness compared to using only one parameter.

**Self-Assessment Questions**

1. The following results are from a methacholine challenge:

<table>
<thead>
<tr>
<th>Step</th>
<th>FEV\textsubscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge</td>
<td>3.10</td>
</tr>
<tr>
<td>Diluent</td>
<td>3.02</td>
</tr>
<tr>
<td>0.031 mg/mL</td>
<td>2.93</td>
</tr>
<tr>
<td>0.0625 mg/mL</td>
<td>2.81</td>
</tr>
<tr>
<td>0.125 mg/mL</td>
<td>2.79</td>
</tr>
<tr>
<td>0.25 mg/mL</td>
<td>2.48</td>
</tr>
<tr>
<td>0.5 mg/mL</td>
<td>2.30</td>
</tr>
</tbody>
</table>

These results are consistent with:

a. Incomplete challenge
b. Positive challenge after the 0.5 mg/mL concentration
c. Positive challenge after the 0.25 mg/mL concentration
d. Negative challenge
2. Which of the following is not an indication for performing a methacholine challenge?
   a. Diagnose hyperresponsive airways
   b. Document the severity of hyperresponsive airways
   c. Test response to a bronchodilator
   d. Assess response to therapy

3. Which of the following is not a factor in the amount of bronchial provocation material reaching the airway?
   a. Nebulizer size
   b. Nebulizer output
   c. Particle size
   d. Inspiratory flow rate

4. All of the following are technical factors affecting the response to bronchial challenge aerosol inhalation except:
   a. Starting lung volume at time of inhalation
   b. Expiratory flow rate
   c. Breath-hold time
   d. Inspiratory flow rate

5. The minimum decrease in FEV₁ that typically qualifies a methacholine challenge as positive is:
   a. 15%
   b. 35%
   c. 10%
   d. 20%

6. A patient’s FEV₁ falls 14% from the prechallenge value after inhalation of the diluent (saline) before a methacholine challenge. You should:
   a. Repeat the FEV₁ after a 10-minute rest.
   b. Repeat the inhalation of diluent.
   c. Cancel the test.
   d. Proceed to the first dose of methacholine.

7. The provocative concentration is calculated from:
   a. Linear interpolation of the log dose
   b. Slope of the dose function
   c. Slope of the percent change over time
   d. The threshold point

8. All of the following are true about the use of mannitol as a bronchial challenge agent except:
   a. It is an indirect agent and correlates well with airway inflammation.
   b. It is a dry powder formulation delivered using a special inhalation device.
   c. There is considerable time allowed between dose steps to measure sGaw.
   d. The percent change is calculated from the 0 mg capsule.
9. The following results are from a methacholine challenge:

<table>
<thead>
<tr>
<th>Step</th>
<th>FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prechallenge</td>
<td>4.55</td>
</tr>
<tr>
<td>Diluent</td>
<td>4.49</td>
</tr>
<tr>
<td>0.0625 mg/mL</td>
<td>4.23</td>
</tr>
<tr>
<td>0.25 mg/mL</td>
<td>4.18</td>
</tr>
<tr>
<td>1 mg/mL</td>
<td>3.82</td>
</tr>
<tr>
<td>4 mg/mL</td>
<td>3.81</td>
</tr>
<tr>
<td>16 mg/mL</td>
<td>3.79</td>
</tr>
</tbody>
</table>

These results are consistent with:

a. A positive methacholine challenge  
b. A normal response  
c. A mildly positive methacholine challenge  
d. An incomplete methacholine challenge

10. All the following are criteria for postponing a bronchial challenge except:

a. Recent viral infection  
b. Aerosolized bronchodilator used within the past 2 hours  
c. Methacholine challenge on previous day  
d. FEV₁ of 1.20 liters

11. Which of the following is recommended by the ATS as the required pulmonary function parameter on bronchial challenge reports?

a. FVC  
b. FEV₁  
c. sGaw  
d. PEFR  
e. All of the above

12. When explaining the bronchial challenge test to a patient, one should:

a. Explain the text in detail to gain patient confidence and cooperation.  
b. Tell the patient that his or her breathing might get worse during the test.  
c. Tell the patient that his or her breathing might get better, get worse, or stay the same.  
d. Tell the patient he or she is going to inhale several types of bronchodilators to measure response.
References


Maximal Inspiratory and Expiratory Pressures

Introduction

The measurement of the maximal inspiratory pressure (\(P_{\text{Imax}}\), sometimes referred to as MIP) and maximal expiratory pressure (\(P_{\text{Emax}}\), sometimes referred to as MEP) assesses the force that respiratory muscles can generate against an occlusion at the mouth. These are static pressures (i.e., measured at no or minimal flow), and they are now a routine procedure in many pulmonary function laboratories.

The primary indication for performing MIP and MEP is to determine the degree of respiratory muscle weakness in patients with neuromuscular disease (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, stroke), obstructive lung disease causing hyperinflation, and unexplained dyspnea. Additionally, the measurement of these pressures can provide valuable information in unexplained reductions in vital capacity and maximal voluntary ventilation, they can be used in weaning patients from mechanical ventilation, and they can provide information about the potential for effective cough and the ability to bring up secretions. This chapter will present a brief look at the relevant physiology, instrumentation used to perform the test, testing technique, and the basic elements of interpretation.
CHAPTER 9 Maximal Inspiratory and Expiratory Pressures

Physiology

The respiratory muscles consist of those that are active during inspiration (inspiratory muscles) and those that remain inactive during quiet breathing but may participate during active breathing, such as during exercise or forced spirometry (expiratory muscles). The respiratory muscles are composed of striated fibers and contract rhythmically and intermittently. The contractile activity can be voluntarily controlled or automatically driven by the respiratory centers.

The most important inspiratory muscle is the diaphragm, which separates the thoracic cavity from the abdominal cavity. When the diaphragm is contracted it moves downward, causing a decrease in pleural pressure and an increase in lung volume.

Other important respiratory muscles include the scalene, intercostals, abdominal wall, and sternocleidomastoid muscles. Other accessory muscles (e.g., pectoralis major and latissimus dorsi) do not ordinarily take an active part in breathing, but they may play a role in hyperventilation and severe exertion.

The MIP test is administered by having the patient attach to the mouthpiece, exhale to residual volume, then inspire as forcefully as possible against an occluded valve (essentially a Mueller maneuver). The measured value is negative (more negative = stronger). This test provides information about the strength of the diaphragm, intercostals, and inspiratory accessory muscles.

The MEP test is administered by having the patient attach to the mouthpiece, inhale as deeply as possible, then expire as forcefully as possible against an occlude valve (essentially a Valsalva maneuver). This test provides information about the strength of the abdominal muscles, intercostals, and other expiratory accessory muscles.

Lower than expected MIP values are seen in patients with neuromuscular disorders, hyperinflation, chest wall injuries, or spinal deformities. Lower than expected MEP values are seen in patients with neuromuscular disorders and emphysema.

Instrumentation

Black and Hyatt developed a simplified instrument that allowed easy determinations of MIP and MEP. The pressures were reported in cm H\textsubscript{2}O and measured by two diaphragm gauges mounted on a metal bar connected to a metal cylinder approximately 15 cm long. The gauges were connected to a pressure tap in the distal end of the cylinder by rigid plastic tubing. One gauge recorded inspiratory pressure, and the other recorded expiratory pressure. The distal end of the cylinder was closed except for a small opening (2 mm diameter) that supposedly prevented facial muscles from producing significant pressures.

As of 2010, manufacturers of pulmonary function equipment offered modules within their testing systems to measure respiratory muscle force, and most incorporate the technique of Black and Hyatt. In addition, there are some stand-alone devices with complimentary software and digital output that measure MIP, MEP, and even sniff nasal inspiratory pressure.

Pressure transducers or gauges used in the instrumentation should have the capability of measuring values to ± 200 to ± 300 cm H\textsubscript{2}O. Flanged mouthpieces are preferred to help gain a better seal.
Calibration of the pressure system should be done every day of testing. Ideally, the pressures can be verified using an oil or water manometer. For quality control, one recommendation is to apply two pressures (e.g., 50 and 200 cm H$_2$O) quarterly to verify range and linearity.

**Testing Technique**

The patient should be sitting. The technologist should instruct the patient on the maneuver, including the need to keep a tight lip seal and to give maximum effort. A tightly-fitting nose clip should always be used. Patients with facial weakness may have problems keeping a tight lip seal and may need some assistance.

For the MIP test, have the patient attach to the mouthpiece and apply the nose clip properly. Instruct the patient to blow out slowly to residual volume, and then inhale against the occluded valve with as much force as possible while keeping the lips sealed tightly around the mouthpiece. The technologist should vigorously coach the patient to suck in hard. The maximum pressure should be maintained for at least 1 second. Obtain at least three maneuvers, and the two highest values should agree within 10%. If the final maneuver has the highest value, obtain additional maneuvers. Allow some time between maneuvers for the patient to rest (e.g., 30 to 60 seconds).

For the MEP test, have the patient attach to the mouthpiece and apply the nose clip properly. Instruct the patient to take a big, deep breath and then exhale against the occluded valve with as much force as possible while keeping the lips sealed tightly around the mouthpiece. The technologist should vigorously coach the patient to blow out hard. Watch the patient carefully to assure there are no leaks. Obtain at least three maneuvers, and the two highest values should agree within 10%. If the final maneuver has the highest value, obtain additional maneuvers. Allow some time between maneuvers for the patient to rest (e.g., 30 to 60 seconds).

As previously mentioned, some patients have difficulty maintaining a good lip seal. This can result in decreased values. Another person can use his or her fingers to secure the patient’s lips, if necessary.

Falsely high MIP values can be obtained when a patient sucks in forcefully with a closed glottis. Similarly, falsely high MEP values can be obtained by pumping the cheeks against a closed glottis. Provide clear instructions and demonstrations, and give appropriate feedback to help obtain accurate results.

**Reporting Results**

The highest value should be reported for both MIP and MEP to the nearest 1 or 5 cm H$_2$O, depending on device resolution. For MIP the highest value is the most negative value.

**Interpretation**

Predicted values for P$_{Imax}$ (MIP) and P$_{Emax}$ (MEP) are available.$^{1,3-7}$ In general, values for MEP and MIP are 65% to 70% lower in women than in men. With aging both MEP and MIP decrease.$^3$
Based on data from Black and Hyatt, the predicted MIP value in healthy men aged 20 to 54 years is $-124 \pm 44$ cm H$_2$O, and the predicted MIP value in healthy women aged 20 to 54 years is $-87 \pm 32$ cm H$_2$O. The predicted MEP value in healthy men aged 20 to 54 years is $233 \pm 84$ cm H$_2$O, and the predicted MEP value in healthy women aged 20 to 54 years is $152 \pm 54$ cm H$_2$O.

MIP and MEP measurements can be helpful in the interpretation of other pulmonary function tests. For example, a low MIP might result in reduced inspiratory flows during the flow–volume loop. A low MEP is often seen in patients with hyperinflation (e.g., emphysema) and might result in decreased expiratory flows. If reduced inspiratory and/or expiratory flows are found, evaluation of maximal inspiratory and expiratory pressures can be helpful.

**Self-Assessment Questions**

1. Which of the following is not a good indication to perform MIPs and MEPs?
   a. Myasthenia gravis
   b. Amyotrophic lateral sclerosis
   c. Pulmonary hypertension
   d. Inability to cough effectively
   e. COPD

2. The respiratory pressures MIPs and MEPs are measured under dynamic conditions (i.e., during airflow).
   a. True
   b. False

3. All of the following are true about MIP except:
   a. The measured value is negative
   b. Provides information about diaphragmatic strength
   c. Provides information about inspiratory accessory muscles
   d. Provides information about abdominal muscles
   e. None of the above

4. Falsely high MIP values can be obtained when a patient sucks in forcefully with a closed glottis.
   a. True
   b. False

5. Patients with facial weakness may have problems performing the MIP and MEP test.
   a. True
   b. False

**References**


Pediatric Pulmonary Function Testing

Introduction

Pediatric pulmonary function testing is unique and considerably more challenging than testing adults. Instrumentation, techniques, and instructions that work for adults may not work for children. Obtaining accurate and reliable data requires the technician to have patience, skill, training, and experience working with children. Often, time-consuming preliminary training and/or instruction is needed to achieve reliable and consistent results. Additionally, the laboratory must be child friendly and located away from areas where painful procedures are done. This chapter presents techniques and practical hints on performing spirometry, lung volumes, airway resistance, and single-breath carbon monoxide diffusing capacity (DL\textsubscript{CO}) in children.

General Considerations

Testing Environment

It is recommended that the testing environment be as child friendly as possible.\cite{1} Many younger patients do not perform the pulmonary function tests well, or they are apprehensive or uncooperative because of distractions in the testing area. Assure that pain-causing instruments...
(e.g., needles and syringes) are out of sight and that there are games, pictures, and videos in clear view. There should also be a fun space for play.

Whether or not the parents should be in the room during testing is a difficult and sensitive issue. Understandably, almost all parents prefer, and often demand, to stay in the testing room with the child. However, some pediatric pulmonary function laboratories find it best to not have the parents in the room because many children perform the test better when they are alone with the technologist. One approach is to explain the test to the parents before taking the child to the testing area. In that explanation, mention that kids often do better without anyone watching them, and suggest that the parents stay in the nearby waiting room and within hearing distance. If the parents insist on being present, you will, of course, have to let them come in. It is definitely easier not to bring the parents into the testing room initially than to ask them to leave after testing has started. An experienced technologist can usually determine what will work best and reassure both the parents and the patient before taking the child to the testing room.

Testing Personnel

The technologist performing the pulmonary function test has a significant impact on the results. Not all pulmonary function technologists are suited for testing children. An ideal technologist for pediatric testing knows how to greet a child and engage in conversation, use expressive body language, use verbal language a child can understand, and be patient, and knows when to stop testing.

Height and Weight

The child’s accurate height, and sometimes weight, are needed to determine reference values. The standing height without shoes should be measured using a calibrated wall-mounted stadiometer, if possible. The weight should be measured using a calibrated electronic scale, if possible, with the child wearing minimal clothing.

The sitting height is sometimes measured and should be done using a sitting stadiometer. Alternatively, the child can be seated on a stool or table that is placed closely against a wall to which a measuring tape is fixed (the knees should be flexed at 90° and flush with the edge of the table or stool).

Working with Children to Get Best Effort and Cooperation

Testing children can be challenging because they can be uncooperative, they have a limited attention span (especially if they are sick), and they are easily distracted. As previously mentioned, it is a critical mistake to test children in an environment where there are lots of distractions and to have nonexperienced personnel perform the testing.

When you first meet the child, introduce yourself and get some conversation going. Express how much you like the child’s really cool T-shirt or shoes. If the child goes to school, ask what grade, and what the name of the child’s teacher or best friend is. Adjust your
position to get close to the same eye level as the child. Mention that you are going to play a blowing game on the computer and how much fun it is going to be. Demonstrate how this blowing game works by blowing on a tissue, party whistle, or pinwheel. Explain the test in words the child can understand, and keep the instructions simple and short. Offer lots of praise with each maneuver.

Children older than 6 years of age can usually perform spirometry testing successfully, and those older than 8 years of age can generally perform lung volumes and DLCO testing successfully. However, they must have the desire, and attitude can be a big problem. Often these kids enjoy performing against others, themselves (i.e., previous maneuvers or testing sessions), or incentive programs on the computer. They do not respond well to criticism, and thus technologists should pay close attention to ensure that comments are enthusiastic and positive. For example, phrases such as “that was great, can you do even better this time?” are better than phrases such as “that wasn’t very good, I know you can do better.”

Children younger than age 6 years present an even greater challenge. Too much coaching (i.e., yelling too loudly) can scare younger children. Use lots of praise after every maneuver. Many attempts or maneuvers may be needed. If the child’s attention span is waning, take a break—color some pictures together (good therapy for the adult too) or take a short walk and get a drink of water or juice.

After the testing is complete (whether it has been successful or unsuccessful), give the child a reward as reinforcement. Younger children like stickers or small toys. Older children will sometimes settle for stickers and small toys but prefer things you sometimes cannot provide (e.g., candy or a chance to play on the computer that runs the spirometer). The point is you want them to look forward to other sessions in the future.

**Spirometry**

**Age Considerations**

Spirometry in children older than 6 years of age is common and often reliable. The 2005 ATS/ERS standardization document provides acceptability, repeatability, and usability recommendations that can generally be applied to children older than 6 years of age. For children 6 years of age or younger, the recommendations in the 2007 ATS/ERS “Pulmonary Function Testing in Preschool Children” document are more appropriate.

A number of recent publications have confirmed that preschool children aged 3 to 6 years have the potential to perform acceptable and repeatable spirometry and peak expiratory flow. For example, Eigen and coworkers evaluated spirometry in healthy children aged 3 to 6 years and found that 82.6% of subjects were successful in generating technically successful flow-volume spirometry results during their first testing session. In that study, the subjects were spirometry naïve, and a highly experienced children’s pulmonary function technologist instructed each child. Although testing in children younger than 6 years of age has been shown to be possible, it can be much more problematic, and some children may have trouble meeting acceptability and repeatability criteria.
Older children and adults are able to exhale for at least 1 second. However, children of preschool age do not always exhale for 1 second, so FEV₁ may not be an accurate measure in this group. As a result, the use of FEV₀.5 and FEV₀.75 have been explored as useful measures.² In some cases and on some spirometers, forced expiratory volumes may not be reported correctly. For example, if the forced expiratory time (FET) is 0.6 seconds, the FEV₀.75 and FEV₁ cannot be reported. However, some spirometers may incorrectly report values for these parameters¹ and have the same value for both. The technologist will have to pay close attention to such issues.

Spirometers

Guidelines on pulmonary function testing in preschool children have been published and include recommendations on spirometer hardware and software.¹ The recommendations for spirometer hardware are similar to those for adults,³ with the exception of instantaneous flow accuracy. For preschool children the device must be capable of measuring instantaneous flow with accuracy within 5%.

Incentive software programs for spirometry have been in existence for many years. These programs instruct and stimulate children in performing the forced expiratory maneuver. The animated software can be clever, with games like blowing out candles or blowing up a balloon. The efficacy of these programs has been studied, and it has been shown they are helpful.⁵,¹¹ It has been recommended that these incentive programs be designed to encourage rapid and prolonged expiration, tidal breathing, and maximal inspiration.¹

Testing

Before any actual data collection takes place, it is important to have a short or extended training period, depending on whether the child has previously performed successful spirometry. During the training period the child should be encouraged to examine and play with the mouthpiece, filter (if applicable), or nose clip. Using pinwheels, party whistles, or even incentive spirometers can be helpful to teach deep inspirations and prolonged expirations.¹ If incentive software is used during testing, this can be demonstrated during the training period to help motivate the child. As the child practices, the difficulty or goal of the incentive software can be increased to assure the maximum score can be achieved or the task can be completed.

FVC maneuvers can be performed with the child standing or sitting. A nose clip should be worn, if possible. Assure the child’s lips are sealed around the mouthpiece. It is critical that the child take a maximal deep breath prior to the FVC maneuver. This should be stressed and practiced in the training session. Testing can be performed using the closed-circuit or open-circuit method (see Chapter 1). The closed-circuit method is best for children because there is less likelihood that air will be lost as the child tries to get the mouthpiece in the mouth while trying to hold his or her breath with full lungs.
The closed-circuit method has the child attach to the mouthpiece with the nose clip in place. The child is asked to breathe quietly for a couple of breaths. Observe the child to assure the mouthpiece is situated properly in the mouth with lips sealed tight. This is very easy for the child to do and provides an opportunity for the child to relax and gain confidence that the test does not hurt. Offer lots of praise and reassure the child that he or she is doing really well. Use short and simple words to encourage the child; for example, “breathe nice and easy, in and out,” or “take slow little breaths in and out.” The level of urgency in the technologist’s voice should be low, with a quiet and gentle tone. This is contrasted with the more animated and louder tone when the child is asked to “blow out all the candles,” or “blast out fast and long.” If the closed-circuit method is not working (e.g., child has a gag reflex), try a different position or the open-circuit method.

At least three FVC maneuvers should be recorded. The number of maneuvers needed to obtain three acceptable FVC maneuvers will vary, and even as many as 10 attempts are not out of the question. The actual limit will vary by patient, but assure that the child does not become exhausted.

Acceptability

Acceptability criteria for preschool children aged 2 to 6 years have been described in a 2007 ATS/ERS guideline for testing preschool children, and acceptability criteria for children aged 7 years and older should follow the 2005 ATS/ERS “Standardization of Spirometry” guideline. The acceptability criteria include the following:

- Rapid rise to peak flow, as shown on flow–volume spirogram
- Back-extrapolation volume
  - 2 to 6 years of age: ≤ 0.080 liter, or < 12.5% of the FVC
  - 7 years of age and older: < 5% of the FVC, or 0.150 liter, whichever is greater
- Smooth expiration
- No evidence of cough in first second or glottis closure
- Satisfactory exhalation
  - 2 to 6 years of age: evidence of a horizontal plateau on volume–time curve
  - 7 years of age and older: at least 3 seconds or a plateau on volume–time curve

Note that many preschool-aged children cannot sustain forced expiration for 1 second, let alone the 3 seconds recommended for children younger than 10 years of age as described in the 2005 ATS/ERS “Standardization of Spirometry” guideline. Thus, the FET should be reported, and other parameters, such as FEV0.5 or FEV0.75, should be used. If expiratory flow ceases at more than 10% of the peak expiratory flow rate, then premature termination can be considered. The 2005 ATS/ERS “Standardization of Spirometry” guideline also includes the concept of a usable curve, which can also be applied to preschool-aged children. A curve can be considered usable if it has a good start and there is no coughing during the first second. Figure 10.1 presents some examples of spirograms with acceptable and unacceptable maneuvers in children.
Repeatability
After at least two acceptable maneuvers have been obtained, the following repeatability criteria should be applied for preschool children (2 to 6 years of age):

- Two highest FVC values are within 0.100 liter or 10% of highest value, whichever is greatest.
- Two highest FEV₁ values are within 0.100 liter or 10% of highest value, whichever is greatest.

Figure 10.1
Examples of flow–volume and volume-time spirometry curves in children. Panel A presents an acceptable maneuver from a 6-year-old boy with asthma. Panel B presents an unacceptable maneuver from a 4-year-old boy with asthma. The maneuver is unacceptable because of early termination or glottic closure. Panel C presents unacceptable results from an 11-year-old girl with uncertain diagnosis. The maneuver is unacceptable because of poor start and technique.
In cases where the child performs several acceptable maneuvers but cannot obtain repeatability, the laboratory should report the results from the single maneuver with highest values and make appropriate comments in the report. If repeatability for children aged 7 years and older should follow the 2005 ATS/ERS “Standardization of Spirometry” guideline:

- Two highest FVC values are within 0.150 liter of each other
- Two highest FEV₁ values are within 0.150 liter of each other

If repeatability in older children is not met, then testing should be continued with eight maneuvers as a reasonable upper limit.

**Reporting Results**

According to the ATS/ERS recommendations for testing preschool children, parameters that should be reported include the following:

- FVC
- FEV₀.₅
- FEV₀.₇₅
- FEV₁
- Repeatability
- Number of maneuvers attempted
- Position for testing (i.e., sitting or standing)
- Whether or not a nose clip was worn
- Back-extrapolated volume
- Forced expiratory time
- Peak expiratory flow rate

**Reference Values**

The most recent recommendations for spirometry reference values in children aged 3 to 6 years include the following studies:

- Eigen and coworkers
- Nystad and coworkers
- Zapletal and Chalupova
- Vilzoni and coworkers

In the United States, the reference values from the National Health and Nutrition Examination Survey (NHANES) III are recommended for children older than 8 years of age. Also, the reference values of Wang and coworkers are recommended for children aged 6 to 8 years.
**Lung Volumes and Airway Resistance**

**Lung Volumes**

The measurement of lung volumes in adults is described in Chapter 2. The techniques for measuring lung volumes in children are much the same. There are two major steps in measuring lung volumes: (a) determining functional residual capacity (FRC), and (b) measurement of the vital capacity (VC) and its subdivisions; for example, inspiratory capacity (IC) and expiratory reserve volume (ERV).

**Measurement of FRC**

The measurement of FRC is most commonly determined with one of three basic techniques: (a) body plethysmography, (b) multiple-breath closed-circuit helium (He) dilution, or (c) multiple-breath open-circuit nitrogen (N2) washout. The multiple-breath gas dilution and washout methods are not always the best choices for testing children because they require the patient to stay attached to the mouthpiece for several minutes. This is very problematic for some children, and they often develop leaks around the mouthpiece as they lose interest and their attention span wanes. Although face masks can be used instead of a mouthpiece, they require putty to create a seal, and they may have a large dead space. In addition, when a single washout or dilution FRC value has been obtained, there is a waiting period (> 5 minutes for He dilution and > 15 minutes for N2 washout) before a second attempt can be made. Again, this can be problematic because this takes too much time for young children.

The body plethysmograph or body box, in contrast, is much more suitable. You can obtain a number of FRC values in a very short amount of time. In addition, children seem to like going into the body box, sometimes called the spaceship. The technology and software on many commercial body box systems has improved considerably so that only minimal effort and panting is needed to determine FRC. As noted in Chapter 2, a body box is considered the most accurate method for measuring FRC because it measures all the gas in the thoracic cage. The gas dilution and washout methods, in contrast, only measure the lung volume communicating with the mouth, which can lead to underestimation of true FRC in those with obstructive lung disease.

When giving instructions to the child, remember to keep them simple. For the body box, instructions and practice should be done with the box door open. Close the door only when the child is ready, and keep the door closed for only short periods of time so the child can take a break and talk to you and/or the parent.

When using a body box to measure FRC, unsatisfactory results may occur when the patient allows the cheeks to puff in and out with the closed shutter panting. This can be corrected by having the patient place his or her hands on the cheeks and hold them still. However, holding the cheeks may cause the child to raise the shoulders, which can lead to a change in FRC.

Recommendations for the multiple breath dilution and washout methods in preschool children have been published.1 Testing is best if done while the child watches a video and sits upright in the lap of the parent or someone the child trusts. For very young children, a small face mask that can be sealed with putty is preferable. The mouthpiece and nose clip are ideal
in eliminating dead space, but not all children can keep their lips sealed long enough. Acceptability and repeatability criteria from the 2005 ATS/ERS lung volume guideline, described in Chapter 2, can be followed for the multiple-breath dilution and washout tests in children.

**Measurement of Vital Capacity**

The second part of measuring lung volumes is to measure the unforced or slow vital capacity (SVC). Provide instructions and training as in forced spirometry (previously described). It is important to stress that the maneuver is not forced but is done in a relaxed and slow manner. A nose clip should be worn, if possible. The maneuver should include several tidal breaths to establish a stable FRC level, followed by a maximum inspiration and then a slow complete expiration. Like in forced spirometry, the two highest SVC values in preschool children should agree within 0.100 liter or 10% of the highest, whichever is greater. For children 7 years and older, the two highest SVC values should agree within 0.150 liter. If these values are not achieved, additional maneuvers may be needed.

When determining lung subdivisions (e.g., RV), there are two recommended methods, as described in Chapter 2. The first and preferred method is to measure ERV immediately after the acquisition of the FRC measurement as linked maneuvers, that is, without the patient coming off the mouthpiece prior to completion of the maneuvers. This may be too difficult for some children, and thus a second method can be utilized. This alternative method includes the measurement of IC immediately after the FRC determination. With this approach, patients can come off the mouthpiece between maneuvers and perform separate VC maneuvers.

**Airway Resistance**

The principles of measuring airway resistance (Raw) in the body plethysmograph are presented in Chapter 4. Briefly, the patient breathes on a mouthpiece-shutter system inside the airtight body box. Airflow and body box pressures are measured by sensitive transducers. The patient is instructed to perform a number of gentle pants (two to three breaths/sec) with the shutter open. Immediately after the open-shutter pants, the shutter system is closed and the patient continues to pant at a slower rate (about one breath/sec). From these maneuvers, estimates of Raw and thoracic gas volume (TGV) are obtained, and specific conductance (sGaw) and/or specific resistance (sRaw) can be determined.

The open- and closed-shutter techniques can usually be performed by older children. However, closed-shutter panting is not always tolerated or may be poorly performed by young children. Omitting the closed-shutter step has been shown to provide an easy method that requires only passive cooperation of the young child, and it provides measurements of specific airway resistance (sRaw). Klug and Bisgaard reported plethysmographic measurements with and without an accompanying adult (that is, the parent would sit in the box with the child). They reported this approach yielded comparable and equally repeatable estimates of sRaw.

The standard commercially available plethysmograph and software are adequate to perform this adaption of the standard Raw measurements testing in young children. For some children, a face mask with a closed nasal portion may be better tolerated than a mouthpiece. Also, it is ideal to have a video to attract and distract the child.
For measurement of the open-shutter-only sRaw parameter, maneuvers in young children should be performed with panting frequencies of about one breath/sec (i.e., 30 to 45 breaths/min), which is the frequency at which most young children breathe spontaneously. However, some coaching may be required. Reference values in children aged 3 to 10 years for this open-shutter-only sRaw technique have been published recently.

**DL,CO**

The measurement of single-breath carbon monoxide diffusing capacity (DL,CO) is described in Chapter 3. The 2005 ATS/ERS guidelines for performing the DL,CO test are applicable for children. The testing technique can be difficult for children, and many will not be able to perform the testing acceptably. For example, the test requires a breath hold of 8 to 12 seconds at maximal inspiratory volume, which is not easily done by younger children. The reference values for DL,CO in children are limited and may not reflect current methodology recommendations.

**Case Presentations**

**Case 10.1**

A 5-year-old boy was seen in the clinic for a follow-up for asthma. He had not had spirometry before, and his physician wanted to get some spirometry testing results, if possible. The mom reported the boy was taking Flovent (fluticasone propionate, 50 mcg twice daily) at home regularly, but he had not had to use his albuterol inhaler. He was not having any coughing or wheezing at night, but he did have an occasional cough during exercise.

**Question**

1. You are asked to perform the spirometry testing on this patient. What steps would you take to assure patient cooperation and acceptable results?

**Answer and Discussion**

In this case, all preschool children and their caregivers watch a 5-minute video explaining what the child will be doing. This usually reduces apprehension for both the patient and the parents. The first issue you will have to deal with is whether to invite the parents into the room while the testing is performed. Because patients in this age group are easily distracted, it is best to not invite the parents or caregiver into the room. Explain the test to the parents before taking the child to the testing area. In that explanation, mention that kids often do better without anyone watching them. Suggest the parents stay close by and within hearing distance. In this case, the mom agreed to remain just outside the testing room.

The next step is to get on the same eye level and greet the child, introduce yourself, and get some conversation going. Comment on his really cool shoes that light up when he walks.
Mention that you are going to play a blowing game on the computer. Start with playing a short game (e.g., ring toss) to further reduce apprehension.

The spirometer software includes an incentive application \( \text{blow the rocket ship to the moon game} \) to help increase the child’s willingness to participate in testing. Since this child had never performed spirometry before, additional time was allowed for training. Spirometry testing was started using a closed-circuit method. The results of the prebronchodilator spirometry testing are shown in Table 10.1 and Figure 10.2.

### Questions

1. Are these test results acceptable and repeatable?
2. What values would you report for FVC and FEV\(_1\)?

### Answers and Discussion

The test results are somewhat variable, which is not unexpected with a young child who is naïve to spirometry. The results are actually pretty good given his age. It appears as if the patient is starting to understand the technique around maneuvers 5 and 6, but maneuver 7 FVC is considerably lower, then on maneuver 8 the FVC value comes back up. This is a good example of the inconsistency with technique that is common in children in this age group.

Repeated maneuvers, under the direction of a skilled technologist, are really important. Maneuver 1 is not acceptable because of poor start and technique. The other maneuvers appear to be acceptable. The last maneuver appears to have the best expiratory spirogram. The highest FVC is 1.21 liters, and the next highest FVC is 1.16 liters. These are repeatable (i.e., within 0.100 liter). The highest FEV\(_1\) is 0.79 liter, and the next highest FEV\(_1\) is 0.73 liter. These are repeatable (i.e., within 0.100 liter).

The highest FVC and FEV\(_1\) from acceptable and repeatable maneuvers should be reported. The highest FVC is 1.21 liters, and the highest FEV\(_1\) is 0.79 liter.

### Table 10.1

<table>
<thead>
<tr>
<th>Pre-Rx</th>
<th>Predicted FVC (L)</th>
<th>% predicted</th>
<th>Predicted FEV(_1) (L)</th>
<th>% predicted</th>
<th>FEV(_1)/FVC</th>
<th>PEFR (L/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneuver 1</td>
<td>1.21</td>
<td>0.84</td>
<td>69</td>
<td>0.97</td>
<td>0.73</td>
<td>75</td>
</tr>
<tr>
<td>Maneuver 2</td>
<td>1.21</td>
<td>1.15</td>
<td>95</td>
<td>0.97</td>
<td>0.73</td>
<td>75</td>
</tr>
<tr>
<td>Maneuver 3</td>
<td>1.21</td>
<td>0.93</td>
<td>77</td>
<td>0.97</td>
<td>0.64</td>
<td>66</td>
</tr>
<tr>
<td>Maneuver 4</td>
<td>1.21</td>
<td>0.99</td>
<td>82</td>
<td>0.97</td>
<td>0.66</td>
<td>68</td>
</tr>
<tr>
<td>Maneuver 5</td>
<td>1.21</td>
<td>1.09</td>
<td>90</td>
<td>0.97</td>
<td>0.73</td>
<td>75</td>
</tr>
<tr>
<td>Maneuver 6</td>
<td>1.21</td>
<td>1.16</td>
<td>96</td>
<td>0.97</td>
<td>0.68</td>
<td>70</td>
</tr>
<tr>
<td>Maneuver 7</td>
<td>1.21</td>
<td>0.98</td>
<td>81</td>
<td>0.97</td>
<td>0.63</td>
<td>65</td>
</tr>
<tr>
<td>Maneuver 8</td>
<td>1.21</td>
<td>1.21</td>
<td>100</td>
<td>0.97</td>
<td>0.79</td>
<td>81</td>
</tr>
</tbody>
</table>
There are no good inspiratory curves (loops) on this patient’s test. Most very young children have difficulty adding a forceful inspiratory arm after blowing out hard and fast. It is usually best to introduce the inspiratory loop at later visits.

Postbronchodilator testing was performed 10 minutes after four puffs of albuterol. The results of the test are presented in \textit{Table 10.2} and \textit{Figure 10.3}.
Table 10.2

Spirometry Results of Each Postbronchodilator Maneuver on 5-Year-Old Boy in Case 10.1

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>FVC (L)</th>
<th>% predicted</th>
<th>FEV1 (L)</th>
<th>% predicted</th>
<th>FEV1/FVC</th>
<th>PEFR (L/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneuver 1</td>
<td>1.21</td>
<td>1.28</td>
<td>106</td>
<td>0.97</td>
<td>0.99</td>
<td>102</td>
</tr>
<tr>
<td>Maneuver 2</td>
<td>1.21</td>
<td>1.23</td>
<td>102</td>
<td>0.97</td>
<td>0.98</td>
<td>101</td>
</tr>
<tr>
<td>Maneuver 3</td>
<td>1.21</td>
<td>1.15</td>
<td>95</td>
<td>0.97</td>
<td>0.89</td>
<td>92</td>
</tr>
<tr>
<td>Maneuver 4</td>
<td>1.21</td>
<td>1.24</td>
<td>102</td>
<td>0.97</td>
<td>0.94</td>
<td>97</td>
</tr>
<tr>
<td>Maneuver 5</td>
<td>1.21</td>
<td>1.28</td>
<td>106</td>
<td>0.97</td>
<td>0.97</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 10.3

Flow–volume spirograms for each maneuver performed by 5-year-old boy in Case 10.1. The first panel (R) is the reported curve.
Questions
1. Are these results acceptable and repeatable?
2. How would you interpret the response to the bronchodilator?

Answers and Discussion
The postbronchodilator testing appears to be acceptable and repeatable. The FVCs are much more consistent, which is probably a sign that the child is mastering the FVC technique with repeated efforts and a break between the pre- and posttesting. The prebronchodilator FEV₁ is 0.79 liter, and the postbronchodilator FEV₁ is 0.99 liter. This represents a 25% and 0.200 liter improvement, which is significant.

Case 10.2
An 11-year-old asthmatic comes to the clinic every 3 months for follow-up examination and spirometry. The spirometry results for March 2010 are shown in Table 10.3. The results of testing 7 months later, in October 2010, are shown in Table 10.4. The child was taking one puff twice per day of an inhaled corticosteroid and long-acting bronchodilator combination product (100/50).

Questions
1. How do you interpret these results?
2. Do lung function changes follow changes in height?

Table 10.3
Prebronchodilator Spirometry Results from Testing in March 2010 on 11-Year-Old Asthmatic in Case 10.2 (Measured Height was 149 cm)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predicted value</th>
<th>Measured value</th>
<th>% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>2.22</td>
<td>2.42</td>
<td>109</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.93</td>
<td>2.07</td>
<td>107</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>87</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>PEFR (L/sec)</td>
<td>4.78</td>
<td>5.80</td>
<td>121</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (L/sec)</td>
<td>2.36</td>
<td>2.28</td>
<td>97</td>
</tr>
<tr>
<td>FET (sec)</td>
<td></td>
<td>7.83</td>
<td></td>
</tr>
<tr>
<td>Back-extrapolated volume (L)</td>
<td></td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>
Spirometry testing based on the tabular data is acceptable with good start of test (low back-extrapolation volume) and no early end to expiration (forced expiratory time [FET] at least 6 seconds). The spirometric data from March 2010 is essentially normal. The spirometric data from October 2010 is mostly normal with a low FEF25–75%. In comparing the spirometry results from March to October 2010 there is an increase in FVC of 0.260 liter, which would be expected given the height change. The FEV1 would usually increase in a similar manner, but in this case it is lower (0.100 liter), which suggests airflow obstruction. This is also seen with the change in FEV1/FVC ratio in this time span (86% to 74%).

Lung volumes including FVC and FEV1 are related to body size. Standing height has consistently been shown to be the best factor for determining predicted values for individual subjects. However, lung growth appears to lag behind the increase in standing height during the growth spurt, and there is a shift in the relationship between lung volume and standing height during adolescence.20,21 This child had a growth spurt (4 cm) between the two testing dates, and the predicted values were adjusted accordingly. But in children the changes in actual values may lag behind the expected values based on standing height. So did this child actually have a decrease in lung function, or are the changes in percent predicted an artifact caused, at least in part, by the changes in predicted values? It appears the right answer is that there was some decrease in this child’s measured values (e.g., decreased FEV1 value), and the increases in predicted values that resulted from the growth in standing height may not be linear with lung growth. Thus, it may be difficult to actually determine change using percent predicted when growth spurts occur. It may be better to compare actual measured values and shapes of spiromgrams to really get a good picture of any change. It was believed this patient did have some worsening in lung function, and an increase in the dose of the inhaled combination product was prescribed.

### Table 10.4

**Prebronchodilator Spirometry Results from Testing in October 2010 on 11-Year Old Asthmatic in Case 10.2 (Measured Height was 153 cm)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predicted value</th>
<th>Measured value</th>
<th>% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>2.39</td>
<td>2.68</td>
<td>112</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.09</td>
<td>1.97</td>
<td>94</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>87</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>PEFR (L/sec)</td>
<td>5.18</td>
<td>5.35</td>
<td>103</td>
</tr>
<tr>
<td>FEF25–75% (L/sec)</td>
<td>2.54</td>
<td>1.48</td>
<td>58</td>
</tr>
<tr>
<td>FET (sec)</td>
<td>7.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back-extrapolated volume (L)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Despite these challenges, children should have their standing height measured every time they have pulmonary function testing. Height might be measured in the clinic and then again in the pulmonary function laboratory. The best tool is an accurate wall-mounted stadiometer. If differences in height are noted between the clinic and laboratory height measurements, assure the height was measured with shoes off and with the patient standing completely erect. Generally, height can be measured to the nearest centimeter, but some laboratories choose to measure to nearest half centimeter.

**Self-Assessment Questions**

1. Which of the following statements is not true regarding the testing environment for children?
   a. Needles and syringes should be hidden from view.
   b. Parents are sometimes helpful and should remain in the testing room for some children.
   c. Space for games, play, videos, and coloring are essential.
   d. Parents should never leave the child alone in the testing room.

2. A 14-year-old girl with cystic fibrosis is scheduled to have pulmonary function tests. Which of the following methods for determining FRC would be most desirable?
   a. Body plethysmography
   b. Nitrogen washout
   c. Helium dilution
   d. Chest x-ray

3. In this same cystic fibrosis patient, the FEV₁/FVC ratio is 51%, indicating significant airflow obstruction. If FRC was determined in this patient by both nitrogen washout and body plethysmography, which of the following outcomes would be expected?
   a. The FRC\textsubscript{pleth} would underestimate FRC because of airflow obstruction.
   b. The FRC\textsubscript{N\textsubscript{2}} would likely underestimate true FRC because of noncommunicating airways.
   c. The FRC\textsubscript{pleth} would be the same as the FRC\textsubscript{N\textsubscript{2}}.
   d. The FRC\textsubscript{N\textsubscript{2}} would likely overestimate the true FRC.

4. According to the ATS/ERS recommendations for spirometry in preschool children, the two highest FEV₁ values from acceptable maneuvers should agree within:
   a. 12% of highest
   b. 0.100 liter or 10% of highest
   c. 0.150 liter
   d. 5%

5. When testing a 5-year-old boy, you find that he cannot blow out for 1 second. The longest he can blow out is about 0.7 seconds. Which of the following could be accurately reported?
   a. FEV₁
   b. FEV\textsubscript{0.75}
   c. FEV\textsubscript{0.5}
   d. FEV\textsubscript{0.3}


Introduction

The measurement and interpretation of blood gases (measurement of arterial oxygen, pH, and carbon dioxide) are a crucial aspect of respiratory diagnostics and care. It is a complicated topic requiring a complete textbook to discuss thoroughly. Given the space constraints of this text, a brief explanation and discussion of the important aspects will be presented. The chapter is divided into five sections: (a) blood gas science, (b) blood gas analysis, (c) interpretation of blood gases, (d) quality management of the blood gas laboratory, and (e) associated technologies.

Blood Gas Science

Physics Laws That Apply to Blood Gases

To appreciate and understand the full scope of blood gas transport, analytic measurements, and the clinical interpretation of results, the science principles that govern blood gas chemistry need to be reviewed.
Dalton’s Law of Partial Pressures

The total pressure of a gaseous mixture is equal to the sum of the partial pressures of its constituent gases. Expressed mathematically Dalton’s law states that for a mixture containing several gases,

\[ P_t = P_1 + P_2 + P_3 \]

where

- \( P_t \) = Total pressure
- \( P_1, P_2, P_3 \) = Partial pressure of constituent gases

Example:

Barometric pressure = \( P_{\text{atm}O_2} + P_{\text{atm}N_2} + P_{\text{atm other gases}} \)

Barometric pressure = 159 + 593 + 8

Barometric pressure = 760 mmHg

Henry’s Law

At a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid. Henry’s law states that the weight of a gas dissolved in a liquid is directly proportional to the weight of the gas above the liquid. The amount of gas that will dissolve into 1 mL of a given liquid at 1 atmosphere (760 mmHg) and at a specified temperature is the solubility coefficient.

The solubility coefficient in plasma at 37°C and 760 mmHg is as follows:

- Oxygen: 0.023 mL
- Carbon dioxide: 0.510 mL

Graham’s Law

The rate of diffusion of a gas through a liquid medium is directly proportional to the solubility of the gas, and it is inversely proportional to the square root of its density or its gram molecular weight. The number of milliliters of a gas that will diffuse a distance of 0.001 mm (1 μ) over a square centimeter surface per minute, at 1 atmosphere (760 mmHg) is the diffusion coefficient of the gas. An example of this law is that carbon dioxide is 19 times more diffusible than oxygen due to its solubility factor.

The diffusion coefficient in plasma at 760 mmHg is as follows:

- Oxygen: 0.153 mL
- Carbon dioxide: 2.89 mL
Oxygen Transport

The basic objective of the heart and lungs is to provide adequate oxygen for aerobic metabolism at the cellular level. This is a multiorgan system function that requires continuous interaction among pulmonary, cardiovascular, hematologic, and cellular physiologies. The overall process of oxygen transport from inspiring ambient gas through electron transfer to the mitochondria is very efficient and performs well in steady state, exercise, and conditions of reduced metabolic requirements. However, when pathophysiologic conditions alter any part of the oxygen transport system, such that oxygen supply does not meet oxygen demand, cellular function can be adversely affected.

Traditionally, the measurement of PaO₂ has been used as a clinical marker of oxygen supply. PaO₂ is the measurement of the partial pressure of O₂ dissolved in the blood. It is reported in mmHg, kilopascals (kPa), or torr. The conversion for mmHg and kPa is 1 mmHg = 0.133 kPa. Thus, a PaO₂ of 80 mmHg = 10.64 kPa. The conversion for mmHg and torr is 1 mmHg = 1 torr. Thus, a PaO₂ of 80 mmHg = 80 torr.

It is important to note that assessments and therapies based only on PaO₂ may not provide enough information to determine whether adequate oxygen supplies are available for metabolism.

The partial pressure of inspired oxygen (PİO₂) is characterized by the total atmospheric pressure or barometric pressure (PB). At sea level (760 mmHg) the PİO₂ is 159 mmHg and represents approximately 21% of the PB. During inspiration, atmospheric gas is warmed to 37° C and mixes with water vapor (47 mmHg) and carbon dioxide. The altered gas composition is reflected in a diluted partial pressure of alveolar oxygen (PaO₂), estimated to be approximately 103 mmHg. Oxygen passively diffuses across the alveolar capillary (A-C) membrane, dissolving in the plasma (PO₂) and binding to the hemoglobin molecule (oxyhemoglobin, O₂Hb) within the erythrocyte. Thebesian veins carrying deoxygenated blood from the myocardium empty into the left heart and contribute to a small anatomic shunt, resulting in an arterial PaO₂ of approximately 100 mmHg.

Systematically, arteries divide and decrease in diameter as they disseminate through organs and tissues. They reduce to arterioles and then transition into capillaries with an average PO₂ of 35 mmHg. The capillary network provides blood supply to the cells. Oxygen is liberated from hemoglobin and transported through the cell membrane to the mitochondria, where cytochrome oxidase catalyzes the oxygen reduction. Throughout this process, oxygen serves as an electron acceptor, necessary in oxidative phosphorylation, the synthesis of adenosine triphosphate (ATP) for energy production. The mitochondrial PO₂ range is between 4 mmHg and 20 mmHg and is conducive to aerobic metabolism. Intracellular PO₂ levels below this point produce anaerobic glycolysis with the production of lactate. The oxygen cascade (Figure 11.1) highlights the oxygen transport sequence and common causes that lead to decreased intracellular oxygen concentrations.

The oxyhemoglobin dissociation curve (Figure 11.2) is a graph that shows the percent saturation of hemoglobin at various partial pressures of oxygen. The curve is commonly expressed by the P½ value. This is the PO₂ at which hemoglobin is 50% saturated with oxygen. P½ decreases, or the curve shifts to the left, in response to alkalosis, hypothermia, and a decrease...
in the organic phosphate concentration of 2,3-diphosphoglycerate (2,3-DPG). DPG binds to deoxyhemoglobin but not the oxygenated form, diminishing the oxygen affinity of hemoglobin. This net effect is essential in enabling hemoglobin to unload oxygen in tissue capillaries. A reduction in red blood cells (RBCs) or anemia is the most common cause of reduced 2,3-DPG. An increase in P50 is produced by conditions promoting acidosis, hyperthermia, and elevation in 2,3-DPG (i.e., polycythemia, acclimatization to high altitude).

The oxyhemoglobin disassociation curve demonstrates that the incremental ability to carry additional oxygen with PO2 values above 55 mmHg does not contribute significantly to oxygen content. Conversely, as PO2 decreases below 55 mmHg, hemoglobin’s ability to carry oxygen is markedly reduced.

**Hypoxemia**

A reduction in arterial blood oxygen levels is referred to as hypoxemia. Clinically significant hypoxemia is defined by a PaO2 of < 55 mmHg, predicted by the P50 and age, but it often decreases due to altered physiology and disease processes. Hypoxemia can also be described
as a fractional arterial oxygen saturation ($F_O^2Hb$) < 88% or an arterial oxygen content ($c_O^2$) < 17.8 mL/dL. Short-term physiologic responses to hypoxemia range from elevated levels of dyspnea and anxiety to tachypnea and tachycardia to glucose intolerance. Prolonged effects of hypoxemia include pulmonary artery hypertension, polycythemia, and altered chemosensitivity of the skeletal muscles. If the severity of hypoxemia is allowed to persist, pathology will develop as a consequence of reduced oxygen at the cellular level (hypoxia), as opposed to just a decrease of oxygen measured in the arterial blood (hypoxemia) (Table 11.1).

**Hypoxia**

Hypoxia is defined as a reduction in cellular oxygen concentration. Traditionally, hypoxia is classified into four etiologic categories: hypoxic (supply issues, such as high altitude, airway obstruction), anemic (carrying issues, such as insufficient Hb), stagnant (transport issues, such as a reduction in cardiac output), and histotoxic (utilization issues, such as inability to unload $O_2$ from Hb or transfer $O_2$ across the mitochondria membrane, as occurs in cyanide poisoning). The commonality in all four hypoxic categories is insufficient oxygen available to the...
mitochondria for normal aerobic metabolism. In some patients more than one type of hypoxia can exist (e.g., COPD patients with ventilation-perfusion [V/Q] mismatch and cor pulmonale). Hypoxic events trigger various physiologic responses that have both protective qualities and untoward reactions.

The formulas found to be clinically valuable in the diagnosis and management of hypoxia are presented in Table 11.2.

### Table 11.1

**Physiologic Responses: Hypoxemia vs. Hypoxia**

<table>
<thead>
<tr>
<th>Hypoxemia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulates peripheral chemoreceptors (carotid and aortic bodies)</td>
<td>Disrupts normal cellular function</td>
</tr>
<tr>
<td>Increases ventilation</td>
<td>Inhibits glucogenesis; metabolism of glucose to ATP</td>
</tr>
<tr>
<td>Increases pulmonary vascular resistance (PVR)</td>
<td>Promotes anaerobic glycolysis</td>
</tr>
<tr>
<td>Increases pulmonary vasoconstriction</td>
<td>Increases lactate production, nonvolatile metabolic acidosis</td>
</tr>
<tr>
<td>Increases blood viscosity through increased hematocrit</td>
<td>Retards CNS function</td>
</tr>
<tr>
<td>Stimulates hematopoiesis</td>
<td>Blunts cognitive behavior</td>
</tr>
<tr>
<td>Increases RBC production</td>
<td>Impairs hand–eye coordination</td>
</tr>
<tr>
<td>Increases 2,3-diphosphoglycerate</td>
<td>Advances tissue/organ dysfunction</td>
</tr>
<tr>
<td>Alters afferent nerve skeletal muscle activity</td>
<td>Promotes early cell death</td>
</tr>
<tr>
<td>Produces muscle fatigue</td>
<td></td>
</tr>
<tr>
<td>Alters metabolism</td>
<td></td>
</tr>
<tr>
<td>Causes glucose intolerance</td>
<td></td>
</tr>
</tbody>
</table>

The presence of free hydrogen ions ([H\(^+\)]) are rare in body fluids, but even in very low concentrations they provide a vital physiologic role. Enzymatic activity and the solubility of salts are dependent on [H\(^+\)] concentration. At chemical neutrality, there is only \(1 \times 10^{-7}\) (1/10,000,000) of a mole of [H\(^+\)] per liter of solution. The concentration of [H\(^+\)] in arterial blood plasma is even less, \(4 \times 10^{-8}\) (4/100,000,000) of a mole of [H\(^+\)] per liter.

Chemically, any solution containing in excess of \(1 \times 10^{-7}\) mole of [H\(^+\)] per liter is considered acidic, and any solution containing less than that concentration is considered alkaline or basic.
Traditionally, an acid is defined as a proton ([H⁺]) donor, and a base is a proton ([H⁺]) acceptor. The chemical characteristics and concentrations of these solutions, specifically of plasma, have direct impact on the health and functionality of human physiology. In 1909, the Danish chemist Dr. Søren Sørensen first introduced the concept of pH, a way of expressing hydrogen ion concentration using a 0–14 scale. The letters P and H stand for pondus hydrogenii or the potential for hydrogen, [H⁺].

Table 11.3 describe the pH and [H⁺] effect as inversely proportional, that is, as hydrogen ion concentration increases, pH decreases, and as hydrogen ion concentration decreases, pH increases. The scale marks a pH of 7.00 as neutral; however, in normal human plasma [H⁺] concentration is slightly lower, thereby producing a marginally higher pH of 7.40.

The normal physiologic range of arterial pH is 7.38–7.42; however, clinical results from 7.35–7.45 would be considered acceptable. A pH result < 7.35 is termed acidemia and > 7.45 is termed alkalemia. The process that decreases pH is known as acidosis, and the process that increases pH is known as alkalosis.
Acid-base balance is an inherent physiologic system designed to maintain body fluids in pH homeostasis, or neutrality. Both the lungs and kidney are responsible for elimination of acids to accomplish homeostasis. The lungs excrete carbonic acid (H$_2$CO$_3$), also referred to as a volatile acid, because it is easily vaporized (i.e., H$_2$CO$_3$ disassociates into water and CO$_2$, whereby the CO$_2$ is exhaled). The kidneys are responsible for the removal of nonvolatile or fixed acids, which are produced as an end product of metabolism (i.e., lactate). It is estimated that 15,000 mEq of acid are excreted by the lungs daily, compared to 70 mEq by the kidneys.

The two primary compounds that contribute to plasma acid-base balance are bicarbonate (HCO$_3^-$) and carbonic acid (H$_2$CO$_3$). The ratio of these compounds ultimately dictates plasma pH, which is expressed in the Henderson–Hasselbalch equation:

$$\text{pH} = -\log_{10} [\text{H}^+]$$

$$\text{pH} = pK + \log (\text{base} \div \text{acid})$$

$$\text{pH} = pK + \log (\text{HCO}_3^- \div \text{H}_2\text{CO}_3)$$

$$\text{pH} = pK + \log [(\text{HCO}_3^-) \div (\text{PCO}_2 \times 0.03)]$$

### Table 11.3

<table>
<thead>
<tr>
<th>pH</th>
<th>[H$^+$] in mmol/L</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10$^{-0}$</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10$^{-2}$</td>
<td>Increasing acidity</td>
</tr>
<tr>
<td>3</td>
<td>10$^{-3}$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10$^{-4}$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10$^{-5}$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10$^{-6}$</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10$^{-7}$</td>
<td>Neutural</td>
</tr>
<tr>
<td>8</td>
<td>10$^{-8}$</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10$^{-9}$</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10$^{-10}$</td>
<td>Increasing alkalinity</td>
</tr>
<tr>
<td>11</td>
<td>10$^{-11}$</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>10$^{-12}$</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>10$^{-13}$</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>10$^{-14}$</td>
<td></td>
</tr>
</tbody>
</table>
\[ pK \text{ (6.1) } = \text{ The pH where 50\% of the } H_2CO_3 \text{ will disassociate to form } HCO_3^- \text{ and } [H^+] \]

\[ H_2CO_3 = \text{ The concentration of } CO_2 \text{ dissolved in plasma (mEq/L or mmol/L); at a temperature of } 37^\circ C, \text{ approximately } 0.03 \text{ mmol of carbon dioxide per mmHg of } Pco_2 \text{ will dissolve in a liter of plasma} \]

Note that the ratio of $HCO_3^-$ to $H_2CO_3$ (20:1) produces a pH of 7.40. Based on this mathematical relationship, in any combinations where $HCO_3^-$ and $H_2CO_3$ yield a 20:1 ratio, the resultant pH will be 7.40.

The plasma bicarbonate concentration increases or decreases as needed to assure the concentration of cations (positively charged ions or electrolytes, i.e., Na\(^+\), K\(^+\), Ca\(^{2+}\)) are equal to the anions (negatively charged ions or electrolytes, i.e., Cl\(^-\), HCO_3^-). This principle that regulates electrolyte equilibration is known as the law of electroneutrality. If disease or therapy causes either a cation or anion’s concentration to change, $HCO_3^-$ will enter or leave the plasma proportionally to maintain an electrically neutral environment. For that reason, the concentration of bicarbonate is never a direct function of its production or elimination, but it depends on the surplus of cations over anions. Although shifts in $HCO_3^-$ can occur within milliseconds, metabolic compensatory changes happen gradually, aided by the renal excretion or retention of electrolytes.

Figure 11.3 is a Gamble diagram of plasma electrolytes. This graphical representation of electrolytes denotes cations from anions and their normal concentrations. It additionally illustrates that the total cation and anion concentrations are equal, demonstrating electroneutrality of the plasma.

**Anion Gap**

The anion gap (AG) is a diagnostic calculation used to identify the presence of an acid-base disorder, most commonly metabolic acidosis. It represents the concentration of all the unmeasured anions in the plasma. The concentration of the organic acids and negatively charged proteins are not normally accounted for in a standard electrolyte panel, thus when comparing the sum of the cations to anions, a gap (expressed in mmol/L or mEq/L) can be computed. The AG is traditionally calculated from the following formula:

\[ AG = [Na^+] - [Cl^- + HCO_3^-] \] or

\[ AG = [Na^+] - [Cl^- + CO_2] \]

where

\[ CO_2 = \text{ Total CO}_2 \text{ obtained from a venous electrolyte panel; sum of } HCO_3^- \text{ and } H_2CO_3 \]
CHAPTER 11 Blood Gases and Associated Technologies

Because potassium is a relatively small value, $K^+$/H$_2$O is often omitted from the equation. The AG normal reference range is 12-4 mEq/L. When the AG approaches 20 mEq/L, an anion gap acidosis (metabolic) is thought to exist. The anion gap is nonspecific. It is increased when the number of unmeasured anions increases, indicating a state of anion gap metabolic acidosis, but it does not indicate what is causing the imbalance. Common conditions that produce an anion gap metabolic acidosis are diabetic ketoacidosis, uremia (renal failure), lactic acidosis, and toxins (i.e., ethylene glycol, methanol, and salicylate).

**Base Excess**

The base excess is a measure of metabolic alkalosis or metabolic acidosis expressed as the amount of strong acid or strong base required to titrate a 1-liter sample of blood to a pH of 7.40. Both positive and negative results are commonly referred to as base excess; however, a negative value may be described as a base deficit. The normal reference range for base excess is ±2 mEq/L.

Base excess is often evaluated in conjunction with an acid-base evaluation and can be used to calculate the administration of buffered solutions to correct acid-base derangements.
Blood gas analyzers can report base excess calculations in two ways: (a) base excess of whole blood (BE\textsubscript{wb}), or (b) base excess of extracellular fluid (BE\textsubscript{ecf}). The BE\textsubscript{wb}, also called in vitro or actual base excess, uses both plasma HCO\textsubscript{3}\^- in its formula and the buffering effects of Hb. The BE\textsubscript{ecf}, also called in vivo base excess or standard base excess, is a quantity that reflects only HCO\textsubscript{3}\^-\textsuperscript{−}, the nonrespiratory component of pH.

**Carbon Dioxide Transport**

Carbon dioxide (CO\textsubscript{2}) is produced as a by product of metabolism and conversion of glucose to fatty acids. Depending on metabolic rate and the nutrients metabolized, approximately 200 mL/min of CO\textsubscript{2} is produced, or 2.4 mL/kg/min. After it is released by the cells, the CO\textsubscript{2} is transported in the blood by two mechanisms: (a) in the erythrocyte (RBC), and (b) in the plasma.

**RBC Transport of CO\textsubscript{2}**

Carbon dioxide is transported three ways within the RBC:

1. HCO\textsubscript{3}\^-: The majority (approximately 70%) of CO\textsubscript{2} transported by the blood is in the RBC in the form of HCO\textsubscript{3}\^-\textsuperscript{−}. Although this is normally a relatively slow reaction, rapid acceleration occurs in the RBC in the presence of the catalyst carbonic anhydrase (CA).

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + [\text{H}^+] \\
\text{CA}
\]

Some of the HCO\textsubscript{3}\^- will diffuse into the plasma in exchange for Cl\^-\textsuperscript{−}, maintaining electrical neutrality of the RBC and plasma. The exchange of these electrolytes is known as the chloride shift, Hamburger phenomenon, or isohydric shift.

2. Carbaminohemoglobin: This substance is formed by CO\textsubscript{2} + HHb → CO\textsubscript{2}HHb after the release of oxygen by the hemoglobin to the tissue. It accounts for nearly 25% of the carbon dioxide exhaled from the lung.

3. PCO\textsubscript{2}: Dissolved CO\textsubscript{2} in the cytoplasm of the RBC is in equilibrium with the plasma PCO\textsubscript{2}.

**Plasma Transport of CO\textsubscript{2}**

Carbon dioxide is transported three ways in the plasma:

1. PCO\textsubscript{2}: Dissolved CO\textsubscript{2} in the plasma is in equilibrium with the PCO\textsubscript{2} in the RBC.

2. HCO\textsubscript{3}\^-: The formation of HCO\textsubscript{3}\^- in the plasma is a slow process due to the absence of carbonic anhydrase. Plasma HCO\textsubscript{3}\^- is in equilibrium with the HCO\textsubscript{3}\^- in the RBC.

3. Carbamino compounds: CO\textsubscript{2} binds with the terminal amine groups of plasma proteins.

PaCO\textsubscript{2} is the measurement of the partial pressure of CO\textsubscript{2} in plasma of arterial blood. It is reported in mmHg, kilopascals (kPa), or torr. The conversion for mmHg and kPa is 1 mmHg = 0.133 kPa. Thus, a PaCO\textsubscript{2} of 40 mmHg = 5.32 kPa. The conversion for mmHg and torr is 1 mmHg = 1 torr. Thus, a PaCO\textsubscript{2} of 40 mmHg = 40 torr.
CHAPTER 11 Blood Gases and Associated Technologies

Blood Gas Analysis

Introduction

Blood gas analysis is the diagnostic test that measures pH, PCO₂ and PO₂. This multianalyte panel is analyzed in one instrument simultaneously from a single specimen. This section will present some background information, a brief description of regulatory issues, and a discussion of the three phases of the blood gas analysis procedure: preanalytic, analytic, and post analytic.

Background

The first three-function (pH, PCO₂, PO₂) blood gas apparatus was built by Severinghaus and Bradley in 1959 (Figure 11.4). Numerous technical advances have occurred since then to improve reliability, increase sample throughput, and minimize the specimen volume required for analysis. However, the most significant clinical advances affecting utility have been to increase the analyte panel to include other assays that evaluate metabolic and renal function and to reduce the size and complexity of operation to permit testing at the point of care (POC).

Twenty-first century blood gas instruments combine blood gas measurements with electrochemical and enzymatic sensor technology to analyze hematocrit, electrolytes, lactate, glucose, BUN (urea) and creatinine. Depending on the clinical scenario, measurement of these analytes with blood gases may provide a more complete picture of the patient’s condition.

Regulations Governing Blood Gas Analysis

In the United States, the Centers for Medicare and Medicaid Services (CMS) dictate that upon purchasing a new blood gas analyzer, validation of instrument performance is required prior to use.

Figure 11.4

First blood gas analyzer.

Blood Gas Analysis

The primary goal of the CLIA program is to ensure quality laboratory testing. CLIA has set guidelines defining the total acceptable error for analytes reported by blood gas and chemistry analyzers. Based on these guidelines, the range of results for a single instrument can vary from state to state. Each state CLIA branch can modify those regulations to more stringent standards and hold the testing facilities in their state to local guidelines.

Validating Blood Gas Analyzers

Before a new analyzer is used for reporting patient results, validation and verification of the instrument performance must be completed and approved by the medical director named on the facility’s CLIA license. Among the specific laboratory tests that are required for this testing are the following:

- **Trueness** is a test to determine how close the measured result approaches the true value. Trueness replaced the previous term *accuracy*, but the test objective remains the same.
- **Precision** is a test to assess the reproducibility of measurements.
- **Clinical reportable range** (CRR) is a test designed to establish the actual range that can be measured and verified by the facility.
- **Linearity** is a test that estimates the degree of sensitivity to incremental changes in analyte concentration and predicts instrument performance at any point along the measurable range.
- **Method correlation** is a test that evaluates patient samples between the new analyzer and the reference instrument in order to determine if both instruments produce similar results.
- **Normal range** is a test to confirm the range for each analyte reported in samples collected from a healthy, nonhospitalized individual.

The CMS administers the Clinical Laboratory Improvement Amendments (CLIA), which regulate all facilities that perform testing on materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment or impairment of any disease, or the assessment of the health of human beings, to meet certain federal requirements. If a facility performs tests for these purposes, it is considered a laboratory under CLIA, and it must apply and obtain a certificate from the CLIA program that corresponds to the complexity of the tests it performs.

Many private agencies have published standards for laboratory best practices. These agencies perform site visits or inspections of facilities to observe and document compliance of laboratory standards. In 2011, these agencies include the College of American Pathologists (CAP), The Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations or JCAHO), and the Commission on Laboratory Accreditation (COLA). These inspecting agencies also offer services to US military hospital laboratories. State governments have a strong role in laboratory standards as well. Each state’s Department of Health manages the CLIA branch for that region. The state CLIA office can set the standards for laboratories in their jurisdiction and also inspect testing facilities. Although the national office of CLIA has published standards, each state CLIA branch can modify those regulations to more stringent standards and hold the testing facilities in their state to local guidelines.
markedly. Table 11.4 lists the CLIA guidelines for acceptable total errors for blood gases, electrolytes, hemoximetry, and other metabolites and chemistries that are often paneled on blood gas analyzers. Table 11.4 also gives a theoretical example of an absolute value of an analyte and, based on the acceptable error limit, what range of results could be reported. It must be noted that most laboratories report results with greater trueness, but due to the inherent methods of the system, perfect accuracy can never be achieved.

**Preanalytic Phase**

The preanalytic phase of testing encompasses procedures prior to analysis, including identification of patient; supplies, storage, transport, and handling of samples; and arterial puncture and sampling.

### Table 11.4

<table>
<thead>
<tr>
<th>Module</th>
<th>Analyte</th>
<th>Reporting units</th>
<th>Acceptable error</th>
<th>Absolute value</th>
<th>Acceptable range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood gases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>n/a</td>
<td>±0.04</td>
<td>7.40</td>
<td>7.36–7.44</td>
<td></td>
</tr>
<tr>
<td><strong>PCO₂</strong></td>
<td>mmHg</td>
<td>±5 or 8%*</td>
<td>40</td>
<td>35–45</td>
<td></td>
</tr>
<tr>
<td><strong>PO₂</strong></td>
<td>mmHg</td>
<td>±3 SD</td>
<td>100</td>
<td>79–121†</td>
<td></td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
<td>%</td>
<td>±6%</td>
<td>45</td>
<td>42–48</td>
<td></td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>mmol/L</td>
<td>±4</td>
<td>140</td>
<td>136–144</td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td>mmol/L</td>
<td>±0.5</td>
<td>4.0</td>
<td>3.5–4.5</td>
<td></td>
</tr>
<tr>
<td><strong>Ca</strong>⁺⁺</td>
<td>mmol/L</td>
<td>±3 SD¹</td>
<td>1.50</td>
<td>1.41–1.59³</td>
<td></td>
</tr>
<tr>
<td><strong>Cl⁻</strong></td>
<td>mmol/L</td>
<td>±5%</td>
<td>102</td>
<td>97–107</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolites and other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td>±6 or 10%*</td>
<td>90</td>
<td>81–99</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>mg/dL</td>
<td>±3 SD or 3.6%‡</td>
<td>18.0</td>
<td>14.4–21.6</td>
<td></td>
</tr>
<tr>
<td><strong>BUN (urea)</strong></td>
<td>mg/dL</td>
<td>±2 or 9%*</td>
<td>15</td>
<td>13–17</td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>mg/dL</td>
<td>0.3 or 15%*</td>
<td>1.5</td>
<td>1.2–1.8</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoximetry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tHb</td>
<td>g/dL</td>
<td>±7%</td>
<td>15</td>
<td>14–16</td>
<td></td>
</tr>
<tr>
<td>O₂Hb</td>
<td>%</td>
<td>±3% or 3 SD²</td>
<td>95.0</td>
<td>92.2–97.9</td>
<td></td>
</tr>
<tr>
<td>COHb</td>
<td>%</td>
<td>±3% or 3 SD²</td>
<td>2.00</td>
<td>1.88–2.06</td>
<td></td>
</tr>
<tr>
<td>MetHb</td>
<td>%</td>
<td>±2%†</td>
<td>1.00</td>
<td>0.98–1.02</td>
<td></td>
</tr>
</tbody>
</table>

*Whichever is greater

No CLIA guideline published; acceptable error reported is CAP proficiency testing criteria

Example based on a peer group SD of 7 mmHg

Example based on a peer group SD of 0.03 mmol/L
Patient Identification

Prior to specimen collection, a formal process of ensuring patient positive identification is required. The Joint Commission recommends using a minimum of two unique identifiers that could include the patient’s full name and date of birth. The patient’s room number or location are not acceptable identifiers. In conjunction with confirming the correct patient, the person performing the sampling should introduce themselves to the patient and briefly explain the procedure. Assistance should be obtained for those patients with communication deficits or language barriers that may prevent understanding and consent.

Supplies, Storage, Transport, and Handling

A specimen for blood gas analysis should be collected in a suitable heparinized plastic syringe. Blood must be anticoagulated to prevent clotting within the analyzer. For convenience, kits are available that contain a preheparinized syringe, needle, needle protection guard to avoid recapping, syringe cap, skin prep solutions, gauze sponge, adhesive bandage, specimen labels, and transport collection bag. Note that not all brands of blood gas syringes are compatible with all blood gas analyzers.

The preheparinized syringes are evaluated by the manufacturer for anticoagulation effectiveness and analyte interferences. It is important to follow the analyzer manufacturer’s recommendation for heparin compatibility with the analytes being measured. Preheparinized syringes may be coated with lyophilized nonbalanced, electrolyte-balanced, or ionized calcium-balanced heparin, or the coating may be liquid nonbalanced or sodium-balanced heparin. Other anticoagulants (e.g., citrate and EDTA) are slightly acidic, which increases the risk of the pH being erroneously reduced and therefore should not be used for blood gas sampling. Specimen volumes less than the minimum recommendation can also be a source of preanalytical error due to the concentration of heparin in the blood specimen.

Before plastic syringes became customary, glass syringes were used for blood gas collection. The syringe was immersed in an ice-water bath to slow white blood cell (WBC) metabolism, thereby retarding oxygen consumption. Syringes made of plastic are more gas permeable than glass, and when cooled they can accelerate a flux that can artificially elevate PO2 results. Therefore it is strongly recommended that specimens obtained in plastic syringes for blood gas measurements be stored at room temperature. If analysis is anticipated to be delayed by more than 30 minutes, the blood should be collected in a glass syringe and placed in an ice-water bath.

Rapid transport of the sample to the blood gas laboratory is essential to the viability of the specimen. When the specimen is received by the laboratory, the analysis should be conducted as soon as possible. If analysis is delayed, a clinically significant decrease in glucose and increase in lactate results occurs, due to RBC metabolism when stored in a heparinized syringe. Within 30 minutes, leukocyte and platelet activity noticeably begin to consume oxygen, thereby reducing PaO2. An extended delay in analysis will also result in an increased PaO2 with a corresponding decrease in pH, which artificially elevates ionized calcium. To assist in expedited transport of specimens to the laboratory, some hospitals have installed pneumatic tube systems. Although these systems can swiftly convey blood gas specimens, they can also be a source of preanalytical error. If very small air bubbles are not removed from the collection device, vibrations and movement of the air within the sample accelerates equilibration and
Erroneous results may be reported. When hand carrying a blood gas sample to the laboratory, the specimen must be contained in such a manner that if it is accidently dropped, the spilled blood will not create a biohazard environment.

Proper specimen labeling is critical to assuring appropriate interpretation of results and adhering to good laboratory practice standards. Included among this documentation are recording the patient’s name, identification number, date, time of sample, sampling site, results of a modified Allen test, and any therapeutic interventions, such as mechanical ventilator settings, supplemental oxygen flow rate, and delivery system. Also of relevance are factors that may significantly affect ventilation and/or perfusion. Exercise, prone positioning, and administration of nitric oxide or exogenous surfactant are pertinent interventions to record.15

The primary goal of POC testing is to reduce the laboratory turnaround time (TAT), which is the elapsed time from obtaining the sample to reporting the results.16 Most POC devices can analyze and report a blood gas panel in less than 90 seconds.17 In addition, like their benchtop counterparts in the laboratory, a variety of analyte panels are available that include hematocrit, electrolytes, glucose, lactate, and chemistries that evaluate renal function.

Procedures designed to protect the health practitioner from biohazard infections need to be diligently followed. These Universal Precautions are accepted standards that are dictated by the Occupational Safety and Health Administration (OSHA), the Centers for Disease Control and Prevention (CDC), and all organizations that oversee best practices for laboratory safety. Among these standards and good laboratory practices are hand washing, donning barrier protective clothing (gloves at minimum), and the avoidance of recapping needles. Accidental needle stick injuries have been associated with the transmission of life-threatening infections, such as HIV, HBV, and HCV, or a local bacterial infection that may cause permanent damage to the structure or function of the puncture site.

**Arterial Puncture and Sampling**

In adult patients, the preferred puncture site is the radial artery. This location is favored due to its access and available collateral circulation distal to the puncture site. Select the artery with the most prominent pulse for puncture. If both the left and right are equivalent, choose the nondominant arm (left arm in right-handed person).

In a stable hydrated patient, collateral circulation should be the primary site-selection criterion. The only site that normally provides effective collateral circulation is the radial artery. The brachial artery bifurcates at the level of the elbow into the radial artery (which runs along the lateral aspect of the forearm) and the ulnar artery (which runs along the medial aspect of the forearm). This arterial blood supply system provides collateral circulation to the distal aspects of the forearm and the hand. In the event that either artery becomes occluded, blood flow to the limb and hand will continue through the other artery. To ensure adequate collateral circulation, the modified Allen test should be performed on all patients when evaluating the radial artery as a possible puncture site. A positive modified Allen test will provide documentation of collateral circulation from the ulnar artery, and the test must be positive before the radial artery can be used for a sample site. Puncture site selection criteria should be strictly followed since the complication rate and severity of injury is directly related to the presence of collateral circulation to the hand via the ulnar artery.
Modified Allen Test Procedure
The modified Allen test procedure is as follows:

1. Have patient clench a tight fist.
2. Compress the radial artery and the ulnar artery of the same hand to obliterate pulses.
3. Have the patient release the fist. Blanching of the hand should be noticeable.
4. With the radial artery still compressed, release the pressure on the ulnar artery.
5. If good collateral circulation is present, blood should return to the hand within 15 seconds as evidenced by the hand returning to its normal color. If the color fails to appear, collateral circulation may be assumed to be inadequate, and the radial artery should not be used.

A patient who is unable to clench and release their fist should be evaluated in an alternative fashion (e.g., use of a pulse oximeter as a perfusion indicator).

Alternative Modified Allen Test Procedure
The alternative modified Allen test procedure is as follows:

1. Attach a pulse oximeter finger sensor to the hand being evaluated and observe the pulsatile waveform.
2. Compress the radial artery and the ulnar artery of the same hand to obliterate pulses. The waveform of the pulse oximeter should flatten.
3. With the radial artery still compressed, release the pressure on the ulnar artery.
4. If collateral circulation is present, the waveform of the pulse oximeter should revert to a similar pattern of perfusion that was observed before the compression of the arteries. However, if no pulsatile signal is noted, collateral circulation may be assumed to be inadequate, and the radial artery should not be used.

Radial Artery Puncture Technique
The radial artery puncture technique is as follows:

1. Collect all supplies and have the necessary items within arm’s reach before beginning the procedure.
2. The most critical step for successful puncture of the radial artery is proper positioning. The arm should rest on a flat surface, and a rolled towel should be placed under the wrist to hyperextend it approximately 60 degrees. This will stabilize the arm and help isolate the artery, reducing the likelihood of the artery rolling from beneath the needle.
3. Thoroughly prep the area with an iodine pad, and then with an alcohol swab using a circular motion moving away from the planned puncture site.
4. Since arteries are deep vessels and cannot be visualized, they must be palpated. There are two commonly used techniques for palpation of the radial artery:
   a. The artery is palpated in the crease of the wrist using the index and middle fingers. When the artery path is determined, the fingers are moved proximally 1–2 cm, and the puncture is made just distal to the index finger.
The artery is palpated in the same manner as in technique (a). When the artery path has been determined, the two fingers are separated 3–4 cm. The puncture site will be located midway between the two fingers.

To perform the actual puncture, hold the syringe as if holding a pencil. The bevel of the needle should be up, and the needle should be held at a 45-degree angle from the skin surface with the needle pointing toward the patient. When prepared, the needle insertion should proceed in a smooth fashion so the needle traverses to the subcutaneous tissue level in one plane. Upon entering the artery, a flash of blood will appear in the hub of the needle. At this point, discontinue advancement of the needle. The syringe should fill in a pulsating fashion. Avoid any unnecessary movement of the syringe while filling is taking place. If a flash occurs but filling stops prior to obtaining the sufficient sample volume, slightly retract the syringe. Frequently the needle bevel will go through the posterior wall of the artery. retracting the syringe will place the needle bevel back in the artery and allow filling to continue.

If the puncture attempt is unsuccessful or incomplete, the needle should be repositioned in an effort to obtain a sample without removing the needle completely.

- Slowly remove the needle until the top of the needle bevel is just beneath the skin. (Proceed slowly because the needle bevel is short, and it is easy to completely remove the needle.)
- Repalpate the artery and reassess the needle position.
- Slowly reposition the needle, being careful not to advance the needle tip into subcutaneous tissues while repositioning.
- Smoothly advance the repositioned needle until a flash appears in the hub of the needle or filling continues. Allow filling to continue until the desired sample has been collected.

If the puncture attempt is unsuccessful after repositioning, a second attempt can be made. If the puncture is still unsuccessful after the second attempt, terminate the procedure. Excessive attempts at repositioning should be avoided due to the increased possibility of needle occlusion from clot formation, which will prevent syringe filling.

After enough blood has filled the syringe, dictated by both the analyzer requirements and syringe/heparin requirements, withdraw the needle and immediately apply pressure directly to puncture site with clean gauze pad. While continuing to hold pressure on the puncture site, properly apply the needle protection guard.

Carefully remove the protected needle, and cap the syringe with a stopper. Never remove an exposed needle. Hold the syringe vertically, gently tap the syringe, and advance the plunger to remove air bubbles.

Continue to hold direct pressure to the puncture site for a minimum of 5 minutes. After 5 minutes, examine the puncture site for bleeding, which may be transcutaneous or subcutaneous in nature. Direct pressure should be continued until all bleeding has ceased. A pressure bandage may then be applied, based on the facility’s protocol.

Complications of Arterial Punctures
Peripheral arterial punctures for assessing the acid-base balance and oxygenation status are regarded as routine and safe. Minor complications include bleeding, hematoma, and vasospasm. More serious complications are rare and might require medical attention. These include infection, vessel obstruction, thrombosis, embolism, and vessel laceration.
Brachial and femoral arterial punctures have been discouraged as sample sites due to the lack of collateral circulation if a severe complication should occur. These anatomic locations should be used as secondary sites if a radial puncture is unsuccessful or if the patient is in shock or cardiac arrest when peripheral pulses are absent.

Significant depletion of blood due to the frequency of testing and volume sampled, termed iatrogenic anemia, can result in significant patient morbidity. Occurrence in newborns often results in blood transfusions, and when produced in adults, it can impede therapeutic progress.

The use of blood conservation devices, withdrawing the minimum sample volume required for analysis, appropriate use of noninvasive monitoring, and judicious ordering of discrete blood tests can reduce this generic complication of laboratory testing.

**Sampling Through an Indwelling Vascular Catheter**

Arterial, umbilical, and pulmonary artery catheters are often used as access devices for blood sampling. Placement of these catheters is common in critical care units and the operating room because they also serve to continuously monitor blood pressure. The use of indwelling catheters eliminates the need for vessel punctures and is preferred when multiple specimens are required over a relatively short time period.

Sampling techniques will vary depending on the system configuration and the use of blood conservation devices. The following are universal considerations when sampling from an indwelling vascular catheter:

- **Infection control:** Indwelling catheters present direct access to the systemic circulation. Attention to aseptic and sterile technique should be applied when manipulating the stopcock and exposing the line.
- **System connections:** Always ensure the tubing and stopcock connections fit appropriately and are hand tight. Cross threading or overtightening may crack the fittings and be a source of leakage that can lead to contamination or accidental hemorrhage. When attaching syringes, avoid accidental air injection.
- **Stopcock position:** The stopcock permits the flow of fluids and blood to be routed in a specific path—from pressure bag to patient, from patient to sampling port, or from pressure bag to sampling port. Therefore, proper position of the stopcock is essential in catheter performance, sample purity, and patient safety.
- **Waste sample removal:** All vascular lines are maintained with a solution, commonly a low concentration of heparin in normal saline, at a minimal drip rate to prevent protein and thrombin adherence to the tip and inside walls of the catheter. Prior to withdrawing the specimen, a waste sample must be evacuated to prevent preanalytical error from hemodilution and contamination from the solution. To ensure the specimen is free of artifacts, a waste volume equaling five to six times the system’s dead space has been recommended. Many neonatal intensive care units allow this waste sample to be reinjected back into the newborn to prevent additional loss of blood. If performing this procedure, care must be taken to maintain the sample’s integrity and sterility during the blood withdrawing maneuvers, and the waste sample must be inspected for clots before returning it back into the patient.
- **Specimen collection:** When sampling, the syringe should self fill. Avoid aspirating the specimen, which may hemolyze the specimen and cause trauma to the vessel.
Flushing the line: After the sampling has been completed, the line needs to be flushed with solution to prevent sediment of blood cells within the indwelling line, tubing, and stopcock. Typically, the maintenance solution that provides the continuous drip is used for this procedure. Catheter functionality is directly related to line care, and adequate flushing aids in system longevity.

Newborn considerations: If blood is withdrawn rapidly, complications of dropping systemic and cerebral blood pressure could occur. In addition, excessive flushing of the catheter system could create a condition of fluid overload in some labile infants.

**Newborn Capillary Heel Sticks**

Capillary blood collected from a newborn’s heel is often used as a source for blood gas testing. The posterior lateral surface of the heel (Figure 11.5) provides a readily accessible site for sampling with a low incidence of significant complications. Although a manual lancet-type device can be used to penetrate the skin and subcutaneous tissue, permanently retracting puncture devices are preferred due to the safety features for both the practitioner and the patient. These devices also have the advantages of creating a precise controlled depth of penetration, affording less bruising and inflicting minimal discomfort.

**Figure 11.5**

Preferred location for newborn heel stick.

*Note:* The safe sampling area to puncture a newborn’s heel is illustrated by the shaded zone. The area is marked by a line extending posteriorly from a point between the fourth and fifth toes and running parallel to the lateral aspect of the heel, and a line extending posteriorly from the middle of the great toe running parallel to the medial aspect of the heel. An incision is made with a self-retracting blade at a precise depth, specific to the age of the newborn, to optimize exposure to the capillary bed and avoid trauma to nerves and bones.
When comparing capillary results with arterial values, pH and PCO2 measurements typically demonstrate good correlation; however, PO2 is not clinically reliable. Capillary PO2 underestimates arterial results, and repeated measurements exhibit poor precision. To improve the PO2 correlation, procedures have been developed to arterialize the capillary blood and thereby improve the utility of the blood gas test. Arterializing capillary blood requires warming the heel to 42° C to enhance blood flow. This can be accomplished with the use of wet warm compresses or disposable chemical heat packs. Although historically there was widespread acceptance of this technique, there is no clinical evidence that this procedure improves PO2 correlation. In summary, acid-base determination from capillary blood gases is both useful and reproducible, but reliance on PO2 should be done with caution.

Capillary tubes conducive for blood gas testing are available in various configurations; however, not all designs are compatible with all blood gas analyzers. Preheparinized tubes have either lyophilized lithium or balanced heparin. To avoid preanalytical errors, check the analyzer’s recommendations regarding heparin type with the analyte panel to be tested. For safety reasons, laboratory guidelines require all capillary tubes be manufactured from plastic.

All blood gas specimens must be thoroughly mixed before analysis, regardless of whether they are stored in syringes or capillary tubes. To assist in this step, some capillary tubes are supplied with a small-diameter short metal stirring bar or rod called a flea. A flea can be inserted into a capillary tube after sample collection. When the specimen is ready for analysis, the operator can slide an external magnet over the length of the tube to mix the blood and then remove one endcap to slide the flea out of the capillary tube.

Preanalytical Error

Errors in blood gas measurement can have numerous sources, but all have the potential consequence of misdiagnosis or enabling inappropriate interventions. A variable that occurs prior to sample analysis is referred to as preanalytical error. Preanalytical errors can result from incorrect sampling site preparation, improper collection procedures, or inappropriate specimen storage. Errors that develop due to specimen incompatibility with the methodology of measurement are termed interference errors. Specific drugs, anticoagulants, and physiologic deviations are examples of interferences that can result in sensor/electrode performance issues that are unique to a manufacture or sensor design and produce inaccurate results. These sources of error are documented in the instrument’s user’s manual and should be reviewed by everyone who is responsible for instrument operation. Table 11.5 lists common sources of erroneous results for analyte panels measured by blood gas analyzers.

Additional sources of error that are not listed in Table 11.5 include the following:

- Heparin-type incompatibility, with selected analytes altering electrolyte results
- Severe leukocytosis and thrombocytosis dramatically consuming PO2 after sampling
- Use of tourniquet in venous blood collection procedure increasing lactate results
- Benzalkonium heparin coated catheters artificially increasing cation results (Na+, K+, Ca++) measured by ion selective electrodes
<table>
<thead>
<tr>
<th>Module</th>
<th>Analyte</th>
<th>Source of error</th>
<th>Type*</th>
<th>Effect</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Blood gases</td>
<td>Air bubble</td>
<td>P</td>
<td>↑</td>
<td>PCO₂ equilibration with air increasing pH proportionately</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delay in analysis</td>
<td>P</td>
<td>↓</td>
<td>Decrease in pH due to cellular metabolism</td>
</tr>
<tr>
<td>PCO₂</td>
<td>Blood gases</td>
<td>Air bubble</td>
<td>P</td>
<td>↓</td>
<td>Plasma equilibrates with ambient air</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delay in analysis</td>
<td>P</td>
<td>↑</td>
<td>Continued CO₂ production from cellular metabolism</td>
</tr>
<tr>
<td>PO₂</td>
<td>Blood gases</td>
<td>Air bubble</td>
<td>P</td>
<td>↑↓</td>
<td>Plasma equilibrates with ambient air</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delay in analysis</td>
<td>P</td>
<td>↓</td>
<td>Continued O₂ consumption by WBC and platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cooling sample</td>
<td>P</td>
<td>↑↓</td>
<td>Plasma equilibrates with ambient air</td>
</tr>
<tr>
<td>Hct</td>
<td>Electrolyte/Chemistries</td>
<td>Hypertonic hemodilution</td>
<td>I</td>
<td>↓</td>
<td>Interference with conductive sensors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotonic hemodilution</td>
<td>I</td>
<td>↑</td>
<td>Interference with conductive sensors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor sample mixing preanalysis</td>
<td>P</td>
<td>↑↓</td>
<td>Settling of cells, nonhomogeneous specimen</td>
</tr>
<tr>
<td>Na⁺</td>
<td>Electrolyte/Chemistries</td>
<td>Excessive liquid sodium heparin</td>
<td>P</td>
<td>↑</td>
<td>Contamination from solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contamination with infusate</td>
<td>P</td>
<td>↓↓</td>
<td>Hemodilution</td>
</tr>
<tr>
<td>K⁺</td>
<td>Electrolyte/Chemistries</td>
<td>Cooling sample/hemolysis</td>
<td>P</td>
<td>↑</td>
<td>Release of potassium from RBC into plasma</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>Electrolyte/Chemistries</td>
<td>Contamination with infusate</td>
<td>P</td>
<td>↓↓</td>
<td>Hemodilution</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Electrolyte/Chemistries</td>
<td>Postsampling elevation in pH</td>
<td>P</td>
<td>↓</td>
<td>[H⁺] competes with calcium for binding sites on albumin/proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postsampling reduction in pH</td>
<td>P</td>
<td>↑</td>
<td>[H⁺] competes with calcium for binding sites on albumin/proteins</td>
</tr>
<tr>
<td>Glucose</td>
<td>Electrolyte/Chemistries</td>
<td>Delay in analysis</td>
<td>P</td>
<td>↓</td>
<td>Continued RBC metabolism</td>
</tr>
<tr>
<td>Lactate</td>
<td>Electrolyte/Chemistries</td>
<td>Delay in analysis</td>
<td>P</td>
<td>↑</td>
<td>Continued RBC metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethylene glycol poisoning</td>
<td>I</td>
<td></td>
<td>Metabolite interference with enzymatic sensors</td>
</tr>
<tr>
<td>Blood Component</td>
<td>Preanalytical Errors</td>
<td>Interference Errors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tHb</td>
<td>Poor sample mixing preanalysis</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contamination with infusate</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperlipemia</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Settling of cells, nonhomogeneous specimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemodilution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference with spectrophotometry due to increased scatter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂Hb</td>
<td>Air bubble</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delay in analysis</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postsampling elevation in pH</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postsampling reduction in pH</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperlipemia</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PO₂ equilibration with air drives binding of O₂ to Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continued O₂ consumption by WBC and platelets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase pH decreases P₅₀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease pH increases P₅₀</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference with spectrophotometry due to increased scatter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COHb</td>
<td>Fetal hemoglobin</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperlipemia</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBF wavelength absorption closely approximates COHb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference with spectrophotometry due to increased scatter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MetHb</td>
<td>Hyperlipemia</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference with spectrophotometry due to increased scatter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P: preanalytical error; I: interference error.
Compounding the preanalytical and interference errors of blood analysis, arterial blood gas (ABG) interpretation can be misleading due to alterations in ventilation during sample collection. Tactile stimulation or the pain associated with specimen collection can cause fluctuations in spontaneous breathing patterns and alter pH and blood gases. If the patient is being supported by mechanical ventilation, abbreviated cycling due to pressure limiting and changes in functional positive end-expiratory pressure (PEEP) levels can also contribute to results that are not consistent with the patient’s true physiologic state. Failure to note these issues can lead to misinterpretation of ABG values and inappropriate patient care decisions.

ABGs are typically performed to evaluate the effects of changes to supplemental oxygen or ventilator settings. The time required to achieve equilibration to interventions will vary with the severity of the underlying disease. Monitoring the stability of pulmonary function with noninvasive monitoring may assist in timing when blood gas collection is appropriate and avoid premature analysis that may misrepresent the patient’s condition.

Meticulous attention to blood collection techniques will ensure a true reflection of the patient’s physiologic status, allowing for appropriate interpretation of results. It is the responsibility of all practitioners involved with blood gas testing to be aware of the unique sources of error that may produce erroneous results for each analyte reported.

**Analytic Phase**

The technology used to analyze pH and blood gases over the past few decades has developed to permit expanded utility and ease of instrument operations, but the methodology of measurement has remained relatively unchanged since the late 1950s. Modifications of current design have also allowed for miniaturization of the electrodes, which has enabled POC testing. Modern blood gas analyzers routinely add a fourth measurement, hematocrit, to the standard blood gas panel. As discussed earlier, electrolytes, chemistries, and tests of renal function are optional analytes that can be incorporated on the testing platform; however, for proposes of this text, the technology used in the most common blood gas panel (pH, PCO₂, PO₂, and hematocrit) will be discussed.

Before the introduction of blood samples, the analyzer’s electrode outputs are calibrated with known high and low concentrations of buffers, calibrated solutions, and gases. Some analyzers are calibrated before each test, and other instruments internally verify calibration at least every 30 minutes. Calibrations are usually referred to as being one or two point, where the electrode response is adjusted at one level (either high or low) or at two levels (both high and low), respectively.

A unique aspect of blood gas analysis that must be considered is the need for barometric pressure measurements. The barometric pressure reading is integrated into the calibration equation of the instrument. *Dalton’s law of partial pressures* describes the relationship between the barometric pressure and its constituent parts as being directly proportional. Therefore, as the barometric pressure changes due to weather patterns or if the analyzer is moved to a location of different altitude, the pressures exerted by the dissolved gases used for the calibration of the PO₂ and PCO₂ electrodes will be affected. To ensure accurate calibration of the blood gas electrodes, the internal instrument barometer should be verified for accuracy at least annually against a National Institute of Standards and Technology (NIST) traceable barometer and be documented.
Analyte analysis begins when a blood specimen is injected or aspirated into the sample chamber for measurement. Because temperature changes affect measured results, the electrode systems and the sample chamber are located inside a temperature-controlled block maintained at 37° C. Typically, when the blood sample contacts the electrodes in the chamber, it produces an electrical output that corresponds to a pH, partial pressure, or hematocrit value. Blood gas analyzers monitor the electrodes’ response continuously and, after a predetermined stabilization period, the instrument will display and/or print the measured results. When analysis is complete, the blood specimen is disposed of in one of two ways. Most analyzers pump the specimen into a waste container, and the electrode-sensor system is flushed with a rinse solution. Some newer units retain the specimen in the sealed reaction cartridge, which is then discarded.

The pH (Sanz) Electrode
The pH measurement is performed using two separate electrodes: a pH-measuring electrode and a reference electrode. Each electrode represents a half cell in which an electrical potential is developed. The measurement electrode is a silver-silver chloride electrode surrounded by a solution of constant pH and enclosed by a glass membrane sensitive to \([\text{H}^+]\). As the sample passes the glass membrane, the difference in \([\text{H}^+]/\text{H}_2\text{O}\) concentration on either side of the membrane changes the potential (voltage) of the electrode. The reference electrode, a silver-silver chloride electrode, produces a constant potential regardless of sample pH. A saturated electrolyte solution (potassium chloride) in the reference electrode and a semipermeable membrane permit current flow from the reference electrode through the sample in the measurement chamber to the measuring electrode. The potential difference is displayed on a voltmeter calibrated in pH units.

The PCO2 (Stowe-Severinghaus) Electrode
The PCO2 electrode system uses principles similar to those for pH measurement. It combines a glass pH-measuring electrode and a silver-silver chloride reference electrode surrounded in a bicarbonate buffer solution. A membrane permeable to CO2 but not to \([\text{H}^+]\) separates the sample from the measuring system. As CO2 diffuses through the membrane and into the buffer solution, the pH of the electrolyte changes because of the difference in carbonic acid concentration as follows:

\[
\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + [\text{H}^+] 
\]

The output of this modified pH electrode is proportional to the PCO2 present in the sample.

The PO2 (Clark) Electrode
The PO2 is measured by a polarographic electrode system consisting of a platinum cathode and a silver-silver chloride anode. An oxygen-permeable membrane separates the blood sample from the measuring system. Oxygen that diffuses through the membrane is reduced at the cathode when a voltage potential is applied between the anode and cathode. The following reaction represents the reduction that occurs at the cathode:

\[
\text{O}_2 + 2\text{H}_2\text{O} + 4\text{e}^- \rightarrow 4\text{OH}^- 
\]
The circuit is completed when silver is oxidized at the anode:

$$4Ag \rightarrow 4Ag^+ + 4e^-$$

The current developed by these reactions is directly proportional to the $P_{O_2}$ of the sample.

**The Hematocrit Electrode**

The methodology used to measure hematocrit with blood gas analyzers is called *conductimetry*. These hematocrit sensors use the principle that whole blood can conduct an electrical current, and this signal can be calibrated to reflect the hematocrit concentration. The plasma, which is rich in electrolytes, provides the conductive pathway. Erythrocytes, leucocytes, and platelets have a nonconductive coating that surrounds their outer membranes and impedes the signal transmission. A reduced electrical conduction implies an increase in the number of nonconductive cells. Conversely, the greater the electrical conduction, the less impedance, or the less blood cells in the sample.

Hematocrit is the percentage of erythrocytes in a whole blood sample. Red blood cells contribute to 98% of all nonconducting mass in a whole blood sample (Table 11.6). Hematocrit sensors convert the electrical conduction signal to the total erythrocyte number or hematocrit concentration.

The conductive method for hematocrit measurement is robust under normal physiological conditions; however, therapies that significantly alter the specimen’s salt concentration can produce a bias. Manufacturers of conductimetric sensors use normal donor whole blood to calibrate instruments. However, some clinical interventions can produce significant hemodilution with hypertonic solutions, causing conductive hematocrit sensors to understate hematocrit concentration. This occurs during cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) procedures when pump priming solutions are mixed with a patient’s systemic blood volume, and in fluid resuscitation protocols for trauma victims.

**Table 11.6**

<table>
<thead>
<tr>
<th>Cells</th>
<th>Average cellular mass (fl)</th>
<th>Average normal value (fl/mm³)</th>
<th>Total cellular mass (fl/mm³)</th>
<th>% cellular mass per mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>198</td>
<td>$5,000 \times 10^3$</td>
<td>990,000</td>
<td>97.94</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytes (70%)</td>
<td>305.0</td>
<td>$5.6 \times 10^3$</td>
<td>17,080</td>
<td>1.72</td>
</tr>
<tr>
<td>Lymphocytes (20%)</td>
<td>52.5</td>
<td>$1.6 \times 10^3$</td>
<td>84</td>
<td>0.01</td>
</tr>
<tr>
<td>Monocytes (10%)</td>
<td>125.0</td>
<td>$0.8 \times 10^3$</td>
<td>100</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelets</td>
<td>11.0</td>
<td>$290 \times 10^3$</td>
<td>3,190</td>
<td>0.32</td>
</tr>
</tbody>
</table>

fl, femtoliter (cubic micrometer); mm³, cubic millimeter; RBC, red blood cell; WBC, white blood cell.

Without accounting for these effects, the hematocrit result produced by conductimetric sensors could be inaccurate and misinterpreted, leading to erroneous interventions and wrong diagnoses. Some manufacturers of blood gas analyzers provide custom correlation adjustments to circumvent these issues. The use of these correction features requires revalidation every 6 months to remain compliant with regulatory standards. In summary, due to the inherent methodology of conductimetry, interpretation of results should be made with caution whenever fluids are rapidly administered.

**Temperature-Corrected Blood Gases**

Accidental and medically induced hypothermia (body core temperature < 35° C) presents challenges in patient management, as do septic patients who are hyperthermic (body core temperature > 39° C). In these conditions the basal metabolic rate is altered, as evidenced by changes in oxygen consumption and carbon dioxide production. As body core temperatures begin to move to extreme limits, the fundamentals of blood gas chemistry also change. The pH, PaCO₂, and PaO₂ are affected due to solubility coefficients, temperature–pressure relationships, and modified binding of oxygen to hemoglobin.

Depending on the severity of the core temperature and the patient’s clinical management, the analysis of blood gases may be requested to be reported in a temperature corrected format. Blood gas analyzers are designed to offer this feature. Although different temperature correction formulas may yield slightly different results, the following can be expected:

- The pH varies inversely with temperature, 0.0147 pH units/°C
- The PCO₂ varies directly with temperature, 4–5%/°C
- The PO₂ varies directly with temperature, 6–7%/°C

It is important when reporting results to clearly document both the corrected and uncorrected values.

**Postanalytic Phase**

The postanalytic phase of testing primarily encompasses reporting results. Accurate and complete documentation, whether performed manually or electronically, is of paramount importance. All patient results should be reported with the analyzer’s normal range (Table 11.7) as documented in the policy and procedures manual. When applicable, communication to the medical staff regarding critical or alert values (Table 11.7) needs to occur in a timely fashion.

Reference ranges are valuable guidelines for the clinician, but they should not be regarded as absolute indicators of health and disease. Reference ranges should be used with caution since values for healthy individuals often overlap significantly with values for persons afflicted with disease. In addition, laboratory values may vary significantly due to method differences and mode of standardization. Reference ranges must be used with caution because they depend on a number of factors, such as sex, age, and normal physiological condition.

**Critical reportable values**, or **alert values**, are defined as test results that are associated with impending morbidity–mortality. The blood gas laboratory policy and procedures manual should document the protocol for how to rapidly communicate critical reportable values to the...
medical staff. Documenting this communication is an essential component of the standards that regulate laboratories. Within Table 11.7 is a partial list of low and high critical values developed from a survey by the College of American Pathologists.26

Error messages received during the analytic phase of testing, and potential erroneous results due to either preanalytical error or interference-related issues, need to be evaluated and recorded. In addition, the names of all individuals associated with the blood gas test need to be recorded in case questions related to the results are investigated.

Table 11.7
Normal Range and Critical Reporting Values of Commonly Measured Analytes

<table>
<thead>
<tr>
<th>Module</th>
<th>Analyte</th>
<th>Units</th>
<th>Normal ranges*</th>
<th>Critical values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood gases</td>
<td>pH</td>
<td>n/a</td>
<td>7.35–7.45</td>
<td>≤ 7.20 ≥ 7.60</td>
</tr>
<tr>
<td></td>
<td>PaCO₂</td>
<td>mmHg</td>
<td>35.0–45.0</td>
<td>≤ 20 ≥ 70</td>
</tr>
<tr>
<td></td>
<td>PaO₂</td>
<td>mmHg</td>
<td>83–108</td>
<td>≤ 40 n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ferry: Breathing air at 1 atm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ferry: Declines with age</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>%</td>
<td></td>
<td>Male: 39–51</td>
<td>≤ 20 ≥ 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: 35–47</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Na⁺</td>
<td>mmol/L</td>
<td>136–146</td>
<td>≤ 120 ≥ 160</td>
</tr>
<tr>
<td></td>
<td>K⁺</td>
<td>mmol/L</td>
<td>3.4–4.5</td>
<td>≤ 2.8 ≥ 6.2</td>
</tr>
<tr>
<td></td>
<td>Ca²⁺</td>
<td>mmol/L</td>
<td>1.15–1.29</td>
<td>≤ 0.8 ≥ 1.5</td>
</tr>
<tr>
<td></td>
<td>Cl⁻</td>
<td>mmol/L</td>
<td>98–106</td>
<td>≤ 80 ≥ 120</td>
</tr>
<tr>
<td>Metabolites and other chemistries</td>
<td>Glucose</td>
<td>mg/dL</td>
<td>70–105</td>
<td>≤ 40 ≥ 450</td>
</tr>
<tr>
<td></td>
<td>Lactate</td>
<td>mg/dL</td>
<td>4.5–14.4</td>
<td>n/a ≥ 36</td>
</tr>
<tr>
<td></td>
<td>BUN</td>
<td>mg/dL</td>
<td>5–23</td>
<td>≤ 3.0 ≥ 80.0</td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td>mg/dL</td>
<td>0.9–1.3</td>
<td>≤ 0.2 ≥ 5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male: 13.5–17.5</td>
<td>≤ 7.0 ≥ 20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: 12.0–16.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O₂Hb</td>
<td>%</td>
<td>94.0–98.0</td>
<td>≤ 75 n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ferry: Breathing air at 1 atm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COHb</td>
<td>%</td>
<td>0.5–1.5</td>
<td>n/a ≥ 15</td>
</tr>
<tr>
<td></td>
<td>MetHb</td>
<td>%</td>
<td>0.0–1.5</td>
<td>n/a ≥ 10</td>
</tr>
</tbody>
</table>

*Reference ranges are for arterial values in the adult population.
**Interpretation of Blood Gases**

The interpretation of blood gases requires a structured, systematic approach. First delineate all results that relate to oxygenation from those that evaluate acid-base balance and ventilation.

**Interpretation of Oxygen Status**

When interpreting oxygenation from an arterial blood gas sample, one must consider the entire spectrum comprising O₂ transport (i.e., PaO₂, FIO₂Hb, and hemoglobin–hematocrit concentration).

A normal PaO₂ is dependent on the barometric pressure, FIO₂, and age. Governed by Dalton’s law of partial pressures and the concepts implied in the alveolar air equation, a general rule of thumb is as follows: For each 10% increase in FIO₂, the P IO₂ increases by 75 mmHg. Assuming normal pulmonary function, the PaO₂ should correspondingly increase by 50 mmHg. In other words, the expected PaO₂ is equal to the oxygen concentration × 5. The result of this calculation is an estimate or an approximation and is convenient for bedside evaluation, but it is not to be used as a variable in physiologic calculations. Refer to the following examples:

- Breathing 40% oxygen, the predicted PaO₂ is approximately 200 mmHg.
- Breathing 60% oxygen, the predicted PaO₂ is approximately 300 mmHg.
- Breathing 100% oxygen, the predicted PaO₂ is approximately 500 mmHg.

The classification for severity of PaO₂ is provided in Table 11.8.

PaO₂ results may appear normal for patients suffering from anemic, stagnant, or histotoxic hypoxia. Hemoximetry used in conjunction with PaO₂ measurements may be invaluable in further assessing the patient’s oxygen status.

**Effects of Age on PaO₂ Reference Ranges**

Reference ranges for PaO₂ are age related. In persons younger than age 60 years who are breathing room air at sea level, PaO₂ values of 80–95 mmHg are considered normal. In persons older than age 60 years, 1 mmHg per year is subtracted from the lower limit of the reference range, with a maximum decrease in range no greater than 20 mmHg.

**Table 11.8**

<table>
<thead>
<tr>
<th>Classification/severity</th>
<th>Adult</th>
<th>Newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxemia</td>
<td>&gt; 100</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Normoxia</td>
<td>80–100</td>
<td>60–90</td>
</tr>
<tr>
<td>Mild hypoxemia</td>
<td>60–79</td>
<td>50–59</td>
</tr>
<tr>
<td>Moderate hypoxemia</td>
<td>45–59</td>
<td>40–49</td>
</tr>
<tr>
<td>Severe hypoxemia</td>
<td>&lt; 45</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>
Special Considerations
Although a low PaO₂ is not considered normal, that does not mean it is not safe. PaO₂ results greater than 55–60 mmHg are considered relatively safe from contributing to comorbidity. In the presence of a normal concentration of hemoglobin, this PaO₂ range will usually produce oxygen saturation results greater than 88% and cT₀₂ greater than 18 mL/dL. Interventions intended to correct to normoxia in individuals with chronic hypercarbia may cause depression of the peripheral chemoreceptors and further complicate their respiratory insufficiency.

Management of newborn hypoxemia requires an in-depth knowledge of congenital cardiac anomalies and the unique cardiopulmonary dynamics of this population, which is not included in this chapter. However, consequences of overcorrecting apparent hypoxemia in newborns can result in the development of retinopathy, leading to blindness or severe alterations in effective cardiac output.

Interpretation of Acid-Base Balance
Interpretation of the acid-base balance of arterial blood begins with assessment of the variables described in the Henderson-Hasselbalch equation: pH, PaCO₂ or H₂CO₃, and HCO₃⁻.

1. A normal pH is in the range of 7.35–7.45:
   - Results < 7.35 indicate academia.
   - Results > 7.45 indicate alkalemia.
   - The classification and/or severity of pH is presented in Table 11.9.²⁷
2. A normal PaCO₂ is in the range of 35–45 mmHg:
   - Results > 45 mmHg indicate hypercarbia and elevate H₂CO₃, thereby promoting acidemia.
   - Results < 35 mmHg indicate hypocarbia and reduce H₂CO₃, thereby promoting alkalemia.
   - PaCO₂ is considered the respiratory component of acid-base balance.
3. A normal HCO₃⁻ is in the range of 24–26 mEq/L:
   - Results < 24 mEq/L promote academia.

Table 11.9

<table>
<thead>
<tr>
<th>pH</th>
<th>Classification/severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7.20</td>
<td>Severe acidemia</td>
</tr>
<tr>
<td>7.20–7.29</td>
<td>Moderate acidemia</td>
</tr>
<tr>
<td>7.30–7.34</td>
<td>Mild acidemia</td>
</tr>
<tr>
<td>7.35–7.45</td>
<td>Normal pH</td>
</tr>
<tr>
<td>7.46–7.50</td>
<td>Mild alkalemia</td>
</tr>
<tr>
<td>7.51–7.55</td>
<td>Moderate alkalemia</td>
</tr>
<tr>
<td>&gt; 7.55</td>
<td>Severe alkalemia</td>
</tr>
</tbody>
</table>
Interpretation of Blood Gases

311

Results > 26 mEq/L promote alkalemia. 
• HCO₃⁻ is considered the metabolic component of acid-base balance.

4. Next, describe the cause of the pH abnormality, either respiratory (Pa CO₂ driven) or due to a metabolic disorder altering HCO₃⁻ concentration.
• pH abnormalities that are produced by only one component, PaCO₂ or HCO₃⁻, are termed pure conditions.
• pH abnormalities that are produced by both PaCO₂ and HCO₃⁻ are termed mixed conditions.
• If both PaCO₂ and HCO₃⁻ are outside of their normal range, first identify which result could have altered the pH in the measured direction. That will give you a clue as to the primary cause of the pH abnormality. In order to maintain pH homeostasis, physiologic changes to either ventilation or electrolyte balance occurs to compensate for the primary acid-base abnormality.
• If the compensatory mechanism has started but the pH is still abnormal, the term partially compensated is used to describe the condition.
• If the compensatory mechanism has shifted the pH to within normal limits, the term compensated is used to describe the condition.
• Table 11.10 illustrates all possible combinations of acid-base disturbances.

Table 11.10

<table>
<thead>
<tr>
<th>pH</th>
<th>PaCO₂ (mmHg)</th>
<th>HCO₃⁻ (mEq/L)</th>
<th>Acid-base disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.35–7.45</td>
<td>35–45</td>
<td>24–26</td>
<td>Normal</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>N*</td>
<td>Pure respiratory acidemia</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>Pure respiratory alkalemia</td>
</tr>
<tr>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>Pure metabolic acidemia</td>
</tr>
<tr>
<td>↑</td>
<td>N</td>
<td>↑</td>
<td>Pure metabolic alkalemia</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Mixed respiratory and metabolic acidemia</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Mixed respiratory and metabolic alkalemia</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Partially compensated respiratory acidemia</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Compensated respiratory acidemia</td>
</tr>
<tr>
<td>7.45</td>
<td>↓</td>
<td>↓</td>
<td>Partially compensated respiratory alkalemia</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Compensated respiratory alkalemia</td>
</tr>
<tr>
<td>7.35</td>
<td>↓</td>
<td>↓</td>
<td>Partially compensated metabolic acidemia</td>
</tr>
<tr>
<td>↑</td>
<td></td>
<td></td>
<td>Compensated metabolic acidemia</td>
</tr>
<tr>
<td>7.45</td>
<td>↑</td>
<td>↑</td>
<td>Partially compensated metabolic alkalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Compensated metabolic alkalemia</td>
</tr>
</tbody>
</table>

*Normal result
A laboratory quality management system (QMS) is a sequential integration of policies and processes that transform a physician’s order into laboratory information. The objectives of QMS are to provide quality, accurate diagnostic test results and reduce the potential for medical errors that waste resources and harm patients. The QMS includes the following components: (a) policy and procedures manual, (b) quality control program, (c) proficiency testing, (d) system audits, (e) operator training and competency certification, and (f) inventory management.

**Quality Management of the Blood Gas Laboratory**

The policy and procedures manual is a set of documents that clearly describes the guidelines related to all testing as defined by the institution. An annual review of the manual and revisions, if appropriate, are required by the medical director named on the CLIA license. In general, the policies provide a framework that accomplishes the following:

- Details patient rights and safety and confidentiality regulations
- Defines authority and levels of responsibility at each phase of testing
- Describes the academic and/or professional requirements for operators
- Outlines training for a new hire orientation period and the ongoing frequency of training throughout employment
- Describes employee safety guidelines in a biohazardous environment
- Defines the quality control program
- Records the frequency of review of the policy and procedures manual by operators
- Describes the activities surrounding documentation of results and correction of errors

**Quality Control**

A robust quality control (QC) program assures that the instruments used for patient testing meet the manufacturers’ specifications for optimal device performance. Periodic monitoring of QC provides data regarding the function of the test system. The system incorporates the three primary elements that will ultimately produce a test result: the instrument, the analyte reagent or disposable cartridge, and the operator performing the test.

**Internal or Electronic Quality Control**

POC devices and some models of benchtop instruments are equipped with a self-contained QC test that checks the integrity of the electronic circuitry of the analyzer. Typically, various levels of current or voltage are passed through the electronic components that analyze the assays. The electronic output of this test determines functionality from a device perspective, but it does not qualify the reagents, cartridges, or the operator. Most manufacturers recommend electronic QC to be performed, at a minimum, every 8 hours during a patient testing day combined with periodic external or liquid quality control to assess the complete test system.
External or Liquid Quality Control (LQC)

All blood gas–electrolyte–hemoximetry analyzers are required to qualify the entire test system to ensure optimal instrument performance and accuracy of reported results. This procedure uses a liquid media to simulate a whole blood sample that contains a controlled concentration of pH, PCO₂, PO₂, electrolytes, and other analytes to be tested. Commercially available LQC is assayed, or tested, and the expected results or recovery are documented. These LQC tests are typically manufactured in concentrations that mimic both normal and abnormal physiologic conditions.

Due to inherent reagent or sensor interferences and manufacturing design characteristics, not all commercially produced LQC material is compatible with every instrument. This incompatibility is known as the matrix effect. It is therefore essential to use the LQC recommended by each instrument’s manufacturer for your specific model. This will ensure LQC tests that produce results in a predefined range.

The frequency of electronic quality control and LQC is determined by each facility based on the manufacturers’ recommendations and the regulatory body that certifies each laboratory. In addition, some institutions may increase their QC testing at the discretion of the medical director who oversees blood gas testing. The guidelines that dictate the QC program are documented in the policy and procedures manual, and the detailed result of each QC test is reviewed for performance and filed for future reference. The QC log must record the following:

- Date and time
- Instrument serial number
- Type of QC test
- Test operator
- Quantitative results
- Manufacture type and lot number of LQC material

Analysis of the QC data should indicate if the results are within predefined limits and/or identify trends or shifts in serial measurements. If the results fall outside of expected ranges, investigation of the root cause followed by corrective action and retesting is required. All records must be retained on-site for inspection for 2 years.

Proficiency Testing

Proficiency testing (PT) is a comprehensive tool in the QMS that evaluates the entire blood gas test: instrument, reagent, cartridge, and operator. PT involves the analysis of specimens with unknown values and statistically compares the results with a peer group. A minimum of 10 laboratories from a regional geographic area comprise a peer group. The reporting facilities in the peer group must use the same model device and test at a similar altitude. PT samples must be analyzed as patient tests within the environment where testing occurs. PT providers assess the individual site’s data and notify the laboratory of how their results compared to the peer group. Results of the PT event are also sent to the regulatory agency designated by the laboratory. PT evaluates the testing system and provides assurance that patient diagnosis and management is transparent regardless of the laboratory conducting the analysis.
All analytes defined by CLIA as “regulated” must participate in a PT program. When evaluating blood gas–electrolytes–hemoximetry instruments, PT assessment should be conducted periodically throughout the year as stipulated by the laboratory certification provider. If the facility has more than one analyzer, CLIA recommends that PT events should be rotated among all analyzers and among all personnel who routinely test patient specimens.

A “satisfactory” performance is set at 80% for each individual testing event. Typical PT programs supply five samples at various levels or concentrations of analytes. This allows for one unacceptable result or deficiency. If a deficiency is cited by the PT provider, the site must investigate and document its findings. The report should include possible contributing factors, such as improper storage or handling of the PT material, if the testing instrument was not in calibration, or if the reagents/cartridges had expired. If the exact cause cannot be identified, the documentation should contain all supporting studies that confirm the instrument was in calibration for all analytes reported at the time of testing.

The PT event cannot be referred to another laboratory for testing, and there can never be communication with other laboratories to discuss results prior to site notification. This statement is to be included in the policy and procedures manual of the blood gas laboratory. If a facility is identified as compromising the intent of the PT program in this manner, the blood gas laboratory will be decertified, and the institution may incur further penalties.

System Audits

Integrated into every QMS is the need for continual improvement. In this regard, system audits are an essential part of every blood gas laboratory. They allow for closer examination of the policies and procedures and can identify possible sources of error before they occur. Auditors should be familiar with the test system but not involved with the development of the policies or procedures.

Auditing the entire process is a necessary step to verify the functionality of QMS. Because there are many steps to each part of the process, each subsection can be divided into component parts, and separate auditors can be assigned to review particular processes.

Parts of QMS that could be audited are the following:

- Patient identification
- Sample collection and handling
- Instrument operation
- Instrument maintenance
- QC data analysis
- Results reporting
- Proficiency testing
- Noncompliance management

Auditing QMS is a proactive process that can enhance the ability to produce a quality patient result and, in turn, provide a high level of confidence in the blood gas laboratory.
Operator Training and Competency Certification

Annual training is required by all regulatory bodies and should entail a review of the policy and procedures manual. The training documentation can consist of a written test after the operator reviews the manual, direct observation of specimen testing, and certification with a skills checklist. The skills checklist should include obtaining a sample, performing an analysis, reporting results, correctly managing critical values, and identifying the location of the policy and procedures manual. Final validation of competency can be demonstrated by successful testing of an unknown sample.

Inventory Management

The date when reagents–cartridges and supplies are received is documented to assist with inventory management. It is also necessary to note when supplies or reagents–cartridges are removed from temperature-controlled storage units because this may affect the product shelf life. For example, if the reagent shelf life has been determined based on refrigeration conditions, and moving the reagent to room temperature shortens that period, then modifying the expiration date on each box or individual reagent package is required.

Daily temperature monitoring and recording of the instrument’s environment, reagents or POC disposable cartridges, and LQC material is mandatory. This requirement is necessary to ensure that the manufacturers’ recommendations for temperature are observed because temperature cycling events in the storage area or testing site may produce inaccurate results.

Associated Technologies

Blood gas analysis is the most commonly requested test performed in the clinical laboratory for evaluating pulmonary function. However, as previously discussed, the discrete measurement of pH and blood gases, with or without electrolyte or hematocrit analysis, is not always clinically appropriate or diagnostically sensitive. Associated technologies have been designed to be used either in conjunction with blood gases to complement or enhance the testing analytic capability or as surrogate devices to provide surveillance monitoring between ABG analyses. These alternate systems are well entrenched in patient management protocols, guidelines, and standards. To ensure safety and appropriate clinical utility, all healthcare practitioners, regardless of discipline, should understand the intended applications and device limitations of these technologies prior to use.

Medical devices used to assess physiologic function fall into two classifications: analyzers and monitors. An analyzer is a diagnostic device that permanently removes body tissues or fluids to make a measurement. The resultant data is accurate and precise, but the test only reflects a single point in time, the moment when the blood was sampled. Unless serial measurements are made, interpretation of test results cannot reflect the progression of the patient’s condition or anticipate the outcomes of interventions. In the United States, analyzers are regulated under CLIA standards and require a laboratory license for operation. Examples of analyzers include blood gas analyzers and hemoximeters (CO-oximeters).
Chapter 11: Blood Gases and Associated Technologies

A monitor also measures physiologic function, but unlike the analyzer, it does not permanently remove the specimen for measurement or disrupt the anatomic pathway for sampling. The greatest benefit of monitors is data trending and constant surveillance of real time patient status. Monitors are not diagnostic devices, and therefore they do not fall under CLIA jurisdiction and are not subject to regulations that apply to the clinical laboratory. Clinical practice guidelines provide standards and recommended applications where monitors have demonstrated safety and efficacy. Examples of monitors include pulse oximeters, pulse CO-oximeters, and transcutaneous and continuous blood gas technologies.

Hemoximetry

Hemoximetry, also known as whole blood CO-oximetry, is the spectrophotometric analysis of the concentration of total hemoglobin (tHb) and the percent saturations of the hemoglobin derivatives: oxyhemoglobin (O₂Hb), reduced or deoxygenated hemoglobin (HHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb). Some hemoximeters also include the measurement of sulfhemoglobin (SulfHb) and fetal hemoglobin (HbF). Hemoximetry of arterial blood is the only clinical laboratory diagnostic test for the evaluation of anemic hypoxia, including carbon monoxide toxicity, methemoglobinemia, and sulfhemoglobinemia. (See Table 11.7 for normal ranges and critical values.)

Multiwavelength spectrophotometry is the analytical method used to measure the different derivatives of hemoglobin. The Beer-Lambert law governs the analysis and states; absorbance varies linearly with both the cell path length and the analyte concentration. In other words, if several light-absorbing compounds are present in a solution (i.e., O₂Hb, HHb, COHb, MetHb), the concentration of each compound can be measured if the compounds differ in their optical absorbances and if optical density is measured at as many wavelengths as there are compounds present.

Commercially available hemoximeters use a minimum of seven light-emitting diodes (LEDs) to measure O₂Hb, HHb, COHb and MetHb (Figure 11.6). Some manufacturers have included as many as 512 different wavelengths to measure the standard hemoglobin derivatives and other assorted dyshemoglobins and to eliminate interferences by light absorbing drugs, dyes, and compounds.

Sampling, storage, and handling requirements for hemoximetry specimens are consistent with those established for ABG testing. Similarly, most sources of preanalytical errors that produce erroneous results with ABG analysis also affect hemoximetry specimens. (See Table 11.5 for a listing of preanalytical errors.)

Whole blood multiwavelength spectrophotometry is the gold standard method to measure oxyhemoglobin saturation because all of the fractions of hemoglobin (O₂Hb, HHb, COHb, MetHb) are used in the calculation. For this reason, the results of oxygen saturation reported from a hemoximeter are the most accurate, but they invariably are lower than results obtained from either a pulse oximeter or a calculation from an ABG. The explanation for these discrepant results is revealed in the formulas used for calculation.

Hemoximetry calculates fractional oxygen saturation (FO₂Hb) as:

\[
\text{FO}_2\text{Hb} = \left( \frac{\text{O}_2\text{Hb}}{\text{tHb}} \right) \times 100
\]

where \( \text{tHb} = (\text{O}_2\text{Hb} + \text{HHb} + \text{COHb} + \text{MetHb}) \)
A pulse oximeter calculates functional oxygen saturation (SpO2) as:

$$\text{SpO}_2 = \frac{(O_2 \text{Hb} \times t\text{Hb})}{t\text{Hb}} \times 100$$

where $t\text{Hb} = (O_2 \text{Hb} + HHb)$

A blood gas analyzer calculates functional oxygen saturation (SO2) as:

$$\text{SO}_2 = \frac{100[(\text{PO}_2')^4 - 67.07(\text{PO}_2')^3 + 2121(\text{PO}_2')^2 - 8332 \times \text{PO}_2']}{[(\text{PO}_2')^4 - 67.07(\text{PO}_2')^3 + 2396(\text{PO}_2')^2 - 31350 \times \text{PO}_2' + 936000]}$$

where

$$\text{PO}_2' = \text{PO}_2 \times 10^{0.48 \times (pH - 7.40)}$$

Oxygen content (ctO2) is an integral calculation provided by most hemoximeters. The ctO2 formula uses the tHb and all fractions of the measured hemoglobin derivatives in its computation. Clinically, ctO2 is evaluated with other cardiopulmonary studies in the assessment of various etiologies of anemic hypoxia, chronic respiratory insufficiency, acute respiratory failure, and the systemic inflammatory response syndrome (SIRS). The ctO2 value is also incorporated into hemodynamic and oxygen transport equations (i.e., cardiac output, pulmonary blood flow, and systemic vascular resistance).
Oxygen content is the sum of the combined volume of oxygen carried by tHb and oxygen dissolved in the plasma, sampled from a specific vascular source (e.g., arterial or mixed venous specimen). The ctO2 calculation is represented in the following formula:

\[
ctO_2 = (tHb \times \text{Hüfner number} \times F_O2Hb) + (P_O2 \times 0.003)
\]

where:
- \( tHb \) = Total hemoglobin concentration in g/dL
- \( \text{Hüfner number} \) = Volume of oxygen in mL bound by 1 g of Hb
- \( F_O2Hb \) = Fractional O2Hb
- \( P_O2 \) = Partial pressure of oxygen dissolved in plasma, expressed in mmHg
- 0.003 = The conversion of 1 mmHg of dissolved oxygen in plasma to the proportional volume, expressed in mL/dL.

Over the course of many decades, publications have recorded different values for the Hüfner number. This has been a source of confusion in both understanding and calculating differences in the net result of oxygen content. In 1894, at the University of Tübingen, Professor Dr. Gustav von Hüfner (1840–1908) found that 1g of hemoglobin could maximally bind 0.0598 mmol of oxygen gas. Multiplying this number by the molar volume of an ideal gas, 22.4 mL/mmol, the value 1.34 mL/g was derived. His experiments used carbon monoxide to calculate the maximal binding potential of hemoglobin and then extrapolated the results for oxygen. Many years later it was discovered that at full saturation, one molecule of hemoglobin tetramer had the capacity to bind 1.39 mL/g. The International Union of Pure and Applied Chemistry (IUPAC) recommend that a factor of 1.36 mL/g in vitro at standard temperature and pressure (STP) be used. Whether the oxygen binding factor is 1.34 or 1.36 or 1.39 can be debated as to its academic validity; however, it is important that within an institution the same value is used to avoid inconsistencies.

The oxygen saturation variable used in the ctO2 formula can produce significant variances if SO2 is exchanged for \( F_O2Hb \). The Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS, National Committee for Clinical Laboratory Standards) stresses that the variables of \( F_O2Hb \), tHb, and \( P_O2 \) need to come from the same sample specimen for clinical accuracy; and \( F_O2Hb \) should not be substituted with a calculated (SO2) value. Standalone hemoximeters do not measure \( P_O2 \) in their test panel. This technologic omission eliminates the plasma portion of the oxygen content formula. As described previously, the contribution that \( P_O2 \) offers to the oxygen content formula is 1% of the total and therefore can be considered negligible under most clinical scenarios. Furthermore, CLSI states, “Clinically significant errors can result from incorporation of such an estimated value for oxygen saturation in further calculations, such as shunt fraction, or by assuming that the value obtained is equivalent to fractional oxyhemoglobin.”

Beyond its use as a laboratory analyzer for the diagnosis of pathologies related to anemic hypoxia, hemoximeters are often used for the evaluation of anatomic and great vessel shunts in the cardiac catheterization laboratory. During right-sided heart catheterization procedures, serial blood samples are drawn from the inferior and superior vena cava, various locations...
within the right atrium and right ventricle, and the pulmonary artery. Analyses of the specimens are performed with close scrutiny of the \( \text{FO}_2\text{Hb} \). When evaluating a patient with normal cardiac and vascular anatomy, all \( \text{FO}_2\text{Hb} \) results sampled are expected to have an \( \text{FO}_2\text{Hb} \) of approximately 70%. However, in the presence of left-to-right shunting, the \( \text{FO}_2\text{Hb} \) result sampled adjacent to a functional communication rises sharply. This is caused by oxygenated blood leaking through a septal wall or vascular anomaly. The protocol of performing serial \( \text{FO}_2\text{Hb} \) measurements in the evaluation of an anatomic or great vessel shunt is called the \textit{saturation step-up procedure}. This term illustrates the graphic representation of multiple relatively low \( \text{FO}_2\text{Hb} \) results followed by one markedly elevated value, depicting a step change increase saturation.

In summary, relative to specific diagnostic sensitivities, a calculated \( \text{SaO}_2 \) from a blood gas analyzer or an \( \text{SpO}_2 \) from pulse oximetry have clinical utility, but they should never be substituted for hemoximetry in cases of suspected carbon monoxide toxicity or methemoglobinemia. Precise measurements of \( \text{FO}_2\text{Hb} \) and \( \text{ctO}_2 \) are required during right-sided cardiac catheterization procedures for detection of anatomic shunts. This unique application of hemoximetry is required to ensure a correct diagnosis and a properly staged severity index.

**Pulse Oximetry**

A pulse oximeter is an optical sensor technology used to estimate the functional arterial oxygen saturation (\( \text{SpO}_2 \)). The benefits of pulse oximetry center on its ease of use, noninvasive design, and rapid assessment of hypoxemia. Pulse oximeters can provide either a spot-check measurement or continuous trending of the patient’s oxygenation. Common clinical applications include the following:

- Titration of supplemental oxygen, PEEP, or continuous positive airway pressure (CPAP)
- When ABG testing would not be practical (i.e., patient transport, sleep study for the diagnosis of obstructive sleep apnea)
- To monitor the effectiveness of supplemental oxygen in a medically supervised cardiopulmonary rehabilitation program

The sensor is composed of two components: a light housing containing two LEDs and a photodetector or photodiode. Some of the light that is directed through the skin is absorbed by muscle, bone, and blood (including hemoglobin), and the remaining light passes through the tissue and is measured by the photodetector. The same optical absorption concept described previously for hemoximetry has been modified for pulse oximetry (Figure 11.7). As the pulsatile arterial blood flow rhythmically surges through the tissue under the sensor, the optical absorption increases due to the added bolus of blood. This intermittently reduces the light measured by the photodetector and differentiates pulsatile flow from a nonpulsatile signal. LED absorption measurements are made during the pulsatile phase of monitoring and after signal averaging; the \( \text{SpO}_2 \) and heart rate are displayed. Some pulse oximeters display the pulsatile graphic pattern and optical signal strength.
Pulse oximeters use LED wavelengths of 660 nm (red light) and 905 to 940 nm (infrared light) because these correspond best to the absorption characteristics of oxyhemoglobin and reduced hemoglobin. The sensor is positioned over an anatomic location (i.e., fingertip, earlobe or pinna, bridge of the nose, foot or toe of a newborn, or forehead). Sensors are available in reusable and disposable configurations and are designed for infant, pediatric, or adult populations. Results from new pulse oximeters should be compared to results from a hemoximeter and/or existing pulse oximeters prior to use to assure consistency.

There are two iterations of pulse oximeter probe designs: transmittance and reflectance sensors. A transmittance sensor, commonly applied to the finger or earlobe, emits light from one side of the skin and a photodetector receives the nonabsorbed light on the other side. A reflectance sensor emits light into the forehead, and a photodetector receives the nonabsorbed light after it has been reflected back from the skull.

The interpretation of SpO2 is based on the oxyhemoglobin disassociation curve (Figure 11.2). Although the curve can shift to the left or right, a general assessment of oxygenation and approximate PaO2 can be estimated within the normoxic and hypoxic ranges. Pulse oximetry is insensitive in evaluation of hyperoxemia due to the factors influencing the oxyhemoglobin disassociation curve. In most adult clinical scenarios, maintaining SpO2 > 90% will usually correspond with a PaO2 > 60 mmHg. Applications in newborn monitoring often require SpO2 readings to be approximately 88% to 92% to avoid complications of retinopathy and blindness.

**Figure 11.7**
Absorption spectra of oxyhemoglobin and reduced hemoglobin.

*Source: CLSI. Pulse oximetry; Approved guidelines 2010;HS3-A,25(5). Courtesy of the Clinical and Laboratory Standards Institute.*
Accuracy and precision of the Sp O2 and heart rate depend on many factors, including the following:

- Choosing a sensor designed for the intended site of measurement.
- Monitoring an area of good perfusion.
- Ensuring the sensor is attached properly and preventing ambient light from filtering through the skin, thereby adding artifacts to the photodetector.
- In patients with congenital cardiac anomalies and functional shunts, altering the sensor’s site position may lead to significant variations in results.

In general, most pulse oximetry manufacturers claim accuracy at 1 SD, ±2% within a range of 70% to 100% SpO2. This practically means that 68% of the time SpO2 results will be within 2% of the correct value.

Proper interpretation of pulse oximetry requires an understanding of its limitations. As previously described, dyshemoglobins are not accounted for in the pulse oximeter oxygen saturation measurement. Therefore, if a patient is suffering from carbon monoxide toxicity or methemoglobinemia, the pulse oximeter will not indicate the presence of hypoxia and the patient may go undiagnosed and be mistreated. Similarly, pulse oximeters do not display any indication of tHb or hematocrit to assess ctO2. For example, in the rapid evaluation of a postsurgical patient who has become progressively tachypneic and hypotensive, a quick glance at the pulse oximeter’s reading of SpO2 > 95% may inappropriately rule out acute hypoxia. The patient may be experiencing internal bleeding, and the hemorrhage is producing significant hypoxia due to loss of oxygen-carrying capacity leading to a subsequent drop in ctO2. Unfortunately, this patient would not show signs of cyanosis, compounding the clinical assessment.

Additionally, it is critical to understand that the pulse oximeter is an oxygenation monitor. It does not provide any indication of ventilation, pH, or PaCO2. Thus, even with an adequate SpO2, there is still a need for blood gases or ventilation monitoring with capnography.

**Pulse CO-oximetry**

Technical advancements in the design of pulse oximeter sensors have led to the ability to measure COHb and MetHb along with O2Hb and HHb (see Figure 11.6). In addition, the pulse CO-oximeter can calculate the total hemoglobin, thereby providing a more accurate reflection of ctO2. From a conceptual perspective, the pulse CO-oximeter has combined the optical absorption capabilities of whole blood hemoximeters with the noninvasive continuous monitoring features of pulse oximetry. Due to incorporating these additional parameters, pulse CO-oximeters offer greater clinical utility than a standard pulse oximeter.

The endogenous production of carbon monoxide has been identified in individuals diagnosed with inflammatory pulmonary disease, chronic obstructive pulmonary disease,33 and obstructive sleep apnea (OSA).34 Cardiovascular events are comorbid risks associated with these conditions and may increase in severity and occurrence with elevated COHb concentrations. Capitalizing on its noninvasive design, pulse CO-oximetry may have a future role in the continuous monitoring of these diseases, especially during a prolonged diagnostic evaluation (i.e., sleep study for OSA or titration of therapy, including CPAP).
The factors affecting the pulse CO-oximeter’s accuracy and precision are similar to pulse oximeters. Appropriate sensor application and fit, ensuring that the sensor site is well perfused, are essential in producing reliable results.

**Transcutaneous Monitoring**

Transcutaneous monitoring provides a noninvasive estimate of PaO₂ and PaCO₂ through measurement of skin-surface electrodes. Similar to other monitors, tcPO₂ and tcPCO₂ are not diagnostic sensors, but they can offer continuous patient oversight for both oxygenation and ventilation parameters. Included among the advantages of tcPO₂ monitoring is the detection of hyperoxemia in newborns that is not possible with pulse oximetry. Monitoring of tcPCO₂ during sleep apnea studies can offer another dimension to the ventilation evaluation that may correlate better to PaCO₂ than capnography.

Many configurations of sensor technology are commercially available, including a single tcPCO₂ sensor; a combined tcPO₂/tcPCO₂ sensor, mainly used in neonatology; and a combined SpO₂/tcPCO₂ sensor, for use in adults and infants. The tcPO₂ sensor is a Clark-type PO₂ electrode, and the tcPCO₂ sensor employs the Stowe-Severinghaus-type PCO₂ technology. Analogous to their analyzer counterparts, transcutaneous sensors require calibration prior to use and periodically thereafter, based on the manufacturer’s recommendations and clinical performance. Transcutaneous sensors have a duel mechanism that measures the analyte and warms the skin to approximately 42–44°C (manufacturer dependent). Elevating the site temperature increases the local perfusion and may improve the correlation between transcutaneous and ABG measurements by accelerated gas diffusion through the skin.

Proper sensor placement requires attention to skin preparation and ensuring that no air bubbles are present beneath the membrane’s surface. A special adhesive ring holds the sensor to the skin. Prior to attachment, clean the site to remove oils or dried fluids, such as vernix on a newborn’s skin, that may prevent sensor adhesion. Sensor placement should always be over soft tissue, never bone (i.e., ribs or clavicles). To prevent thermal injuries, especially in newborns, the sensor site must be relocated at least every 4 hours, and more frequently in premature infants to avoid burns. Approximately 10–15 minutes after sensor placement, when the monitoring trends appear stable, an ABG test should be performed to assess correlation. Subsequent correlations should be conducted when significant trends in monitored results are not consistent with either the patient’s condition or therapy.

Like pulse oximetry, the performance of transcutaneous monitoring is largely dependent on perfusion and the quality of tissue at the sensor site. Vasopressors and other drugs that alter perfusion or cardiac output can markedly influence both correlation and sensor response time. An acute decrease in tcPO₂ may indicate a drop in perfusion. To evaluate this trend, an ABG correlation should be performed. A widening oxygen gradient, PaO₂-tcPO₂, helps to confirm hypoperfusion. When performing a correlation test in newborns with a functional shunt, blood should be sampled from vasculature that is perfusing the transcutaneous sensor. If the specimen is derived from another site, poor correlation may be observed. In adults, skin thickness can...
impact correlation and response time, prompting sensor relocation. If applicable, moving the sensor to the earlobe may result in better performance.

Blood Gas Monitoring

Blood gas monitors are devices that measure blood gases similar to an analyzer, but they do not permanently remove the specimen from the patient for measurement. These devices can be categorized into two primary technologies: in vivo (intra-arterial) and ex vivo (patient attached).

Intra-arterial Blood Gas Monitoring

Innovations in optical engineering have allowed miniature blood gas and temperature sensors (optodes) to be incorporated into fiberoptic filaments. When bundled, these single-patient probes can be threaded through a peripheral arterial catheter or an umbilical catheter for once per second measurements. Unlike intermittent discrete blood gas analysis, continuous blood gas monitoring offers the benefits of both real-time data and trend analysis. Among the clinical benefits derived from this minimally invasive technology are the following:

- Qualification of physiologic equilibration after interventions
- Reduced time to optimize oxygenation and ventilation settings
- Continuous blood gas surveillance provided, with warning of unexpected events that could compromise cardiopulmonary function

Patient-Attached and In-Line Blood Gas Monitoring

Electrochemical and optical sensors can be adapted into a cassette attached to a patient’s indwelling arterial catheter for either automatic time-cycled sampling, or, upon clinical need, an on-demand discrete specimen can be triggered for analysis. Serial sampling can occur to observe trends of the effects of an intervention. To add clinical utility, electrolytes, glucose, and other blood chemistry tests can be incorporated with the blood gas sensors.

Patient-attached blood gas monitoring requires the single-patient cassette to be connected to a vascular catheter where a special tubing circuit permits blood to flow from the patient to the sensors. Upon completion of the measurement, the blood is reinfused back to the patient, and the tubing circuit is flushed. Blood volume and flow during sampling and reinfusion are controlled to ensure patient safety. Systems appropriate for use in adult, pediatric, and newborn populations are available. The monitoring system requires a unique infusate solution to maintain sensor calibration and inhibit clotting of the circuit and catheter.

A hybrid of the patient-attached monitor connects the blood gas cartridge to a cardiopulmonary bypass or extracorporeal membrane oxygenator circuit. Blood emanating from the venous outflow (preoxygenator) passes by the sensors, and a monitoring screen displays continuous results of blood gases, potassium, and hemoglobin–hematocrit analytes. By evaluating the critical tests in real time, rapid interventions can occur with potential improvement of outcomes.
Case Presentations

Case 11.1

A college freshman was found unconscious in his dormitory room several hours after a fraternity party and was brought to the emergency department of a nearby hospital. The physical examination revealed general cyanosis; shallow breathing with diminished but clear breath sounds; blood pressure 80/60; heart rate 138; and a pulse oximeter reading of 80% (room air). The patient was administered oxygen via nasal cannula at 5 L/min. Within 5 minutes the SpO₂ trend elevated to 95%. An arterial blood gas and electrolyte panel were ordered, and the following results were reported 30 minutes after admission:

<table>
<thead>
<tr>
<th>Acid-base balance</th>
<th>Oxygenation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.25</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>60</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>25.4</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>1.1</td>
</tr>
<tr>
<td>Cl⁻ (mmol/L)</td>
<td>100</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>140</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>4</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>1.20</td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fio₂ on NC 5 L/min</td>
<td>~ 0.35</td>
<td>PaO₂ (mmHg)</td>
<td>85</td>
</tr>
<tr>
<td>SaO₂</td>
<td>96%</td>
<td>Hematocrit</td>
<td>45%</td>
</tr>
</tbody>
</table>

Questions

1. Interpret the acid-base balance.
2. What is the anion gap?
3. Is the PaO₂ normal (appropriate)?

Answers and Discussion

1. Pure respiratory acidemia. The acidic pH was caused solely by hypercarbia, the respiratory component of acid-base balance (bicarbonate remained normal).
2. 16 mEq/L, normal. AG = [Na⁺] = [Cl⁻ + HCO₃⁻].
3. Although a PaO₂ of 85 mmHg is in a safe range, the estimated PaO₂ breathing an Fio₂ of 0.35 is 175 mmHg (oxygen concentration × 5). The initial hypoxemia was most likely due to hypoventilation (hypoxic hypoxia).

Case 11.2

A 62-year-old male is being evaluated in the pulmonary laboratory for progressive shortness of breath on exertion. The pertinent history reveals a chronic productive cough, hospitalization...
for pneumonia three times in the past 20 months, and an 88-pack-year cigarette smoking exposure. The physical examination demonstrates hyperresonant breath sounds, use of accessory muscles, moderate pedal edema, and hypertrophic osteoarthropathy (clubbing) of the fingers; and a pulse oximeter reading of SpO₂ 86% (room air). An arterial blood gas and electrolyte panel was ordered to assist in the evaluation. The results are as follows:

<table>
<thead>
<tr>
<th>Acid-base balance</th>
<th>Oxygenation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>FiO₂ on room air</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>PaO₂ (mmHg)</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>SaO₂</td>
</tr>
<tr>
<td>BE₆ (mEq/L)</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>Cl⁻ (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.36</td>
</tr>
<tr>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>+9.2</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questions

1. Interpret the acid-base balance.
2. What is the patient’s oxygen status?
3. How does the hematocrit concentration affect the patient’s physiologic condition?

Answers and Discussion

1. Compensated respiratory acidemia. The acidic affect of hypercarbia is buffered by increased bicarbonate.
2. Moderate hypoxemia. This condition may have progressed over an extended period as evidenced by the compensated acid-base balance, polycythemia, and clubbing.
3. The hematocrit is markedly elevated, probably as a secondary effect of chronic hypoxemia. Although the oxygen content has increased, the increased viscosity of the blood promotes stagnant hypoxia, and the net effect may ultimately diminish oxygen transport.

Case 11.3

An 18-year-old female diagnosed with type 2 diabetes went on a 1-week vacation and failed to pack her insulin. On the morning of day five, she was difficult to arouse and appeared incoherent. The teenager was transported to the emergency department for evaluation. The initial inspection observed deep and labored breathing (Kussmaul breathing pattern); hypotension; heart rate 130;
and a pulse oximeter reading of 98% (room air). An arterial blood gas and electrolyte panel was ordered, and the results are as follows:

<table>
<thead>
<tr>
<th>Acid-base balance</th>
<th>Oxygenation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.21</td>
<td>Fio2 at room air 0.21</td>
</tr>
<tr>
<td>PaCO2 (mmHg) 16</td>
<td>PaO2 (mmHg) 110</td>
</tr>
<tr>
<td>HCO3− (mEq/L) 6.2</td>
<td>SaO2 99%</td>
</tr>
<tr>
<td>BE (mEq/L) -19.6</td>
<td>Hematocrit 45%</td>
</tr>
<tr>
<td>Cl− (mmol/L) 80</td>
<td></td>
</tr>
<tr>
<td>Na+ (mmol/L) 125</td>
<td></td>
</tr>
<tr>
<td>K+ (mmol/L) 3.7</td>
<td></td>
</tr>
<tr>
<td>Ca++ (mmol/L) 1.23</td>
<td></td>
</tr>
</tbody>
</table>

**Questions**

1. Interpret the acid-base balance.
2. What is the anion gap?
3. What is the patient’s oxygen status?

**Answers and Discussion**

1. Partially compensated metabolic acidemia. The acidic driver is the severely decreased bicarbonate concentration, most likely caused by increased organic acids (ketones). In an attempt to maintain acid-base balance homeostasis, alveolar ventilation dramatically elevated, producing significant hypocarbia and buffering the pH.

2. 39 mEq/L. The anion gap further illustrates the severity of the primary metabolic acidosis. This case represents a classic diabetic ketoacidosis (DKA).

3. Normal. Due to the rules that govern the alveolar air equation, as PaCO2 changes, PaO2 can shift proportionately in an inverse direction. Hypocarbia, in the presence of good pulmonary function, can mildly increase PaO2 > 100 mmHg when breathing room air at sea level.

**Case 11.4**

A 70-year-old female was admitted for cholecystectomy surgery. Postoperatively a nasogastric tube was inserted and left in place for 4 days. A blood gas and electrolyte panel was ordered after she was observed to be in tachycardia with occasional PVCs, a pulse oximeter reading of SpO2 93% (room air). Her arterial blood gas and electrolyte panel revealed the following:

<table>
<thead>
<tr>
<th>Acid-base balance</th>
<th>Oxygenation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.52</td>
<td>Fio2 at room air 0.21</td>
</tr>
<tr>
<td>PaCO2 (mmHg) 42</td>
<td>PaO2 (mmHg) 72</td>
</tr>
</tbody>
</table>
Questions

1. Interpret the acid-base balance.
2. What is the significance of the BEb?
3. What is the patient’s oxygen status?

Answers and Discussion

1. Pure metabolic alkalemia. The increased bicarbonate is the driver that increased pH, with no indication of respiratory compensation (normocarbia).
2. The BEb indicates a significant concentration of plasma buffer (bicarbonate). This condition was most likely due to excessive gastric acid drainage from the nasogastric tube, which decreased plasma Cl⁻. To maintain electrical neutrality, bicarbonate increases to replace the anion loss, thereby maintaining electroneutrality.
3. Normal for a 70-year-old individual. PaO₂ ranges are age dependent.

Case 11.5

A 51-year-old male was exposed to smoke inhalation in a house fire. Rescue services transported the victim to a local emergency department for care. Upon arrival, the patient was dyspneic and lethargic. His blood pressure was markedly elevated, ECG monitoring indicated mild tachycardia, and pulse oximeter reading of SpO₂ 95% (room air). A routine blood gas was obtained for further evaluation, and the results are as follows:

<table>
<thead>
<tr>
<th>Acid-base balance</th>
<th>Oxygenation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.28</td>
<td>FiO₂ at room air 0.21</td>
</tr>
<tr>
<td>PaCO₂ (mmHg) 56</td>
<td>PaO₂ (mmHg) 72</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L) 26</td>
<td>SaO₂ 94%</td>
</tr>
<tr>
<td>BEb (mEq/L) -0.7</td>
<td>Hematocrit 48%</td>
</tr>
</tbody>
</table>

Questions

1. Interpret the acid-base balance.
2. What is the patient’s oxygen status?
CHAPTER 11 Blood Gases and Associated Technologies

Answers and Discussion

1. Pure respiratory acidemia of moderate severity. There is no indication of metabolic compensation as evidenced by a normal bicarbonate and BE.

2. All oxygen parameters appear to be normal; however, when carbon monoxide toxicity is suspected (i.e., smoke inhalation in a fire victim), \( \text{PaO}_2 \) and standard pulse oximetry will not detect the presence of COHb or be able to monitor the anemic hypoxemia. Hemoximetry or CO-oximetry analysis is required.

After the blood gases were evaluated, another arterial sample was obtained for a hemoximetry panel. The results are as follows:

<table>
<thead>
<tr>
<th>Hemoximetry panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>tHb 15.2 g/dL</td>
</tr>
<tr>
<td>( \text{FO}_2\text{Hb} ) 58%</td>
</tr>
<tr>
<td>COHb 28%</td>
</tr>
<tr>
<td>MetHb 5%</td>
</tr>
<tr>
<td>( \text{ctO}_2 ) 12.02 mL/dL</td>
</tr>
</tbody>
</table>

Questions

1. Evaluate the patient’s oxygenation status based on the hemoximetry results.

2. Why is there a significant discrepancy between the oxygen saturation measured by the pulse oximeter and calculated by the blood gas analyzer when compared to the hemoximeter?

Answers and Discussion

1. Severe hypoxemia (\( \text{ctO}_2 \) is reduced by approximately 40%) due to anemic hypoxia caused by carbon monoxide toxicity.

2. Both the pulse oximeter and the calculation performed by the blood gas analyzer report a functional oxygen saturation, whereby the hemoximeter measures fractional oxygen saturation. Devices that report functional oxygen saturation do not detect anemic hypoxia, and therefore elevations in COHb, MetHb, or anemia as sources of pathology can be missed, leading to a delay in timely and appropriate patient management.

Self-Assessment Questions

1. The barometric pressure in Denver, Colorado is 625 mmHg. What is the \( \text{P}_\text{O}_2 \)?
   a. 465 mmHg
   b. 131 mmHg
Self-Assessment Questions

2. An increase in \( P_{50} \) has what effect on oxygen delivery?
   a. Promotes \( O_2 \) binding to Hb
   b. Decreases \( O_2 \) diffusion across the alveolar capillary (A-C) membrane
   c. Promotes the unloading of \( CO_2 \) from Hb
   d. Promotes the unloading of \( O_2 \) from Hb
   e. Increases pH

3. What is the estimated \( PaO_2 \) when breathing 50% oxygen?
   a. 250 mmHg
   b. 325 mmHg
   c. 400 mmHg
   d. 450 mmHg
   e. 100 mmHg

4. The ratio of 20:1 bicarbonate to carbonic acid would yield what acid-base balance condition?
   a. Normal
   b. Partially compensated respiratory acidemia
   c. Mixed respiratory and metabolic alkalemia
   d. Compensated respiratory acidemia
   e. Diabetic ketoacidosis

5. A significant decrease in chloride produces what acid-base balance abnormality?
   a. Metabolic academia
   b. Respiratory alkalemia
   c. Metabolic alkalemia
   d. Respiratory acidemia
   e. None

6. Interpret the following acid-base balance status: \( pH \ 7.32, \ PaCO_2 \ 56 \ mmHg, \ HCO_3^- \ 27 \ mEq/L, \ BE \ 0.7 \ mEq/L, \ PaO_2 \ 75 \ mmHg, \ SaO_2 \ 95\% \).
   a. Partially compensated metabolic alkalosis
   b. Partially compensated respiratory alkalosis
   c. Partially compensated respiratory acidosis
   d. Partially compensated metabolic acidosis
   e. Primary lactic acidosis

7. What US regulations govern blood gas laboratories?
   a. United States Pharmacopeia
   b. FDA standard 21CFR489
   c. Clinical Laboratory Improvement Amendments (CLIA)
   d. Clinical and Laboratory Standards Institute (CLSI)
   e. ISO standard 13485

8. If a blood gas is analyzed within 30 minutes, the specimen should be immersed in an ice water bath to prevent what event?
   a. Depreciation of \( PaO_2 \) due to the metabolic effects of the leukocytes
   b. Increase in \( PaCO_2 \) and decrease in \( pH \) due to metabolic effects of the leukocytes
c. Prevent blood clotting and hemolysis
d. a and b
e. The specimen should remain at room temperature and not be cooled

9. Prior to a radial puncture a modified Allen test is performed to assess what function?
   a. Perfusion of the ulnar artery and collateral circulation to the hand
   b. Perfusion of the brachial artery and collateral circulation to the forearm
   c. Perfusion of the radial artery and collateral circulation to the forearm
   d. Perfusion of the radial artery and collateral circulation to the hand
   e. Perfusion of the radial artery and collateral circulation to the splanchnic circulation

10. Fractional oxyhemoglobin saturation ($F_O_2Hb$) accounts for what hemoglobin derivatives in its calculation?
    a. $O_2Hb$, $HHb$, $COHb$, and $MetHb$
    b. $O_2Hb$, $HHb$, HbF, and $CO_2Hb$
    c. $O_2Hb$, $HHb$, lactate, and $HCO_3^-$
    d. $O_2Hb$, $HHb$, COHb, and tHb
    e. $Na^+$, $K^+$, $Cl^-$, and $iCa$

11. When evaluating a patient for carbon monoxide toxicity, what test panel(s) should be performed?
    a. Blood gases and electrolytes
    b. Blood gases and pulse oximetry
    c. Hemoximetry
    d. Blood gases and hemoglobin–hematocrit
    e. CBC, H&H, Chem8 panel

12. Transcutaneous tcPO2 and tcPCO2 sensors in a neonatal application:
    a. Need to be calibrated prior to use and every 4 hours to maintain accuracy
    b. Require an initial blood gas correlation and sensor repositioning at least every 4 hours
    c. Need to be sterilized every 24 hours to avoid transmission of a staphylococcal infection
    d. Require an initial blood gas correlation and every 3 hours when positioned
    e. Must be repositioned every 24 hours to avoid skin injury

References


Pulmonary Function Testing
Reference (Predicted) Values

Introduction
It is a common practice to compare each measured or calculated variable in a patient’s pulmonary function test with reference or predicted values based on data from healthy subjects. This comparison provides the basis for interpretation.

Studies designed to establish normal or reference values are large undertakings. An investigator must first choose and define a population (e.g., urban men, 18 years of age and older) and, using a detailed questionnaire, find subjects who are nonsmokers (or those who have never smoked) and who do not have any present or past acute or chronic respiratory problems (such as shortness of breath, cough, or wheezing). Next, these healthy subjects are given pulmonary function tests, and their results make up the reference, or normal, values. Of course, enough healthy subjects of the specified age and gender must be tested to make the study useful.

The healthy subjects with similar characteristics for the variables that affect lung function (i.e., gender, age, height, and race or ethnic origin) can be grouped together. For example, if we performed spirometry on 100 healthy Caucasian men, all 40 years old and 68 inches tall, the results for FVC could be grouped together. Although most of the FVC values would be close to the mean value, some would be higher and some would be lower because of natural
variability. Typically, a symmetrical distribution around the mean creates a bell-shaped pattern (Figure 12.1). The width of this distribution is described by its standard deviation. Approximately 95% of the values in this type of distribution are within the boundaries of ±2 standard deviations. In this example, the mean FVC is 4.8 liters, and the range of FVC values between ±2 standard deviations is 3.6 to 6.0 liters. However, on most pulmonary function reports the range is not reported, only the mean value.

The reference values for pulmonary function testing vary predictably with physical characteristics such as age and height. The older we get after maturity, the smaller our lungs get. In general, the taller one is, the larger the lungs. In addition, there are differences between men and women, with men having larger lungs and higher flow rates and DL_{CO} values than women.

Lung volumes also vary with body size and body proportions, and these characteristics are influenced by race and ethnic origins. African Americans, for example, have smaller lungs than Caucasians. This has been explained, in part, by trunk length to height differences. Other factors include fat-free mass and chest dimensions. As a result of these differences, race-specific reference equations are recommended. If race-specific reference values are not available, then a race adjustment factor can be applied.

**General Considerations**

**Determining Age, Height, Weight, and Race/Ethnicity**

In order to determine accurate reference values for a patient, age (on day of test), height (without shoes), and weight (wearing indoor clothes without shoes) should be obtained or measured at the time of testing. Height is particularly important in determining reference values, and the laboratory should not rely on patient-stated height. Height should be measured, using an accurate device or stadiometer, without shoes and with the patient standing erect with the feet together. When height cannot be measured, estimate height using arm span.

Sitting
height may be required for some reference equations (e.g., those with dwarfism). Weight, though not used for most reference equations, is used to determine body mass index and is used in the interpretation of pulmonary function test data.

Patients should be asked to identify their own race or ethnic origin. As previously mentioned race/ethnic-specific reference equations should be used whenever possible. If race/ethnic-specific reference values are not available, then an adjustment factor can be used. These factors vary with race. For example, reference values for FVC and FEV₁ based on a Caucasian population would be reduced by 12% (a factor of 0.88) for use with an African American patient. Similarly, reference values for FVC and FEV₁ based on a Caucasian population would be reduced by 6% for Asian Americans.

Determining What Is Normal and Abnormal

There are two approaches commonly used to determine what is normal and what is abnormal. These are: (a) the 95% confidence interval and (b) the 80% method.

With the 95% confidence interval (CI) method, values below the fifth percentile (i.e., the lowest 5% of the reference population) are assumed to be below the expected range (i.e., below normal). A false positive rate of approximately 5% is expected and considered acceptable.

The use of the 95% CI to determine the lower limit of normal (LLN) is considered statistically sound and is a more acceptable method.

The 95% CI can be calculated as shown in the following equation, using the standard error of the estimate (SEE), which is sometimes reported in the reference study publication.

\[
95\% \text{ CI} = 1.64 \times \text{SEE}
\]

For example, the predicted FVC for a 45-year-old man who is 68 inches tall is 4.46 liters using the reference study done by Knudson et al. in 1976. The reported SEE for the FVC was 0.601. The 95% CI is calculated as follows:

\[
95\% \text{ CI} = 1.64 \times 0.601 = 0.986
\]

The LLN using the 95% CI method would be:

\[
\text{LLN} = \text{Predicted value} - 95\% \text{ CI}, \text{ or} \\
\text{LLN} = 4.46 - 0.99 = 3.47 \text{ liters}
\]

In some publications, the LLN using the 95% CI is included, and no additional calculations are needed.

The second approach to identifying the LLN is the 80% method. This approach is used by some clinicians because of its simplicity. To calculate the LLN using this method, just multiply the predicted value by 0.80. The main shortcoming of this method is that calculating
the LLN using this fixed percentage of the predicted value for all pulmonary function parameters is not statistically sound and may result in important errors.

If the LLN for the FVC is calculated using the 80% method on the same 45-year-old man previously noted (i.e., predicted FVC = 4.46 liters), it would be:

\[
\text{LLN} = 0.80 \times 4.46 = 3.57 \text{ liters}
\]

As of 2010, the recommendation by the ATS and ERS was to use the 95% CI method to define the LLN.⁴

Selecting Reference Values for the Laboratory

Selecting a reference study for the laboratory requires careful thought. Two main factors to consider are: (a) the population used in the reference study and (b) the methods and instrumentation used in the reference study.

The reference study population should be similar to the laboratory’s patient population with respect to age range, body size, gender, race/ethnicity, and socioeconomic and environmental characteristics.⁴,⁹ If possible, all parameters should be taken from the same source.

Ideally, the laboratory uses the same or similar methods and instrumentation as those used in the reference study. Reference studies that collected data before 1979 may not have used the ATS guidelines that are commonly used in today’s laboratories. Also, many early studies used volume-displacement spirometers, and there may be differences between flow-sensing and volume-displacement instrumentation.

Race or Ethnic Considerations

As previously mentioned, patients should be asked to identify their race/ethnic group, and race-specific reference equations should be used, if available.

Although it is preferable to use reference equations that are based on a patient’s race/ethnicity, this may not be possible. There are many different ethnic origins to consider, especially in the United States (e.g., American Indian, Asian, African American, Caucasian, Hispanic), and the availability of valid studies for a specific race using present-day methodology may be limited.

The use of a racial adjustment factor is not as valid as specific race/ethnic reference values, but it is considered a reasonable option.⁴ When using such a factor, a fixed percentage is applied to reference values for Caucasians. Some commercial pulmonary function systems allow the user to adjust all the Caucasian reference values by applying a fixed factor (e.g., 0.88) for all races. But herein lies the weakness of this approach—the differences among ethnic groups vary, and to adjust them by applying a constant scaling factor for all pulmonary function parameters is wrong.

One recommendation is to use an adjustment factor of 0.88 for African American patients for FVC, FEV₁, and total lung capacity (TLC), and use 0.93 for functional residual capacity (FRC) and residual volume (RV).⁹ Additionally, an adjustment factor of 0.94 is recommended for Asian Americans.¹¹,¹² A race adjustment factor is not used for Hispanics. If a race adjustment
factor is used, a descriptive comment should be included in the report along with the factor that was applied.

Yet another approach is not to modify the reference values using adjustment factors because these reference values were selected with care, apply to the majority population tested in the laboratory, and match the methods and instrumentation used by the laboratory. If a patient of different ethnic origin is tested, the written interpretation can include allowances for abnormal results thought to be related to racial differences.

Reference Values for Spirometry

The 2005 ATS/ERS guidelines on pulmonary function testing recommends using the ethnically appropriate third National Health and Nutrition Examination Survey (NHANES III) reference equations for patients aged 8 to 80 years in the United States. For children younger than 8 years of age in the United States, it is recommended to use the equations of Wang and coworkers. See Chapter 10 for recommendations regarding preschool children.

In Europe, although no official recommendation was made by the 2005 ATS/ERS guidelines, it was noted that the reference equations published in the 1993 ERS statement are most often used for patients aged 18 to 70 years, and the equations from Quanjer and coworkers are used for children.

The NHANES III was conducted from 1988 to 1994. Spirometry data was collected on 20,627 participants aged 8 years and older in three race/ethnic groups (Caucasian, African American, and Mexican American). NHANES III used standardized instrumentation and procedures that met the 1987 ATS spirometry guidelines and included a central quality control center that evaluated technician performance.

Because three race/ethnic groups (Caucasian, African American, and Mexican American) were included, NHANES III provided race/ethnicity-specific equations. In addition, the NHANES III reference study provides reference values for FEV₁.

Spirometry reference values for short-limbed dwarfish have been published and require the measurement of sitting height.

The study from Wang and coworkers is the recommended reference study for children younger than 8 years of age. The study included 13,737 children from six communities across the United States that were examined from 1974 to 1989.

The combined reference equations in the 1993 ERS statement are the most commonly used in Europe for adult patients aged 18 to 70 years, with a height range of 155 to 195 cm for males and 145 to 180 cm for females. These are summary equations based on a number of other studies from various sources prior to 1983. Essentially, these equations are an overall mean of data in the literature. However, the studies used for the summary equations are somewhat old, and there is a strong need for new studies to derive updated reference equations.

Reference Values for Lung Volumes

There are no recommendations from the 2005 ATS/ERS Task Force on Standardization of Lung Function Testing for reference equations used for lung volumes. Many laboratories use the summary equations published by the ATS and ERS, and these are presented in Table 12.1.
Other adult reference studies that are used include Grimby and Soderholm,21 Goldman and Becklake,22 and Roberts and coworkers.22

For children, the reference studies of Zapletal and coworkers23 and Weng and Jevison24 are commonly used for FRC, RV, and TLC. A useful compilation of reference values for children was published by Quanjer and coworkers.16

### Reference Values for $DL_{CO}$

Like lung volumes, there are no recommendations from the 2005 ATS/ERS task force for a single set of reference equations for $DL_{CO}$. This is mainly because of the interlaboratory differences in methods, adjustments, and altitude. The task force did recommend that reference values for alveolar volume (VA), $DL_{CO}$, and $DL_{CO}$ corrected for lung volume ($KCO$ or $DL_{CO}/VA$) should come from the same source.4 Laboratories should carefully select reference values that match the methods and population tested.

There are a number of good candidate studies to consider for adults which are described in terms of methods in Chapter 3. They include Crapo and Morris,25 Miller and coworkers,26 Paoletti and coworkers,27 Roca and coworkers,28 Gulsvik and coworkers,29 and Knudson and coworkers30 (Table 12.2).

Unfortunately, these reference studies are a bit dated and do not adhere to the 2005 ATS/ERS $DL_{CO}$ testing recommendations. Thompson and coworkers31 presented data on a set of reference equations for $DL_{CO}$ and VA in a large, healthy, middle-aged, and older population using modern computerized instrumentation following the 2005 recommendations. This study included approximately 972 male and female subjects between the ages of 45 and 71 years. Single-breath $DL_{CO}$ was measured in duplicate using a computerized system with gas chromatograph, and the test gas contained 0.3% carbon monoxide, 0.5% neon, 20.6% oxygen, and the balance was nitrogen. The $DL_{CO}$ results were systematically lower than other

### Reference Equations for Lung Volumes and the 95% Confidence Interval

<table>
<thead>
<tr>
<th>Volume</th>
<th>Equation</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>$7.99 \times \text{Height in meters} - 7.08$, 95% CI = ± 1.37</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>$1.31 \times \text{Height in meters} + 0.022 \times \text{age}$, 95% CI = ± 0.67</td>
<td></td>
</tr>
<tr>
<td>FRC (L)</td>
<td>$2.34 \times \text{Height in meters} + 0.01 \times \text{age} - 1.09$, 95% CI = ± 0.99</td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>$6.60 \times \text{Height in meters} - 5.79$, 95% CI = ± 1.18</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>$1.81 \times \text{Height in meters} + 0.016 \times \text{age}$ - 2.00, 95% CI = ± 0.58</td>
<td></td>
</tr>
<tr>
<td>FRC (L)</td>
<td>$2.24 \times \text{Height in meters} + 0.001 \times \text{age} - 1.00$, 95% CI = ± 0.82</td>
<td></td>
</tr>
</tbody>
</table>

Table 12.2

Reference Equations for Single-Breath DL_{CO}*

Crapo 25

Men:
\[ DL_{CO} = 0.416(H_t cm) - 0.219(age) - 26.34; \text{ SEE} = 4.83 \]
\[ DL_{CO}/VA = 7.08 - 0.034(age); \text{ SEE} = 0.84 \]

Women:
\[ DL_{CO} = 0.256(H_t cm) - 0.144(age) - 26.34; \text{ SEE} = 3.57 \]
\[ DL_{CO}/VA = 6.58 - 0.025(age); \text{ SEE} = 0.078 \]

Paolletti 27

Men age \(\geq 19\):
\[ DL_{CO} = 0.4410(H_t cm) - 0.1936(age) - 31.3822; \text{ SEE} = 5.79 \]
\[ VA = 0.099(H_t cm) - 0.0176(age) - 9.814; \text{ SEE} = 0.729 \]

Women age \(\geq 18\):
\[ DL_{CO} = 0.1569(H_t cm) - 0.0677(age) - 5.0767; \text{ SEE} = 4.31 \]
\[ VA = 0.0573(H_t cm) - 0.0054(age) - 3.9085; \text{ SEE} = 0.078 \]

Knudson 30

Men age < 25:
\[ DL_{CO} = 0.328(H_t cm) + 0.722(age) - 30.9685; \text{ SEE} = 3.97 \]
\[ VA = 0.0976(H_t cm) + 10.6484; \text{ SEE} = 0.9057 \]

Men age \(\geq 25\):
\[ DL_{CO} = 0.3551(H_t cm) + 0.2741(age) - 11.3527; \text{ SEE} = 4.57 \]
\[ VA = 0.0884(H_t cm) - 8.5668; \text{ SEE} = 0.7962 \]

Women age < 20:
\[ DL_{CO} = 0.3808(H_t cm) - 32.9232; \text{ SEE} = 3.52 \]
\[ VA = 0.0666(H_t cm) + 0.1093(age) - 7.6673; \text{ SEE} = 0.6362 \]

Women age \(\geq 20\):
\[ DL_{CO} = 0.1872(H_t cm) - 0.146(age) + 3.8821; \text{ SEE} = 4.50 \]
\[ VA = 0.071(H_t cm) + 6.4396; \text{ SEE} = 0.5145 \]

Miller 26

Men:
\[ DL_{CO} = 0.418(H_t cm) - 0.229(age) + 12.911; \text{ SEE} = 4.84 \]
\[ VA = 0.193(H_t cm) - 6.4896; \text{ SEE} = 0.83 \]

Women:
\[ DL_{CO} = 0.4068(H_t cm) - 0.1111(age) + 2.238; \text{ SEE} = 3.95 \]
\[ VA = 0.1641(H_t cm) + 5.4404; \text{ SEE} = 0.67 \]

Gulsvik 29

Men:
\[ TL_{CO} (\text{mmol/min/kPa}) = 12.17(H_t cm) - 0.057(age) - 8.05 \]
\[ VA = 11.078(H_t cm) - 12.31 \]

Women:
\[ TL_{CO} (\text{mmol/min/kPa}) = 9.11(H_t cm) - 0.043(age) - 4.93 \]
\[ VA = 7.376(H_t cm) - 6.65 \]

*The equations are provided in mL/min/mmHg or the SI Units of mmol/min/kPa, alveolar volume (liters at BTPS), and the standard error of the estimate (SEE). To convert mmol/min/kPa to mL/min/mmHg, multiply the DL_{CO} value in mmol/min/kPa by 2.987.
studies, possibly because this study used an older population. The reference values in this study were the most similar to the values of Miller and coworkers.26

For children, the reference studies of Demuth and Howatt,32 Cotes and coworkers,33 and Nasr and coworkers34 are widely used.

Reference Values for Airway Resistance and Specific Conductance

A detailed discussion of airway resistance (Raw) and specific conductance and specific resistance is presented in Chapter 4. In DuBois and colleagues’ original study,35 healthy adult subjects had a mean Raw of 1.5 cm H\textsubscript{2}O/liter/sec \pm 0.49 (1 standard deviation). The range was 0.6 to 2.4 cm H\textsubscript{2}O/liter/sec. Viljanen and coworkers36 found a mean Raw in males of 1.37 \pm 0.53 and in females of 1.80 \pm 0.7 cm H\textsubscript{2}O/liter/sec.

Reference values for the specific conductance (sGaw) measurement in the body box have also been described. Pelzer and Thomson37 found that for 23 male nonsmokers the mean sGaw was 0.251 \pm 0.079 and for 24 female nonsmokers it was 0.224 \pm 0.075 liters/sec/cm H\textsubscript{2}O/liter. Viljanen and coworkers36 found that the mean sGaw was 0.21 \pm 0.09 for males and 0.20 \pm 0.07 for females.

From these studies it seems reasonable to suggest that in adults Raw values that exceed 2.5 cm H\textsubscript{2}O/liter/sec would be greater than the normal range. Also, sGaw values that are lower than 0.12 liters/sec/cm H\textsubscript{2}O/liter would fall below the normal range.

For children, the reference values of Kirkby and coworkers38 can be used for specific resistance (sRaw). In this study, sRaw data (using an open-shutter-only technique) were collected in healthy Caucasian children aged 3–10 years using the body plethysmograph. The upper 95% confidence limit of normal was approximately 1.6 kPa/sec (16 cm H\textsubscript{2}O/sec) (for age 3 years) to approximately 1.35 kPa/sec (13.5 cm H\textsubscript{2}O/sec) (for age 10 years).

Reference Values for Other Tests

The most commonly used reference studies for CPET are described in Chapter 5. Reference values for maximal inspiratory and expiratory pressures are found in Chapter 9.

References


Appendix A
Answers to Self-Assessment Questions

Chapter 1: Forced Spirometry and Related Tests
1. c  6. b  11. c
2. c  7. b  12. c
3. c  8. e  13. d
4. b  9. c  14. c
5. e  10. c  15. a

Chapter 2: Lung Volumes
1. c  6. b  11. a
2. b  7. a  12. c
3. b  8. d  13. b
4. c  9. e  14. c
5. a  10. c  15. d

Chapter 3: Single-Breath Carbon Monoxide Diffusing Capacity
1. a  5. b  9. b
2. d  6. d 10. d
3. b  7. d  11. b
4. a  8. c  12. c
## Chapter 4: Airway Resistance by Body Plethysmography

1. c  6. b  11. b  16. e  21. c  26. b  31. e  36. a  41. c  46. e
2. b  7. e  12. b  17. b  22. b  27. b  32. a  37. a  42. a  47. b
3. b  8. d  13. b  18. b  23. a  28. c  33. b  38. c  43. b  48. b
4. e  9. b  14. e  19. b  24. a  29. a  34. b  39. b  44. b  49. b
5. a  10. b  15. c  20. a  25. b  30. b  35. b  40. a  45. b  50. a

## Chapter 5: Cardiopulmonary Exercise Test

1. b  6. c  11. b  16. c  21. b  26. b  31. e  36. a  41. c  46. e
2. e  7. a  12. b  17. b  22. b  27. b  32. a  37. a  42. a  47. c
3. b  8. c  13. b  18. b  23. a  28. c  33. b  38. c  43. b  48. b
4. d  9. a  14. e  19. b  24. a  29. a  34. b  39. b  44. b  49. b
5. b  10. a  15. c  20. a  25. b  30. b  35. b  40. a  45. b  50. a

## Chapter 6: Six-Minute Walk Test

1. c  4. b  7. a  10. b
2. a  5. b  8. c
3. e  6. a

## Chapter 7: Exercise-Induced Bronchoconstriction Test

1. a  4. a  7. a  10. a
2. b  5. c
3. a

## Chapter 8: Bronchial Challenge Testing with Pharmacological Agents

1. b  5. d  9. b  13. b
2. c  6. b  10. c
3. a  7. a  11. b
4. b  8. c  12. c

## Chapter 9: Maximal Inspiratory and Expiratory Pressures

1. c  4. a
2. d  5. a
3. b
Answers to Self-Assessment Questions

Chapter 10: Pediatric Pulmonary Function Testing

1. d  
2. a  
3. b  
4. b  
5. c

Chapter 11: Blood Gases and Associated Technologies

1. b  
2. d  
3. a  
4. a  
5. c  
6. c  
7. c  
8. e  
9. a  
10. a  
11. c  
12. b
APPENDIX B
Conversion of Volumes

1. Conversion of Gas Volumes from ATPS to BTPS

\[
V_{\text{BTPS}} = V_{\text{ATPS}} \times \frac{P_B - P_{H_2O}}{P_B - 47} \times \frac{310}{273 + T}
\]

where
- \(V_{\text{BTPS}}\) = Volume of gas at body temperature and pressure saturated with water vapor
- \(V_{\text{ATPS}}\) = Volume of gas at ambient temperature and pressure saturated with water vapor
- \(P_B\) = Barometric pressure (mmHg)
- \(P_{H_2O}\) = Vapor pressure of water at ambient temperature \(T\) from Table B.1
- \(47\) = Vapor pressure of water (\(P_{H_2O}\)) at 37°C
- \(310\) = Absolute body temperature
- \(T\) = Ambient or room temperature
- \(273\) = Absolute 0°C

Table B.1

<table>
<thead>
<tr>
<th>°C</th>
<th>(P_{H_2O}) (mmHg)</th>
<th>°C</th>
<th>(P_{H_2O}) (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

(Continued)
Example calculation: The FVC is 3.4 liters at ATPS (ambient temperature and pressure, saturated with water vapor) when the room temperature is 23°C and PB is 700 mmHg. The BTPS (body temperature and pressure, saturated with water vapor) equivalent is calculated in the following way:

\[
V_{\text{BTPS}} = V_{\text{ATPS}} \times \frac{PB - PH_{2O}}{PB - 47} \times \frac{310}{273 + T}
\]

\[
V_{\text{BTPS}} = 3.40 \times \frac{700 - 21}{700 - 47} \times \frac{310}{273 + 23}
\]

\[
V_{\text{BTPS}} = 3.40 \times \frac{679}{653} \times \frac{310}{296}
\]

\[
V_{\text{BTPS}} = 3.40 \times 1.0398 \times 1.0473
\]

\[
V_{\text{BTPS}} = 3.40 \times 1.089
\]

\[
V_{\text{BTPS}} = 3.70 \text{ liters}
\]

### 2. Conversion of Gas Volumes from ATPS to STPD

\[
V_{\text{STPD}} = V_{\text{ATPS}} \times \frac{PB - PH_{2O}}{760} \times \frac{273}{273 + T}
\]

where

- \(V_{\text{STPD}}\) = Volume of gas at standard temperature and pressure dry
- \(V_{\text{ATPS}}\) = Volume of gas at ambient temperature and pressure saturated with water vapor
- \(PB\) = Barometric pressure
- \(PH_{2O}\) = Vapor pressure of water at \(T\) (see Table B.1)
- \(273\) = Absolute 0°C
- \(T\) = Ambient or room temperature
Example calculation: The volume in a collection bag is 11.5 liters at ATPS (ambient temperature and pressure saturated with water vapor) when the room temperature is 24° C and the PB is 720 mmHg. The STPD (standard temperature and pressure, dry) equivalent is calculated in the following way:

\[
V_{\text{STPD}} = V_{\text{ATPS}} \times \frac{P_{\text{B}} - P_{\text{H}_2\text{O}}}{760} \times \frac{273}{273 + T}
\]

\[
V_{\text{STPD}} = 11.5 \times \frac{720 - 22}{760} \times \frac{273}{273 + 24}
\]

\[
V_{\text{STPD}} = 11.5 \times 0.918 \times 0.919
\]

\[
V_{\text{STPD}} = 11.5 \times 0.844
\]

\[
V_{\text{STPD}} = 9.71 \text{ liters}
\]

3. Conversion of Gas Volumes from ATPD to STPD

\[
V_{\text{STPD}} = V_{\text{ATPD}} \times \frac{P_{\text{B}}}{760} \times \frac{273}{273 + T}
\]

where

- \(V_{\text{STPD}}\) = Volume of gas at standard temperature and pressure, dry
- \(V_{\text{ATPD}}\) = Volume of gas at ambient temperature and pressure, dry
- \(P_{\text{B}}\) = Barometric pressure (mmHg)
- \(273\) = Absolute 0° C
- \(T\) = Ambient or room temperature
- \(760\) = Standard barometric pressure at sea level

Example calculation: The inspired volume during a single-breath diffusing capacity test is 2.85 liters at ATPD (ambient temperature and pressure, dry, since the inspired gas is stored in a cylinder) when the room temperature is 24° C and the barometric pressure (PB) is 705 mmHg. The STPD (standard temperature and pressure, dry) equivalent is calculated the following way:

\[
V_{\text{STPD}} = V_{\text{ATPD}} \times \frac{P_{\text{B}}}{760} \times \frac{273}{273 + T}
\]

\[
V_{\text{STPD}} = 2.85 \times \frac{705}{760} \times \frac{273}{273 + 24}
\]

\[
V_{\text{STPD}} = 2.85 \times 0.928 \times 0.919
\]

\[
V_{\text{STPD}} = 2.85 \times 0.853
\]

\[
V_{\text{STPD}} = 2.43 \text{ liters}
\]
Appendix C
Mathematics of Boyle’s Law

Boyle’s law states that if temperature is held constant, the volume of gas in a container varies inversely with changes in pressure, and the product of pressure and volume within the system is constant. It is applied to measure the volume of gas in the lungs using the body plethysmograph. The volume of gas measured, whether it is in communication with the open airways or trapped in the lungs, is called the thoracic gas volume (TGV). When TGV is determined in the body plethysmograph at the end of a normal exhalation, it is a measurement of functional residual capacity (FRCpleth).

Mathematically, the law is stated as:

\[ P_1V_1 = P_2V_2 \]

where

- \( P_1 \) and \( V_1 \) = Absolute pressure and lung volume values before the panting maneuver
- \( P_2 \) and \( V_2 \) = Absolute pressure and lung volume values after the panting maneuver

If \( P_2 = P_1 + \Delta P \) and \( V_2 = V_1 + \Delta V \), then

\[ P_1V_1 = (P_1 + \Delta P)(V_1 + \Delta V) \]

where

- \( P_1 \) = Alveolar pressure
- \( \Delta P \) = Change in pressure during panting against shutter
- \( V_1 \) = Thoracic gas volume (usually at FRC)
- \( \Delta V \) = Change in TGV due to compression and decompression

Expanding, the equation becomes:

\[ P_1V_1 = P_1V_1 + P_1\Delta V + \Delta P V_1 + \Delta P \Delta V \]
Because $\Delta P \Delta V$ is relatively small, it can be omitted and the equation becomes:

$$P_1V_1 = P_1V_1 + P_1\Delta V + \Delta PV_1$$

When solved:

$$0 = P_1\Delta V + \Delta PV_1$$

$$\Delta PV_1 = -P_1\Delta V$$

$$V_1 = \frac{-P_1\Delta V}{\Delta P}$$

where:

- $P_1$ = Alveolar pressure
- $\Delta V$ = Change in body box volume when panting
- $\Delta P$ = Change in alveolar pressure (measured at mouth) when panting against closed shutter
- $V_1$ = TGV when shutter is closed, usually at FRC

The negative sign of $P_1$ is ignored.
Appendix D
Pulmonary Terms, Symbols, and Definitions

Gases

\( V \)  
Gas volume. The particular gas as well as its pressure, water vapor conditions, and other special conditions must be specified in text or indicated by appropriate qualifying symbols.

\( F \)  
Fractional concentration of a gas.

\( PB \)  
Barometric pressure.

\( STPD \)  
Standard conditions; temperature 0°C, pressure 760 mmHg and dry (0 water vapor).

\( BTPS \)  
Body conditions; body temperature, ambient pressure, and saturated with water vapor at these conditions.

\( ATPD \)  
Ambient temperature and pressure, saturated with water vapor at these conditions.

\( f \)  
Respiratory frequency (breaths per minute).

\( t \)  
Time.

Forced Spirometry

\( FVC \)  
Forced vital capacity; vital capacity performed with a maximally forced expiratory effort. This is sometimes referred to as FEVC.

\( FIVC \)  
Forced inspiratory vital capacity; the maximal volume of air inspired with a maximally forced effort from a position of maximal expiration.

\( FEV_1 \)  
Forced expiratory volume in 1 second. The volume of air exhaled in the first second of the FVC. The general symbol is FEV\(_t\), where \( t \) is the specific time interval during the performance of the FVC. Times other than 1 second are used, for example, FEV\(_1\) and FEV\(_6\).
APPENDIX D  Pulmonary Terms, Symbols, and Definitions

FEV1/FVC%  Forced expiratory volume in 1 second to FVC ratio, as a percentage. The general symbol (FEV1/FVC) can be applied for other times (e.g., FEV6/FVC%).

FEF  Forced expiratory flow, related to some portion of the FVC curve. Modifiers refer to the amount of the FVC already exhaled when the measurement is made. For example:
- FEF75%: Instantaneous forced expiratory flow after 75% of the FVC has been exhaled.
- FEF25%: Instantaneous forced expiratory flow after 25% of the FVC has been exhaled.

FEFmax  The maximal forced expiratory flow achieved during an FVC.

PEF  The highest forced or peak expiratory flow measured with a peak flow meter.

Vmax  Forced expiratory flow, related to the total lung capacity or the actual volume of the lung at which the measurement is made. Modifiers refer to the amount of lung volume remaining when the measurement is made. For example:
- Vmax75% is the instantaneous forced expiratory flow when the lung is at 75% of its TLC.

FEF25–75%  Mean forced expiratory flow during the middle half of the FVC.

MVV  Maximal voluntary ventilation. The volume of air expired in a specified period during repetitive maximal respiratory effort at an unrestricted frequency.

FET25–75%  The time required to deliver the FEF25–75%.

FIF  Forced inspiratory flow. As with FEF, the appropriate modifiers must be used to designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of the measurement. For example:
- FIF50%: Instantaneous inspiratory flow after 50% of the vital capacity has been inspired from residual volume.

Lung Volumes

RV  Residual volume; that volume of air remaining in the lungs after maximal exhalation, or TLC – VC. The method of measurement should be indicated in the text or, when necessary, by appropriate qualifying symbols.

ERV  Expiratory reserve volume; the maximal volume of air that can be exhaled from the resting end-tidal position.

TV  Tidal volume; that volume of air inhaled or exhaled with each breath during normal breathing. The symbol VT is also used.
Pulmonary Terms, Symbols, and Definitions

**IRV**  
Inspiratory reserve volume; the maximal volume of air inhaled from the end-inspiratory level during normal breathing.

**IC**  
Inspiratory capacity; the maximum amount of air that can be inhaled from tidal volume end-expiratory level, or the sum of IRV and TV.

**IVC**  
Inspiratory vital capacity; the maximum volume of air inhaled from the point of maximum expiration.

**VC**  
Vital capacity; the maximum volume of air exhaled from the point of maximum inspiration. The VC can be performed forcefully (FVC) or slowly (SVC).

**FRC**  
Functional residual capacity; the volume of air in the lungs at tidal volume end-expiratory level, or the sum of RV and ERV. The method of measurement should be indicated, as with RV.

**TLC**  
Total lung capacity; the sum of all volume compartments or the volume of air in the lungs after maximal inspiration. The method of measurement should be indicated.

**RV/TLC%**  
Residual volume to total lung capacity ratio, expressed as a percentage.

**TGV**  
Thoracic gas volume; the volume of air in the thorax at any point in time and any level of thoracic compression.

### Diffusing Capacity

**DL_{CO}**  
Diffusing capacity of the lung expressed as volume (STPD) of carbon monoxide uptake per unit alveolar-capillary pressure difference. A modifier can be used to designate the technique (e.g., DL_{CO_{sb}} is single breath carbon monoxide diffusing capacity). It is also described as D, and carbon monoxide is assumed to be the test gas.

**D_{m}**  
Rate of diffusion of a gas across the alveolar-capillary membrane.

**\(\Theta_{x}\)**  
Reaction rate coefficient for red cells; the volume of gas (x) that will combine per minute with 1 unit volume of blood per unit gas tension. If the specific gas is not stated, \(\Theta\) is assumed to refer to the reaction rate for CO and is a function of existing O2 tension.

**Q_{c}**  
Capillary blood volume (usually expressed as Vc in the literature, a symbol inconsistent with those recommended for blood volumes). When determined from the following equation, Qc represents the effective pulmonary capillary blood volume, that is, capillary blood volume in intimate association with alveolar gas.

\[
\frac{1}{D} = \frac{1}{D_{m}} + \frac{1}{\Theta Q_{c}}
\]
**APPENDIX D Pulmonary Terms, Symbols, and Definitions**

**DL,CO/VA** Diffusion of carbon monoxide per unit of alveolar volume with DL,CO expressed in STPD and VA expressed as liters BTPS. The term Krogh constant is sometimes used to represent this relationship.

**Ventilation**

- **VE** Expired volume per minute (BTPS).
- **VI** Inspired volume per minute (BTPS).
- **VCO2** Carbon dioxide production per minute (STPD).
- **VO2** Oxygen consumption per minute (STPD).
- **VA** Alveolar ventilation per minute (BTPS).
- **VD** Ventilation per minute of the physiologic dead space (wasted ventilation), BTPS, defined by the following equation:

\[
VD = \frac{VE (Paco_2 - PteCO_2)}{(Paco_2 - Pico_2)}
\]

- **VDf** The physiologic dead space volume defined as VD/f.
- **VDan** Ventilation per minute of the anatomic dead space; that portion of the conducting airway in which no significant gas exchange occurs (BTPS) or Vdan that is the volume of the anatomic dead space.
- **VDAlv** Ventilation of the alveolar dead space (BTPS), defined by the following equation:

\[
VDAlv = VD - VDan
\]

- **VAeff** Effective alveolar ventilation defined as:

\[
VAeff = VE - VD
\]

- **VDreb** Rebreathing ventilation. Ventilation per minute of the rebreathing volume of any external respiratory apparatus (ATPS) or VDreb, the rebreathing volume of an external respiratory device.

**Mechanics of Breathing**

**Pressure Terms**

- **P** A general symbol for pressure.
- **Paw** Pressure in the airway, level to be specified.
- **Pawo** Pressure at the airway opening
Pulmonary Terms, Symbols, and Definitions

Intrapleural pressure.

Alveolar pressure.

Transpulmonary pressure.

Esophageal pressure used to estimate \( P_{pl} \).

---

**Flow–Pressure Relationship Terms**

\( R \)  
A general symbol for resistance, pressure per unit flow.

\( \text{Raw} \)  
Airway resistance.

\( RL \)  
Total pulmonary resistance, measured by relating flow-dependent transpulmonary pressure to airflow at the mouth.

\( \text{Rus} \)  
Resistance of the airways on the alveolar side (upstream) of the point in the airways where intraluminal pressure equals \( P_{pl} \), measured under conditions of maximum expiratory flow.

\( \text{Rds} \)  
Resistance of the airways on the oral side (downstream) of the point in the airways where intraluminal pressure equals \( P_{pl} \).

\( \text{Gaw} \)  
Airway conductance, the reciprocal of \( \text{Raw} \).

\( \text{Gaw}/VL \)  
Specific conductance, expressed per liter of lung volume at which \( G \) is measured; sometimes referred to as \( sGaw \).

---

**Pressure–Volume Relationship Terms**

\( C \)  
A general symbol for compliance; volume change per unit of applied pressure change.

\( C_{dyn} \)  
Dynamic compliance; compliance measured at point of zero gas flow at the mouth during active breathing.

\( C_{st} \)  
Static compliance; compliance determined from measurements made during conditions of prolonged interruption of airflow.

\( C/VL \)  
Specific compliance.

\( E \)  
Elastance; pressure per unit of volume change; the reciprocal of compliance.

\( P_{st} \)  
Static transpulmonary pressure at a specified lung volume; for example, \( P_{stTLC} \) is static recoil pressure measured at TLC.

\( P_{stTLC}/TLC \)  
Coefficient of lung retraction expressed as cm H\(_{2}\)O per liter of TLC.

\( W \)  
A general symbol for the mechanical work of breathing; requires use of appropriate qualifying symbols and description of specific conditions.
Appendix E
Calculation of Mean and Standard Deviation

Measures of central tendency are numbers that represent some central value that data are grouped around. The most common measure is the mean ($\bar{X}$) or arithmetic average. The mean is the sum of all the observations divided by the number of observations:

$$\bar{X} = \frac{\Sigma X}{n}$$

where

$\bar{X}$ = Mean
$\Sigma$ = Sum of
$X$ = Observations
$n$ = Number of observations

Example: A laboratory is establishing the mean and standard deviation for biological controls. A healthy employee has performed spirometry once each week for the past 5 weeks. The FVC values are shown below:

<table>
<thead>
<tr>
<th>Week</th>
<th>FVC (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.85</td>
</tr>
<tr>
<td>2</td>
<td>4.93</td>
</tr>
<tr>
<td>3</td>
<td>4.82</td>
</tr>
<tr>
<td>4</td>
<td>4.90</td>
</tr>
<tr>
<td>5</td>
<td>4.98</td>
</tr>
</tbody>
</table>
APPENDIX E Calculation of Mean and Standard Deviation

The mean would be calculated as follows:

\[ \bar{X} = \frac{(4.85 + 4.93 + 4.82 + 4.90 + 4.98)}{5} = \frac{24.48}{5} = 4.896 \text{ L} \]

Measures of central tendency are incomplete without measures of variability, the most common of which is the standard deviation (S, or sometimes abbreviated SD). The SD shows how much variation there is from the average or mean value. A low SD indicates data points are close to the mean. A high SD indicates data are spread out.

The SD is calculated as follows:

\[ SD = \sqrt{\frac{\sum (X - \bar{X})^2}{n}} \]

where
- SD = Standard deviation
- \( \Sigma \) = Sum of
- X = Observation value
- \( \bar{X} \) = Mean
- n = Number of observations

Using data in the previous example, the SD would be calculated as follows using a mean FVC of 4.896 L.

<table>
<thead>
<tr>
<th>X</th>
<th>X - ( \bar{X} )</th>
<th>((X - \bar{X})^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.85</td>
<td>-0.046</td>
<td>0.002</td>
</tr>
<tr>
<td>4.93</td>
<td>0.034</td>
<td>0.001</td>
</tr>
<tr>
<td>4.82</td>
<td>0.076</td>
<td>0.006</td>
</tr>
<tr>
<td>4.92</td>
<td>0.004</td>
<td>0.000</td>
</tr>
<tr>
<td>4.98</td>
<td>0.084</td>
<td>0.007</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td>0.016</td>
</tr>
</tbody>
</table>

We will assume a normal distribution for these data. Thus, 68.3% of the values will be within ±1 SD of the mean, 95.5% will be within ±2 SDs of the mean, and 99.7% will be within ±3 SDs of the mean.

In this example, 1 SD = 0.057, 2 SD = 0.114, and 3 SD = 0.171. Thus, the range of FVC values within ±2 SDs of the mean is 4.896 ± 0.114, or 4.782 to 5.010 L.
Index

**Note:** Italicized page locators indicate figures/photos; tables are noted with a *.
Index

Airway obstruction, 52
Airway resistance
  body box for measurement of, 77
  defined, 143, 146
  determining, for each open- and closed-shutter set, 148–149
  factors related to, 144
  hyperbolic relationship between lung volume and, 144, 145
  measurement of, 143, 144
  in body box, 147
  when looping or bending is present, 154
  reference values for, 340
  measurements of, in body box, 154
Airway resistance by body plethysmography, 143–157
  calculations, 149–151
  physiology, 144–145
  quality control, 155–156
  reference values and basic interpretation, 154
  technical considerations, 151–154
  technique, 146–149
Airways
  collapsibility of, 4, 6
  downstream, 6, 6
  lower, 2, 3
  upstream, 6, 6, 7
Airway size, airway resistance and, 144
Albuterol, 50, 51
  spirometry on 20-year-old asthmatic man, before/after two puffs of, from MDI, 219
  withholding, for amount of time shown prior to mannitol challenge test, 244
  withholding, for amount of time shown prior to methacholine challenge test, 232
  withholding, prior to EIB test, 214, 214
Alert values, 307
Airlinearity, infrared absorption
  CO analyzer and, 119
Alkalemia, 287
Alkalosis, 287
Allen, N. D., 229
Alpha receptors, bronchodilators and, 50
Alternative modified Allen test, 297
Altitude and PAO2, ATS/ERS guidelines, formulas for, 127
Alveolar-arterial oxygen gradient, 164, 165
  college student/cross-country, CPET case, 184
Alveolar-capillary (A-C) membrane, rate of diffusion of gases across, 114–115
Alveolar pressure gradient, determining, when there is airflow, 146–147
Alveolar sample, DL,CO technique and, 122
Alveolar volume (VA), 99
  ATS/ERS guidelines, formulas for, 126
  calculating, 124
  single-breath CO diffusing capacity and DL,CO corrected in 56-year-old woman, 133, 134, 134
Alveoli/alveolus, 3
diffusion of gases from, to hemoglobin molecule, 115
American Heart Association, 171
  acceptability criteria for preschool children and guidelines of, 267
  bronchial challenge testing recommendations for FEV1, 235
  DL,CO test guidelines by, children and, 272
  “Guidelines for Methacholine and Exercise Challenge Testing,” 233
  interpretation scheme/categorization of bronchial responsiveness, 241
  95% CI method to define LLN recommended by, 336
  Provocholine dilutions based on fourfold guideline scheme, 226
  Provocholine dilutions based on twofold guideline scheme, 226
  Provocholine package insert and dosing schemes recommended by, 231, 231
  “Pulmonary Function Testing in Preschool Children,” 265
  reporting parameters for testing preschool children, 269
  six-minute walk test guidelines, 204
  2005 guidelines on pulmonary function testing, 337
Amyotrophic lateral sclerosis, MIP/MEP measurements in patients with, 257
Anaerobic metabolism, exercise, ventilatory ceiling and, 161
Anaerobic threshold, 16, 160
  clinical application of, 168
Index

Asthma cases

- methacholine challenges and, 224
- pulmonary function results before/after bronchodilator (six actuations of albuterol from MDI), 63
- pulmonary function results before/after bronchodilator (two actuations of albuterol from MDI), 61
- spirometric results of each trial before/after bronchodilator on 16-year-old male, 59
- spirometric results of each trial before/after bronchodilator on 20-year-old man, 219
- spirometry on 20-year-old man, before/after pretreatment and after treadmill exercise while breathing cold, dry air, 220
- spirometry on 20-year-old man, before/after two puffs of albuterol from MDI, 219
- spirometry on 20-year-old man, before/after treadmill exercise, 219
- spirometry on 20-year-old man, before/after treadmill exercise while breathing cold, dry air, 219
- spirometry on 20-year-old man, before/after treadmill exercise while breathing cold, dry air, 220
- spirometry on 20-year-old man, before/after treadmill exercise, 219
- spirometry on 20-year-old man, before/after treadmill exercise while breathing cold, dry air, 219
- follow-up for 11-year-old: case presentation, 276–277
- answers and discussion, 277
- background, 276
- prebronchodilator spirometry results, March 2010 test, 276
- prebronchodilator spirometry results, October 2010 testing, 277
- follow-up for 5-year-old boy: case presentation, 272–276
- background, 272
- flow-volume spirometry for, 274, 275
- questions, answers, and discussion, 272–273, 276
- spirometry results of each postbronchodilator maneuver, 275
- spirometry results of each prebronchodilator maneuver, 273
- Mannitol challenges and, 241–242
- ventilatory response of asthmatic child for 6 minutes of running, 212

Asthma patients

- exercise and, 211
- ventilatory response, asthmatic vs. normal subjects and, 213
- ventilatory response of asthmatic child for 6 minutes of running, 212
- exercise and: case presentation spirometry on 20-year-old man, before/after pretreatment and after treadmill exercise while breathing cold, dry air, 220
- spirometry on 20-year-old man, before/after two puffs of albuterol from MDI, 219
- spirometry of 20-year-old man before/after treadmill exercise while breathing cold, dry air, 220
- spirometry on 20-year-old man, before/after treadmill exercise, 219
- spirometry on 20-year-old man, before/after treadmill exercise while breathing cold, dry air, 219
- follow-up for 11-year-old: case presentation, 276–277
- answers and discussion, 277
- background, 276
- prebronchodilator spirometry results, March 2010 test, 276
- prebronchodilator spirometry results, October 2010 testing, 277
- follow-up for 5-year-old boy: case presentation, 272–276
- background, 272
- flow-volume spirometry for, 274, 275
- questions, answers, and discussion, 272–273, 276
- spirometry results of each postbronchodilator maneuver, 275
- spirometry results of each prebronchodilator maneuver, 273
- Mannitol challenges and, 241–242
- ventilatory response of asthmatic child for 6 minutes of running, 212

Asian Americans, reference values for laboratory and, 336

Assumed dead-space method, 116

Asthma

- increased resistance and, 7

Arterial blood gases, assessing, cardiopulmonary exercise test and, 159

Arterial blood sampling, CPET and safety of, 175–176

Arterial carbon dioxide level, 164

Arterial catheters

- inserting, methods for, 176
- safety and low infection rate with, 175

Arterializing capillary blood, 301

Arterial-mixed venous oxygen content, hypoxia monitoring and, 287

Arterial oxygen level, 164

Arterial puncturing and sampling, 296–301, 304

alternative modified Allen test procedure, 297

collateral circulation and, 296

complications with arterial punctures, 298–299

location for, 296

modified Allen test procedure, 297

newborn capillary heel sticks, 300, 300–301

radial artery puncture technique, 297–298

sampling through indwelling vascular catheter, 299–300

Arteries, oxygen transport and, 283

Asian Americans, reference values for laboratory and, 336

Assumed dead-space method, 116

Asthma

- increased resistance and, 7

Methacholine challenges and, 224

Asthma cases
discussion, 61, 62

pulmonary function results before/after bronchodilator (six actuations of albuterol from MDI), 63

pulmonary function results before/after bronchodilator (two actuations of albuterol from MDI), 61

spirometric results of each trial before/after bronchodilator on 16-year-old male, 59

Asthma patients

- exercise and, 211

ventilatory response, asthmatic vs. normal subjects and, 213

ventilatory response of asthmatic child for 6 minutes of running, 212

exercise and: case presentation spirometry on 20-year-old man, before/after pretreatment and after treadmill exercise while breathing cold, dry air, 220

spirometry on 20-year-old man, before/after two puffs of albuterol from MDI, 219

spirometry of 20-year-old man before/after treadmill exercise while breathing cold, dry air, 220

spirometry on 20-year-old man, before/after treadmill exercise, 219

spirometry on 20-year-old man, before/after treadmill exercise while breathing cold, dry air, 219

follow-up for 11-year-old: case presentation, 276–277

answers and discussion, 277

background, 276

prebronchodilator spirometry results, March 2010 test, 276

prebronchodilator spirometry results, October 2010 testing, 277

follow-up for 5-year-old boy: case presentation, 272–276

background, 272

flow-volume spirometry for, 274, 275

questions, answers, and discussion, 272–273, 276

spirometry results of each postbronchodilator maneuver, 275

spirometry results of each prebronchodilator maneuver, 273

Mannitol challenges and, 241–242

ventilatory response of asthmatic child for 6 minutes of running, 212

Arterial acidemia, 146

Arterial blood gases, assessing, cardiopulmonary exercise test and, 159

Arterial blood sampling, CPET and safety of, 175–176

Arterial carbon dioxide level, 164

Arterial catheters

- inserting, methods for, 176
- safety and low infection rate with, 175

Arterializing capillary blood, 301

Arterial-mixed venous oxygen content, hypoxia monitoring and, 287

Arterial oxygen level, 164

Arterial puncturing and sampling, 296–301, 304

alternative modified Allen test procedure, 297

collateral circulation and, 296

complications with arterial punctures, 298–299

location for, 296

modified Allen test procedure, 297

newborn capillary heel sticks, 300, 300–301

radial artery puncture technique, 297–298

sampling through indwelling vascular catheter, 299–300

Arteries, oxygen transport and, 283

Asian Americans, reference values for laboratory and, 336

Assumed dead-space method, 116

Asthma

- increased resistance and, 7

Methacholine challenges and, 224
analytic phase, 304–307
hemotocrit electrode, 306–307
PCO2 (Stowe-Severinghaus) electrode, 305
pH (Sanz) electrode, 305
PO2 (Clark) electrode, 305–306
temperature-corrected blood gases, 307

first, 292, 292
functional oxygen saturation
calculation with, 317

normal range/critical reporting values of analytes,
308

postanalytic phase, 307–308
preanalytic phase, 294–301, 304
arterial puncture and handling, 296–301
common sources or erroneous results, 302–303
patient identification, 295
preanalytical error, 301
validating, 293–294

Blood gases, normal range and critical reporting values
of, 308

Blood gas interpretation, 309–311
oxygen status, 309–310
effects of age on PaO2 reference
ranges, 309
special considerations, 310
Blood gas laboratory, quality management of, 312–315
Blood gas monitoring, 323
Blood gas science, 281–291
physical laws applying to blood gases
acid-base balance, 288–291
carbon dioxide transport, 291
gases and, 286–287
hypoxemia, 284–285
hypoxia, 285–286
oxygen transport, 223
physicist, 283–284
physicist, 283–284

Blood gas science, 281–291
dalton’s law of partial pressures, 282
Graham’s law, 282
Henry’s law, 282
Hemoglobin, oxygen binding, 282

Blood lactate, determining AT in CPET and
measurement of, 168

Blood plasma-red blood cell barrier,
diffusion of gases and, 114
Blood pressure
assessing, cardiopulmonary
exercise test and, 159
CPET and, 171
Blow the rocket ship to the moon game (spirometer
software), 273

Body box, 77, 105, 146
quality control for, 155–156
case presentation, 249–251
mannitol challenge test, 241–249
methacholine challenge test, 224–241
Bronchial provocative breathing test, 223
Bronchial responsiveness, ATS interpretation scheme/categorization of, 241
Bronchioles, terminal, 2
Bronchoconstriction, 144. See also Exercise-induced bronchoconstriction test suggestion and,
233
Bronchodilatation, suggestion and, 233
Bronchodilator response, interpretation of, 53–54
Bronchodilator(s)
African Americans and lung volume case, flow-volume spirogram showing before/after use of,
106
flow-volume curves before/after administration of, 56-year-old woman, 133
flow-volume curves before/after administration of, 57-year-old woman with PAH, 138
forced spirometry data on two patients before/after use of, 55
hospital pulmonary function lab data for patient with dyspnea, before/after use of, 103
inhaled withholding, for amount of time shown prior to mannitol challenge test, 244
withholding, for amount of time shown prior to methacholine challenge test, 232
long- and short-acting, withholding and, 62
pulmonary function data on 57-year-old woman with PAH before/after use of, 137
pulmonary function values before/after, in African Americans and lung volume case, 105t,
107t
routine administration of, 50
spirometric results in flow-volume graph, showing five maneuvers before, and three maneuvers after Rx, 60
Bronchospasm, 52
Bronchus, right and left main stem, 2, 3
Brown, C. D., 207
Bruce protocol, 174
BTPS, 177
to ATBS factor, temperature correction and, 37, 38t
Budesonide, 51t
withholding, for amount of time shown prior to methacholine challenge test, 232t
Bulk-addition technique, FRCHe measurement and, 93
Burgos, F., 58
Butland, R., .., 202
Body box pressure
calibration factor, 79, 80
closed-shutter panting and mouth pressure relative to, 149, 150
S-shaped curve during open-shutter panting, showing flow relative to, 149
Body plethysmographs
reference values for specific conductance in children and use of, 340
types of, 146
Body plethysmography. See also Airway resistance by body plethysmography
type for, 77
EIB assessment and, 215
FRC measurement with, 69, 77–88, 105
flow box, 80, 82
methodology, 77
physiology and instrumentation, 78–83
plethysmograph display showing mouth pressure and body box pressure during closed-shutter panting, 79
quality control, 88
testing technique, 84–85
variable-pressure box, 80, 81
volume-displacement box, 82–83, 83
FRC testing in children and, 270–271
plethysmograph display of poorly done closed-shutter panting maneuver, 87
plethysmograph display of properly done closed-shutter panting maneuver, 86
Body temperature and pressure saturated with water vapor. See BTPS
Borg scale
quantifying symptoms during CPET with, 181
10-point, six-minute walk test and, 205
Boyle’s law
body box operating principle and, 78
RV measurement and, 77
Breath-by-breath method, description of, 173
Breath hold, DL,CO technique and, 121
Breath-hold time, ATS/ERS calculation recommendations for, 124–125
Breathing circuit
with closed-circuit He dilution technique, 90
cross contamination issues and, 101–102
Breathing reserve, defined, 162
Breathing valves, CPET and, 172, 172
Breathlessness, quantifying, during CPET, 181
Bronchial challenge testing with pharmacological agents, 223–251

ECG and blood pressure, 171
gas analyzers, 171–172
pulse oximeter, 171
treadmill and cycle ergometer, 170–171
measurement of minute ventilation and gas exchange
breath by breath, 173
mixing chamber, 173
measurements and calculations, 176–181
calculations, 177–181
exercise measurements, 176–177
quantifying symptoms, 181
rest measurements, 176
patient preparation, 175
patient safety, 168–170
absolute and relative contraindications to CPET, 169
common indications for terminating exercise testing, 170
protocols
comparison of, 175
constant-work steady-state protocol, 174–175
maximal symptom-limited incremental cycle ergometer protocol, 174
maximal symptom-limited incremental treadmill protocol, 174
purpose of, 201
quality control, 181–182
reference or normal values, 182
terms and normal responses to exercise, 160–168
cardiovascular response, 166
ergy delivery and utilization, 166–168
gas exchange, 163–166
ventilatory response, 160–163
work and power, 168
testing methodology, 173–176
Cardiovascular disease, low DL,CO values with, 132
Cardiovascular measurements, restrictive process in 64-year-old man, CPET case, 194
Cardiovascular response
college student/cross-country runner, CPET case, 186
dyspnea in 50-year-old man, CPET case, 187
to exercise, 166
62-year-old woman, 90-pack-year smoker, CPET case, 191
Case presentations
blood gases-related, 324–328
cardiopulmonary exercise test, 182–196
exercise-induced bronchoconstriction test, 218–220
forced spirometry, 59–63
lung volumes, 102–107
mannitol challenge test, 249–251
methacholine challenge test, 249–251
pediatric pulmonary function testing, 272–277
single-breath carbon monoxide diffusing capacity, 133–138
Cations, 289
Caucasian men, frequency distribution of FVC value obtained from, 334
Caucasian population, African population vs., pulmonary function and, 106–107
Caucasians lung volumes in, 334
reference values and, 335
for laboratory, 336
Centers for Disease Control and Prevention (CDC), 296
infection control guidelines by, 58, 101, 102
Centers for Medicare and Medicaid Services, 292
Cetirizine, withholding, for amount of time shown prior to mannitol challenge test, 244
Chai, H., 229
Chalupova, J., 269
Charles’ law, temperature correction and, 36–37
Chest dimensions, lung volumes and, 334
Chest film, lung volume measurement and drawbacks with, 99
Chest roentgenogram (x-ray), static lung volume measurement with, 69
Children, See also Pediatric pulmonary function testing exercise-induced asthma in, 211
peak flow meters for EIB assessment in, 215
Raw and sGaw ranges in, 154
reference values for DL,CO, reference studies used for, 340
reference values for specific conductance in, using body plethysmograph, 340
testing, challenges with, 264–265
Chronic obstructive pulmonary disease, 224
reduced airflow in, 7
spirometry and measuring impact of, 2
Ciclesonide, 511
withholding, for amount of time shown prior to methacholine challenge test, 232
CLIA. See Clinical Laboratory Improvement
Amendments
Clinical and Laboratory Standards Institute, 318
Clinical Laboratory Improvement Amendments acceptable total error limit, 294, 294t
primary goal of, 294, 293
proficiency testing for blood gas laboratory and, 314
Clinical reportable range, for blood gas analyzers, 314
Closed-circuit bag-in-box system, 116, 117, 118
Closed-circuit He dilution technique, example, FRC calculation, 91–92
Closed-circuit method, pediatric pulmonary function testing and, 266, 267
Closed-circuit technique, spirometry testing and, 27
Closed-shutter panting maneuver, 79
acceptable, obtaining several sets of, 148
children and challenges with, 271
hypothetical numbers for, example, 150–151
mouth pressure relative to body box pressure created during, 149, 150
plethysmograph display showing mouth pressure and body box pressure relationship during, 79
poorly done, 87
properly done, 86
proper technique for, 85, 85
relationship between mouth pressure and body box pressure with, 147–148, 148
Closing volume, single-breath N₂ method and, 99
Clinical and Laboratory Standards Institute, 318
Clinical Laboratory Improvement Amendments acceptable total error limit, 294, 294t
primary goal of, 294, 293
proficiency testing for blood gas laboratory and, 314
reportable range, for blood gas analyzers, 314
Compensated conditions, 311
Compensated respiratory acidemia, in 62-year-old male with shortness of breath, 325
Compliance, 3
Computed tomography lung volume measurement and, 100
static lung volume measurement with, 69, 70
Computerized pulmonary function testing systems, 74
Comroe, J., 77
Conductimetric sensors, hemotocrit results produced by, 307
Conductive airways, resistance to airflow and, 1
Constant-volume box, 80, 146
Cold, dry air, EIB and patient breathing in, 216, 218, 219
background, 216
interpretation, 213–215
t, 220, 220
infection control guidelines by, 58, 101, 102
College of American Pathologists, 293
low and high critical values developed by, 308
College student/cross-country runner CPET case, 183–186
background, 183
interpretation, 183–185
ventilatory, cardiovascular, and gas exchange measurements from final minutes of rest and maximal exercise, 184
ventilatory response, 183, 185
Commission on Laboratory Accreditation, 293
Compensated conditions, 311
Compensated respiratory acidemia, in 62-year-old male with shortness of breath, 325
Compliance, 3
Computed tomography lung volume measurement and, 100
static lung volume measurement with, 69, 70
Computerized pulmonary function testing systems, 74
Comroe, J., 77
Conductimetric sensors, hemotocrit results produced by, 307
Conductive airways, resistance to airflow and, 1
Constant-volume box, 80, 146
Cold, dry air, EIB and patient breathing in, 216, 218, 219
background, 216
interpretation, 213–215
t, 220, 220
infection control guidelines by, 58, 101, 102
College of American Pathologists, 293
low and high critical values developed by, 308
College student/cross-country runner CPET case, 183–186
background, 183
interpretation, 183–185
ventilatory, cardiovascular, and gas exchange measurements from final minutes of rest and maximal exercise, 184
ventilatory response, 183, 185
Commission on Laboratory Accreditation, 293
Compensated conditions, 311
Compensated respiratory acidemia, in 62-year-old male with shortness of breath, 325
Compliance, 3
Computed tomography lung volume measurement and, 100
static lung volume measurement with, 69, 70
Computerized pulmonary function testing systems, 74
Comroe, J., 77
Conductimetric sensors, hemotocrit results produced by, 307
Conductive airways, resistance to airflow and, 1
Constant-volume box, 80, 146
Cold, dry air, EIB and patient breathing in, 216, 218, 219
background, 216
interpretation, 213–215
t, 220, 220
infection control guidelines by, 58, 101, 102
College of American Pathologists, 293
low and high critical values developed by, 308
College student/cross-country runner CPET case, 183–186
background, 183
interpretation, 183–185
ventilatory, cardiovascular, and gas exchange measurements from final minutes of rest and maximal exercise, 184
ventilatory response, 183, 185
Commission on Laboratory Accreditation, 293
Compensated conditions, 311
Compensated respiratory acidemia, in 62-year-old male with shortness of breath, 325
Compliance, 3
Computed tomography lung volume measurement and, 100
static lung volume measurement with, 69, 70
Computerized pulmonary function testing systems, 74
Comroe, J., 77
Conductimetric sensors, hemotocrit results produced by, 307
Conductive airways, resistance to airflow and, 1
Constant-volume box, 80, 146
Cold, dry air, EIB and patient breathing in, 216, 218, 219
background, 216
interpretation, 213–215
t, 220, 220
infection control guidelines by, 58, 101, 102
College of American Pathologists, 293
low and high critical values developed by, 308
College student/cross-country runner CPET case, 183–186
background, 183
interpretation, 183–185
ventilatory, cardiovascular, and gas exchange measurements from final minutes of rest and maximal exercise, 184
ventilatory response, 183, 185
Commission on Laboratory Accreditation, 293
Compensated conditions, 311
Compensated respiratory acidemia, in 62-year-old male with shortness of breath, 325
Compliance, 3
Computed tomography lung volume measurement and, 100
static lung volume measurement with, 69, 70
Computerized pulmonary function testing systems, 74
Comroe, J., 77
Conductimetric sensors, hemotocrit results produced by, 307
Conductive airways, resistance to airflow and, 1
Constant-volume box, 80, 146
Index

Constant work rate exercise protocol, 177
Constant-work steady-state protocol, 174–175
Continuous-addition technique, FRCm, measurement and, 93
Continuous-flow technique, arterial catheter insertion and, 176
Cooper, K. H., 202
COPD. See Chronic obstructive pulmonary disease
Corticosteroids
inhaled, 511
withholding, for amount of time shown prior to mannitol challenge test, 244
Cotes, J. E., 130, 340
Coughing, spirometry testing and, 30, 30–31
CPET. See Cardiopulmonary exercise test
Craco, R. O., 130, 338
Critical reportable values, 307
CRR. See Clinical reportable range
CT. See Computed tomography
cO2, calculation, formula for, 318
Cycle ergometer
CPET and, 170–171
symptom-limited incremental exercise protocol and, 177
Cycling, as asthmogenic form of exercise, 213, 213

D
Dalton’s law of partial pressure, 282, 304, 309
Dead space, of DL,CO system, knowing, 128
Demuth, G. R., 340
Deoxyhemoglobin, 316
Devilbiss 646 nebulizer, 230
Diabetic ketoacidosis case presentation
acid-base balance/oxygenation status, 326–327
background, 325
Diaphragm, 3, 3, 258
Diaphragm-type spirometer, 10–11, 12
Diastolic blood pressure
college student/cross-country runner, CPET case, 186
dyspnea in 50-year-old man, CPET case, 189
exercise and, 166, 167
restrictive process in 64-year-old man, CPET case, 196
Differential pressure device (pneumotachograph), 13–14, 14
Diffusing capacity
Diffusing capacity, measuring by using carbon monoxide, techniques for, 113
Diffusion, process of, defined, 113
Diffusion abnormality, in 21-year-old nonsmoking man, case presentation, 135–136, 135
Diffusion coefficient, 282
Diluent, for reconstituting methacholine powder, 225, 232
Direct stimulants, bronchial challenge testing and, 223
Dizziness, spirometry testing and, 26, 29
DKA. See Diabetic ketoacidosis
DL, CO test, 99
DL,CO
calculating, 124
children and difficulties with, 272
increasing, conditions or changes related to, 116
lowering, conditions or changes related to, 115
reference values for, 338, 340
DL,CO instrumentation, 116–119
analyzers, 118, 118–119
calibration check of, 119
closed-circuit bag-in-box system, 116, 117, 118
inspired gas composition, 119
DL,CO simulator, quality control for, 129
DL,CO testing techniques, 120–123
basic maneuver, 120
patient preparation, 120
practical hints, 122–123
recommendations, 120–122
alveolar sample, 122
breath hold, 121
expiratory maneuver, 121
inspiratory maneuver, 121, 121
number of maneuvers and repeatability, 122
reporting values, 122
washout volume, 122
DL,CO/VA, defined, 132
DL,CO values
calculating, 127
high, causes of, 132
low, causes of, 132
quantifying severity of, 132
DL,CO with 3-liter syringe, 128–129
Dose-response curve, FEV1, 240, 240
Dosimeter
defined, 229
five-breath method and, 229–230
variation of, 230
nebulizer output measurement and, 227
Dosing schemes, methacholine challenge test, 230–232
Downstream airways, 6, 6
DPG, 284
Driving pressure, airflow determination and, 7
Dry rolling-seal spirometer, 8, 10
Dry-seal Stead-Wells spirometer, 9
DuBois, A. B., 77, 154, 340
Dyspnea, unexplained, MIP/MEP measurements in patients with, 257
Dyspnea case study, 102–105
discussion, 104–105
flow-volume spirogram performed in hospital pulmonary function laboratory, before/after administration of bronchodilator, 104
hospital pulmonary function laboratory data before/after bronchodilator, 103
office pulmonary function data before/after bronchodilator, 102
questions and answers, 104
volume-time spirogram performed in doctor's office before/after administration of bronchodilator, 103
Dyspnea in 50-year-old man
CPET case, 186–190
background, 186–187
interpretation, 188–190
ventilatory, cardiovascular, and gas exchange measurements from final minutes of rest and maximal exercise, 187
ventilatory response, 188
Dyspnea on exertion, respiratory disease and, 159

E
Early terminations, spirometry testing and, 31–32, 33
ECG. See Electrocardiograph
EIA. See Exercise-induced asthma
EBB. See Exercise-induced bronchoconstriction
Eigen, H., 265, 269
80% method, 335–336
Elastic recoil
airway resistance and, 144
emphysema and lost of, 4, 7
Elastic recoil pressure, 7
Electrocardiogram, CPET and, 171
Electrocardiograph
assessing, cardiopulmonary exercise test and, 159
college student/cross-country runner, CPET case, 185
exercise-induced bronchoconstriction test and, 215, 217
restrictive process in 64-year-old man, CPET case, 196
62-year-old woman, 90-pack-year smoker, CPET case, 190
Electrochemical cell analyzer, 118
Electrochemical fuel cell principles, CPET and O2 analysis, 172
Electrolytes, normal range and critical reporting values of, 308t
Electronically braked cycle ergometers, 171, 174
exercise-induced bronchoconstriction test and, 216
Electronic quality control, for blood gas laboratory, 312
Ellipse method
lung volume measurement with, 99
TLC measurement from chest roentgenograms and use of, 103
EMCO. See Extracorporeal membrane oxygenation
Emphysema
loss of elastic recoil and, 4, 7, 144
low DLCO values with, 132
overly compliant lungs and, 4, 5
severe, flow-volume loop showing, 48
End-expiratory level, 70
End-tidal CO method, 116
Energy delivery/utilization, exercise and, 166–168
Enright, P. L., 207
Entire range procedure, for spirometers, 22
Epidemiology Standardization Project, 130, 131
Equal pressure point
defined, 6
dynamic compression of airways and, 6
maximal flow achieved and, 7
Equilibration, FRCHe measurement and, 93
Errors
interference, 301, 304
preanalytical, 301, 302–303, 304
ERS. See European Respiratory Society
ERV. See Expiratory reserve volume
Escherichia coli, 58
ESP. See Epidemiology Standardization Project
Ethnicity
lung volumes and, 334
reference values and, 334–335
selected for laboratory, 336–337
European Respiratory Society, 20, 22, 24, 26, 50, 53, 113, 114, 120, 132
acceptability criteria for preschool children and guidelines of, 267
children and DLCO test guidelines by, 272
95% CI method to define LLN recommended by, 336
“Pulmonary Function Testing in Preschool Children,” 265
pulmonary function test recommendations by, 269
reporting parameters for testing preschool children by, 269
2005 guidelines on pulmonary function testing, 337
Exercise, 223
assessing adult responses to, 182–183
cardiovascular response to, 166
energy delivery/utilization and, 166–168
gas exchange and, 163–166
ventilatory response to, 160–163
work and power relative to, 168
Exercise-induced asthma, prevalence of, 211
Exercise-induced bronchoconstriction
exercise intensity and severity of, 213
exercise test for, 159
extensive study of, 212
percentage of asthmatics with, 211
Exercise-induced bronchoconstriction test, 159, 211–220
absolute and relative contraindications for, 215
case presentation, 218–220
common indications for terminating testing, 218
medications to be withheld for at least amount of time shown prior to, 214
physiology, 211–214
testing technique, 214–218
assessment of response, 217–218
electrocardiograph, 215
exercise, 216
inhalate, 215–216
patient preparation and contraindications, 214–215
patient safety, 217
pulmonary function tests, 215
testing protocol, 216–217
Exercise measurements, CPET and, 176–177
Exercise test. See also Cardiopulmonary exercise test
value of, and types of, 159
Exhaled gas concentrations and volumes, cardiopulmonary exercise test and measurement of, 160
Expiration
gas flow and, 146
passive vs. active, 3
Expiratory loops, full, 34
Expiratory maneuver, DL,CO technique and, 121
Expiratory reserve volume, 70, 71
measurement of, 76
for obstructive, restrictive, and mixed obstructive and restrictive lung diseases, 74
testing children and measurement of, 271
External intercostals, 2
External quality control, for blood gas laboratory, 313
Extracorporeal membrane oxygenation, 306
Extracorporeal membrane oxygenator circuit, 323
Extrapolated volume, defined, 39

F
Fat-free mass, lung volumes in, 334

FEF_{25-75}
defined, 40
response to bronchodilator for, 53
FEF_{50} divided by FIF_{50}, 43
Fenoterol, withholding, prior to EIB test, 214, 214
FEV_{0.5}, pediatric pulmonary function testing and, 266
FEV_{0.75}, pediatric pulmonary function testing and, 266
FEV_{1}, See Forced expiratory volume in 1 second
FEV, measurement of, back-extrapolation technique in, 41
FEV/FVC ratio, airflow limitation vs. restriction, 52
FEV values
examples, from methacholine challenge test, 236
from mannitol challenge test, 246, 246
Fexofenadine, withholding, for amount of time shown prior to mannitol challenge test, 244

FIF_{25}, 43
FIF_{50}, 43
FIF_{75}, 43
FIF_{max}, 43
Filley method, 116
First generation of airways, 2
Five-breath method, 228, 229–230
Fixed acids, 288
Fixed obstruction, flow-volume loop showing, 43, 47
Flovent, 272
Flow, open-shutter panting and body box pressure relative to, 149
Flow, pressure, resistance relationship, pneumotachograph and, 13
Flow-body plethysmograph (variable volume), 82
Flow box, 80–81, 82, 146
Flow-sensing spirometers, 13–18
characteristics of, summary, 18
pneumotachograph, 13–14, 14
thermistor or heated-wire anemometer, 13, 14, 16, 17
ultrasonic, 13, 17–18, 18
Flow-volume curve display, 19
Flow-volume curves, examples of, in children, 268
Flow-volume display, for spirometers, 18, 19, 20
Flow-volume graphs
acceptable spirometry shown on, 34
of forced spirometry, 41, 43
spirometric results, showing five maneuvers before bronchodilator and three maneuvers after Rx, 60
of two forced spirometry efforts, 44
unacceptable spirometry due to early termination of exhalation and, 33
Flow-volume loops, 34–35
Forced spirometry data examples, on two patients before/after bronchodilator, 55r
interpretation guide for, 54
Forced spirometry maneuver, display of, in volume-time format on chart paper used on spirometers that rotate, 40
Forced vital capacity, 2, 72
airflow limitation vs. restriction and, 52
response to bronchodilator for, 53
spirometry and measurement of, 37–40, 39
values
frequency distribution of, obtained from Caucasian men, 334
between maneuver repeatability and, 33
Fornerotol, withholding, for amount of time shown prior to methacholine challenge test, 232r
Formoterol, 51r
withholding, for amount of time shown prior to mannitol challenge test, 244r
Forster, R. E., 114
Four-way valve, closed-circuit bag-in-box system and, 118
Fractional oxygen saturation, calculating, 316
FRC. See Functional residual capacity
Functional oxygen saturation, calculating, 317
Functional residual capacity, 3–4, 70, 70, 71
determining, basic techniques, 69
measurement of, 72
for obstructive, restrictive, and mixed obstructive and restrictive lung diseases, 74r
testing children and measurement of, 270–271
Functional residual capacity measurement with body plethysmography, 77–88
physiology and instrumentation, 78–83
quality control, 88
testing technique, 84–85
by multiple-breath closed-circuit He dilution, 77, 88–93
instrumentation, 88–89
physiology and calculations, 90–91
quality control, 93
testing technique, 92–93
by multiple-breath open-circuit N2 washout, 77, 94–99
physiology and instrumentation, 94–97
quality control, 99
testing technique, 97–99
FVC. See Forced vital capacity
FVC maneuver
evaluating, three main parts for, 29
flow-volume curve seen during, 19
volume-time curve seen during, 19
Heart, oxygen transport and, 283
Heart rate
college student/cross-country runner, CPET case, 184, 186
dyspnea in 50-year-old man, CPET case, 189, 189exercise, cardiac output and, 166oxygen consumption and, 167restrictive process in 64-year-old man, CPET case, 195
Heated-wire anemometer, 14, 16, 16–17
Heat exchanger, exercise-induced bronchoconstriction test and, 216
Height, reference values and, 334
Hematocrit, defined, 306
Hematocrit electrode, 306–307
Hemoglobin, reduced, absorption spectra of oxyhemoglobin, 320
Hemoglobin derivatives, hemoximetry and, 316
Hemoglobin molecule, diffusion of gases from alveolus to, 115
Hemotocrit measurement, with modern blood gas analyzers, 304
Hemoximeters, various uses for, 318–319
Hemoximetry, defined, 316
normal range and critical reporting values of, 308
Hemoximetry panel, for smoke inhalation by 51-year-old male in house fire, 328
Henderson-Hasselbalch equation, 288–289, 310
Henry’s law, 282
Histamine, 223
Homeostasis, pH, 288
Horizontal bellows spirometer, 11
Horizontal rolling-seal spirometer, 10
Housing, upper and lower, diaphragm-type spirometer, 29
Howatt, W. F., 340
Huffmann, Gustav von, 318
Humidity, exercise-induced bronchoconstriction test and, 215
Hutchinson, John, 7
Hydrone, R. E., 258, 260
Hydrogen ions, pH and, 286–287
Hyperresponsive airways evaluation of, 223methylcholine challenge test and, 224
Hyperresponsiveness, viral infections and, 233
Hypertonic aerosols, 223
Hypotonic aerosols, 223
Hypoxemia
Index

Interference errors, 301, 304
Internal quality control, for blood gas laboratory, 312
International Union of Pure and Applied Chemistry, 318
Interstitial lung disease
low DL,CO values with, 132
lung volume compartments and, 72
Intra-arterial blood gas monitoring, 323
Intra-arterial blood pressure, CPET and, 171
Inventory management, for blood gas laboratory, 315
Ipratropium, withholding, prior to EIB test, 214
Ipratropium bromide, 51, 51
withholding, for amount of time shown prior to mannitol challenge test, 244
withholding, for amount of time shown prior to methacholine challenge test, 232
IRV. See Inspiratory reserve volume
Isoproterenol, withholding, prior to EIB test, 214, 214
Isovolume FEF25-75%, 40
calculating, volume adjustment technique for, 42
IUPAC. See International Union of Pure and Applied Chemistry

Iatrogenic anemia, 299
IC. See Inspiratory capacity
Indirect stimulants, bronchial challenge testing and, 223
Indwelling catheters, sampling through, 299
Inert tracer gas, in single-breath method, function of, 116
Infection control
indwelling vascular catheter and, 299
lungs volumes and, 101–102
recommendations for, in pulmonary function laboratory, 58–59
Infrared CO analyzer, 118, 118
description of, 118
drawbacks with, 119
Inhalate, exercise-induced bronchoconstriction test and, 215–216
Inhaled beta sympathomimetic agents, withholding, prior to EIB test, 214, 214
In-line blood gas monitoring, 323
Inspiration, 2, 146
Inspiratory capacity, 70, 70
measurement of, 76
for obstructive, restrictive, and mixed obstructive and restrictive lung diseases, 74
for children and measurement of, 270–271
Inspiratory flow, flow-volume loop and, 42–44
Inspiratory loops, full, 34
Inspiratory maneuvers
acceptable and unacceptable, 127
DL,CO technique, 121
Inspiratory reserve volume, 70, 70, 71
Inspired oxygen, partial pressure of, 283
Inspired volume, ATS/ERS guidelines, formulas for, 126
Instrumental factors, appearance of open-shutter S-shaped V/PBB relationship and, 151–152
Integration, flow-sensing spirometers and, 13
Intercostals, 258
Law of electroneutrality, 284–285
description and effects of, 284–285
hypoxia vs, 286
moderate, in 62-year-old male with shortness of breath, 325
newborn, management of, 310
severe, smoke inhalation by 51-year-old male in house fire with, 328
Hypoxia
categories of, 285–286
common causes of, 284
hypoxemia vs, 286
monitoring, formulas for, 287
Hypoxia vs., 286
Kirkby, J., 340
Klungs, B., 271
Knudson, R. J., 130, 131, 335, 338
Krogh, August, 114
Krogh, Marie, 114
Kussmaul breathing pattern, 325
Kyphoscoliosis, 25
Lactic acid threshold, 16
Laboratory, reference values selected for, 336–337
Laboratory best practices, for blood gas analysis, 293.
See also Quality management of blood gas laboratory
Law of electroneutrality, 289
leaks

detected, measurement of N2 and, 96
with volume-displacing spirometers, 12

LEDs. See Light-emitting diodes

Leukotriene modifiers

withholding, for amount of time shown prior to
mannitol challenge test, 244
withholding, for amount of time shown prior to
methacholine challenge test, 232

Levison, H., 338

Light, R. W., 53

Light-emitting diodes, 316

Linear interpolation formula

for calculation of PC20FEV1, for methacholine
challenge, 239

for PD15, for mannitol challenge, 247, 248

Linearity checks, for gas analyzers, 127

Linearity test, for blood gas analyzers, 293

Liquid quality control, for blood gas laboratory, 313

LLN. See Lower limit of normal

Long-acting bronchodilators, 62

Lord, P. W., 154

Lower airways, 2, 3

Lower limit of normal, 335, 336

LQC. See Liquid quality control

Lung reference values, lung volumes and, 100–101

Lung resistance, measurement of, 143

Lungs

gas transfer and, 2
mechanical properties of, 3
overly compliant, emphysema and, 4, 5
oxygen transport and, 283
physiology, 2–7

Lung volume, 69–110

body size/proportions and, 334
case presentations, 102–107
in children, 270–271
measurement of FRC, 270–271
measurement of vital capacity, 271

compartments and subdivisions based on volume-
time spirogram, 70

FRC measurement, 77–99
with body plethysmography, 77–88
by multiple-breath closed-circuit He dilution, 89–93
by multiple-breath open-circuit N2 washout, 94–99
hyperbolic relationship between Raw and, 144, 145
infection control and, 101–102
linear relationship between airway conductance and, 144–145, 146
measurement of, 69
other methods, 99–100

measurement of VC, 73–76
determining lung subdivisions, 76
repeatability and reporting, 74
overview, 69–70
reference equations for, 338
reference values for, 100–101, 337–338
subdivisions: volumes and capacities, 70–73

Lymphocytes, 306

M

Magnetic resonance imaging, lung volume
measurement and, 100

Males (adult), ATS/ERS guidelines, DL,CO values
and, 136

Man-box (or man-can), 77

Mannitol, 211, 223
description of, 241, 242

Mannitol challenge test, 241–249
Aridol kit and dose steps for, 243

case presentation, 249–251
contraindications for, 242

dosage and administration, 242–243
expressing the results for, 247–249, 247

graphic representation of results from, 248
indications for, 241–242
medications to withhold for at least amount of time
shown prior to, 244
negative response for, 247
patient preparation, 243–244

cola drinks, coffee, tea, chocolate, 243
exercise, 244
medications, 243
smoking, 244
viral infections, 244
positive response for, 246
procedure, 245
pulmonary function tests, 245
percent change calculations, 246
safety, 244
tabular representation of results from, 247

Manual calculations, 36

Manual volume-displacement spirometers, 36

Mason-Likar adaptation, of 12-lead ECG, CPET and, 171

Mass-flow sensors, 14, 16, 173

Mass median diameter, for nebulizer, 227

Mass spectrometer analyzers, 118

Mass spectrometers, measurement of N2 with, 96

Matrix effect, 313

Maximal expiratory pressure (PEmax)
indication for, 257
instrumentation, 258–259
interpretation, predicted values for, 259–260
aerosol delivery variables, 226–228
ATS interpretation scheme/categorization of bronchial responsiveness, 241

basic elements of interpretation, 240–241
case presentation, 249–251
discussion of results for, 250–251
graphic representation of results for, 250
results of spirometry and specific conductance from, with percent change from postdiluent values, 249
for 32-year-old female, avid runner, 249
contraindications, 224
data from, in tabular format and representative flow-volume curves, 237
dose-response curve for FEV1, 240, 240
dosing schemes, 230–232
dosing, 230–231
starting dose, 231
use of diluent step, 232
example, 239
expressing the results, 236–240
indications for, 224
medications to withhold for at least amount of time shown prior to, 232
methacholine chloride, 225
patient preparation, 232–233
antigen and occupational exposures, 233
cola drinks, coffee, tea, chocolate, and smoking, 233
medications, 232–233
suggestion, 233
viral infections, 233
PC20FEV1 values and severity classifications, 241
plotting of percent change in FEV1 and, 238
preparing the solutions, 225–226
procedure, 234
provocative concentration calculation in, 239
pulmonary function tests, 235–236
how to calculate the percent change, 235–236
what to measure, 235
when measurements are made, 235
safety, 233–234
methacholine chloride, description of, 225
Methhemoglobin, 316
Method correlation test, for blood gas analyzers, 293
Midexpiratory time, 40–41, 42
Minute ventilation
measurement of, 160
CPET and, 173
Minute ventilation, defined, 177
MIP, See Maximal inspiratory pressure (PImax)
Mixed conditions, 311

Index

physiology, 258
reporting results, 259
testing technique, 259
Maximal forced expiratory flow (FEFmax), 41
Maximal inspiratory pressure (PImax)
indication for, 257
instrumentation, 258–259
interpretation, predicted values for, 259–260
measurement of, 257
physiology, 258
reporting results, 259
testing technique, 259
Maximal midexpiratory flow, 40
Maximal O2 consumption, 164, 165
Maximal symptom-limited incremental cycle ergometer protocol, 174
Maximal symptom-linked incremental treadmill protocol, 174
Maximum breathing capacity, 56
Maximum heart rate, formula for, 166
Maximum voluntary ventilation, 56–57
approximation of, formula for, 57
defined, 2, 56
estimation of, 162
measurement of, 160–161
reference values for test, 57
MBC. See Maximum breathing capacity
McGavin, C. R., 202
MDI. See Metered dose inhalers
Mechanical properties of lung, 3
Medical Graphics Corporation, pneumotachs manufactured by, 14
Men
MEP/MIP values in, 259, 260
pulmonary arterial hypertension and, 138
MEP. See Maximal expiratory pressure (PEmax)
MET. See Metabolic equivalent of task; Midexpiratory time
Metabolic alkalemia, in teenager with diabetic ketoacidosis, 327
Metabolic equivalent of task, 168
Metabolites, normal range and critical reporting values of, 308
Metaproterenol, withholding, prior to EIB test, 214, 214
Metered dose inhalers, using, method for, 50
Methacholine, 211, 223
Methacholine challenge test, 224–241
aerosol delivery techniques, 228–230
five-breath method, 229–230
two-minute tidal breathing method, 229
Mixed obstructive and restrictive lung disease diagnosing, 52
lung volume compartments and, 73
status for, 74r
Mixing chamber method, description of, 173
Miyamoto, S., 207
MMD. See Mass median diameter
MMEF. See Maximal midexpiratory flow
Modified Allen test, 296, 297
Modified Borg scale, quantifying symptoms during CPET with, 181
Monitoring and feedback, for spirometers, 22
Monitors, 315, 316
Monocytes, 306r
Montelukast, 51r
withholding, for amount of time shown prior to mannitol challenge test, 244r
withholding, for amount of time shown prior to methacholine challenge test, 232r
Morgan, M. D. L., 182
Morris, A. H., 130, 338
Morris, J. F., 106
Mouthpiece
DL,CO testing techniques and use of, 120
FRC testing in children and use of, 270–271
MIP/MEP tests and use of, 259
pediatric pulmonary function testing and use of, 266, 267
Mouth pressure
closed-shutter maneuver, slope of body box volume and, 79, 85
closed-shutter panting and body box pressure relative to, 149, 150
Mouth pressure calibration pressure, 80
Multigas analyzer, 119
Multiple-breath closed-circuit He dilution
FRC measurement by, 69, 88–93
complete system for, 89
instrumentation, 88–89
methodology, 88
physiology and calculations, 90–92
quality control, 93
testing technique, 92–93
FRC testing in children and, 270–271
Multiple-breath open-circuit N2 washout
FRC measurement by, 69, 77, 94–99
physiology and instrumentation, 94, 96–97
quality control, 99
testing technique, 97–99
FRC testing in children and, 270–271
Mungall, I. P., 202
MVV. See Maximum voluntary ventilation
Myasthenia gravis, MIP/MEP measurements in patients with, 257
Mycobacterium tuberculosis, infection control and, 102

N
Nasr, S. Z., 340
National Health and Nutrition Examination Survey, reference equations, 337
National Health and Nutrition Examination Survey (NHANES) III, reference values from, for children older than 8 years of age, 269
National Institute of Standards and Technology, 304
Naughton protocol, 174
Nebulizer, transferring methacholine solution from, to airway, 227–228
Nebulizer output at different flow rates, 228
methacholine challenge test and measurement of, 227
variance in, among different nebulizer brands, 228
Nedocromil withholding, for amount of time shown prior to mannitol challenge test, 244
withholding, for amount of time shown prior to methacholine challenge test, 232
NIST. See National Institute of Standards and Technology
Noncontinuous technique, arterial catheter insertion and, 176
Nonvolatile acids, 288
Normal range test, for blood gas analyzers, 293
Nose clips, 26
closed-shutter maneuver and use of, 85
dl,co testing techniques and use of, 120
exercise-induced bronchoconstriction test and use of, 216
FRC testing in children and use of, 270–271
loose, equilibration and, 93
MIP/MEP tests and use of, 259
open-circuit method and use of, 95
patient in flow box with, 82
patient in pressure box with, 81
patient in volume box with, 83
Oxygen cascade, 284
Oxygen consumption
e exercise, anaerobic metabolism and, 161
heart rate relative to, 167
Oxygen content
defined, 318
hemoximeters and, 317
hypoxia monitoring and, 287
Oxygen delivery, hypoxia monitoring and, 287
Oxygen extraction ratio, hypoxia monitoring and, 287
Oxygen index, hypoxia monitoring and, 287
Oxygen saturation
assessing, cardiopulmonary exercise test and, 159
in patients with exercise-induced bronchoconstriction, 213–214
Oxygen uptake, hypoxia monitoring and, 287
Oxygen use, spirometry testing and, 27
Oxyhemoglobin, 316
absorption spectra of, 320
Oxyhemoglobin dissociation curve, 283, 284, 285, 320
Oxyhemoglobin saturation, measuring, 316
PaCO₂, defined, 291
PAH. See Pulmonary arterial hypertension
Panting maneuvers
closed-shutter, 147–148, 148, 149, 150
distortion observed with, 152
open-shutter, 147, 147, 148, 149, 150, 152, 153
PaO₂
classification of, 309
measurement of, 283
PaO₂/FIO₂ ratio, hypoxia monitoring and, 287
Paoletti, P., 130, 338
Operator training and competency certification, for
blood gas laboratory, 315
OSA. See Obstructive sleep apnea
OSHA. See Occupational Safety and Health Administration
O₂ pulse, 166
calculation of, 178
Oxidative phosphorylation, 283
Oxygen, transport of, 283–284

N₂ analyzers
measurement of N₂ with, 96
N₂ washout test and use of, 98
Nugent, K. M., 53
Nystad, W., 269

Obstruction, defined, 52
Obstructive airway disease, 52
Obstructive lung disease
lung volume compartments and their status for, 74
tMIP/MEP measurements in patients with, 257
Obstructive sleep apnea, pulse CO-oximetry and, 321
Occupational Safety and Health Administration, 102, 296
Ogilvie, C. M., 116
Ogilvie technique, 130
breath-hold time and, 124, 125
Older patients, spirometry and, 56. See also Age/aging
Open-circuit method
early modern technique for, 94, 95
pediatric pulmonary function testing and, 266
spirometry testing and, 27
Open-shutter panting maneuver
acceptable, obtaining several sets of, 148
children and measurement of, 271, 272
hypothetical numbers for, example, 150–151
pattern during Raw maneuver in body box in patient with airflow obstruction, 152, 153
pattern during Raw maneuver in body box when panting is too fast, 152, 153
for Raw, relationship between flow and body box pressure, 147, 147
during Raw maneuver in body box, when panting is too slow, 152, 152
S-shaped curve during, showing relationship between flow and body box pressure, 149
Open-shutter S-shaped V/Pₑₑₑ relationship
biological factors related to, 152
instrumental factors related to, 151–152
Operator training and competency certification, for
blood gas laboratory, 315
OSA. See Obstructive sleep apnea
OSHA. See Occupational Safety and Health Administration
O₂ pulse, 166
calculation of, 178
Oxidative phosphorylation, 283
Oxygen, transport of, 283–284

P

Paco₂, defined, 291
PAH. See Pulmonary arterial hypertension

Partially compensated conditions, 311
Partial pressure
Dalton’s law of, 282, 304, 309
of inspired oxygen, 283
Passive expiration, 3
Patient attached blood gas monitoring, 323
Patient mouth port, closed-circuit bag-in-box system and, 118
Patient preparation
for exercise-induced bronchoconstriction test, 214–215
for mannitol challenge test, 243–244
for six-minute walk test, 204
for spirometry testing, 24–26
age, height, and weight, 25
Percent change calculating bronchodilator response, 53
mannitol challenge test, 246, 246
methacholine challenge test, 235–236
in FEV₁, plotted against noncumulative log dose in mg/mL and against dose in mg/mL, 238
Percent fall index, for quantifying EIB, 217–218
PFT. See Pulmonary function test
pH hydrogen ions and, 286–287
meaning of, 287
relationship between H⁺ and, 287, 288
pH homeostasis, 288
Phosphodiesterase 5 (PDE5) inhibitor, pulmonary hypertension and, 137
pH (Sanz) electrode, 305
pH severity, classification of, 310
Physiologic dead space, 163–164
calculation of, 179
Pitot-type sensors, 173
Planimeter, defined, 99
Planimetry technique, TLC measurement from chest roentgenograms and, 100
Plasma, 287
Plasma electrolytes, Gamble diagram of, 289, 290
Plasma transport of carbon dioxide, 291
Plastic syringes, 295
Platelets, 306
Pleura, 3
Pleural pressure, 7
Pneumonecctomy, 144
Pneumotachograph (or pneumotach), 13–14, 14, 173
for flow box, 80, 81
PO₂ (Clark) electrode, 305–306
POC testing, primary goal of, 296
Polycythemia, high DL,CO values with, 136
Positive end-expiratory pressure, misinterpretation of ABG values and, 304
Potential for hydrogen (H⁺), relationship between pH and, 287, 288
Power, work, force and, 168
Preanalytical errors avoiding, 301
sources of, 301, 302r–303r, 304
Precision test, for blood gas analyzers, 293
Predicted values, race-specific, 105–107. See also Reference (predicted) values
Pelzer, A. M., 154, 340
Pelzer, A. M., 154, 340
Percent change calculating bronchodilator response, 53
mannitol challenge test, 246, 246
methacholine challenge test, 235–236
in FEV₁, plotted against noncumulative log dose in mg/mL and against dose in mg/mL, 238
Percent fall index, for quantifying EIB, 217–218
PFT. See Pulmonary function test
pH hydrogen ions and, 286–287
meaning of, 287
relationship between H⁺ and, 287, 288
pH homeostasis, 288
Phosphodiesterase 5 (PDE5) inhibitor, pulmonary hypertension and, 137
pH (Sanz) electrode, 305
pH severity, classification of, 310
Physiologic dead space, 163–164
calculation of, 179
Pitot-type sensors, 173
Planimeter, defined, 99
Planimetry technique, TLC measurement from chest roentgenograms and, 100
Plasma, 287
Plasma electrolytes, Gamble diagram of, 289, 290
Plasma transport of carbon dioxide, 291
Plastic syringes, 295
Platelets, 306
Pleura, 3
Pleural pressure, 7
Pneumonecctomy, 144
Pneumotachograph (or pneumotach), 13–14, 14, 173
for flow box, 80, 81
PO₂ (Clark) electrode, 305–306
POC testing, primary goal of, 296
Polycythemia, high DL,CO values with, 136
Positive end-expiratory pressure, misinterpretation of ABG values and, 304
Potential for hydrogen (H⁺), relationship between pH and, 287, 288
Power, work, force and, 168
Preanalytical errors avoiding, 301
sources of, 301, 302r–303r, 304
Precision test, for blood gas analyzers, 293
Predicted values, race-specific, 105–107. See also Reference (predicted) values
Pulmonary function testing, 159. See also Pediatric pulmonary function testing
ATS/ERS 2005 guidelines on, 337
exercise-induced bronchoconstriction test and, 215,
216–217
interpretation of, 52–55
airflow limitation vs. restriction, 52–53
bronchodilator response, 53–54
mannitol challenge test, 245–246
calculating percent change, 246, 246r
methacholine challenge test and, 235–236
how to calculate the percent change, 235–236
what to measure, 235
when measurements are made, 235
reporting bronchodilator therapy and, 51
results and reference regression line with 95% confidence intervals on two patients, 49
“Pulmonary Function Testing in Preschool Children” (ATS/ERS), 265
Pulmonary function testing reference values, 333–340
age, height, weight, and race/ethnicity, 334–335
determining what is normal and abnormal, 335–336
for airway resistance and specific conductance, 340
for DL,CO, 338, 340
for lung volumes, 337–338
for other tests, 340
overview, 333–334
selecting, for laboratory, 336–337
race or ethnic considerations, 336–337
for spirometry, 337
Pulmonary function testing systems, computerized, 74
Pulmonary function test reports, comments on, 45–47
Pulmonary response, to exercise, 160
Pulmonary vascular diseases, low DL,CO values with, 132
Pulse CO-oximetry, 321–322
Pulse oximeters
CPET and, 171
defined, 319
LED wavelengths for, 320
Pulse oximetry, 319–321
assessing, cardiopulmonary exercise test and, 159
benefits and clinical applications of, 319
functional oxygen saturation calculation with, 317
proper interpretation of, 321
sensor components for, 319–320
Pure conditions, 311
Pusher plate, diaphragm-type spirometer, 12

21-year-old nonsmoking man
discussion, 135–136
pulmonary function data before/after bronchodilator, 135r
Pulmonary function test cases
56-year-old woman
discussion, 133–134
flow-volume curves before/after administration of bronchodilator, 133
pulmonary function data before/after bronchodilator, 134r
single-breath CO diffusing capacity and DL,CO corrected for VA, 134r
Preheparinized syringes, 295
Preschool children
acceptability criteria for, 267
repeatability criteria for, 268–269
spirometry and, 265–266
Pressure box, flow box converted into, 81
Pressure change, equal pressure point and, 7
Pressure differences (or gradients); spontaneous breathing and, 144
Pressure transducer
eartreial blood pressure measurement with, 176
for variable-pressure box, 80
Pressure volume curves, three, 4, 5
preVent Pneumotach, 15
Prieto, L., 229
Proficiency testing, for blood gas laboratory, 313–314
Provocoholine
methacholine sold as, 224
package insert
ATS recommended dosing schemes and, 231r
dilution scheme recommended in, 230–231
preparing dilutions based on fourfold ATS guideline scheme, 228r
preparing dilutions based on twofold ATS guideline scheme, 228r
preparing solutions, 225–226
method for preparing package-insert dilutions, 225r
stability and storage of, 225
PT. See Proficiency testing
Pulmonary arterial hypertension, description of, 138
Pulmonary arterial hypertension case presentation
discussion, 136–138
flow-volume curves before/after administration of bronchodilator, 138
patient presentation, 136
pulmonary function data before/after bronchodilator, 138r
Pulmonary artery catheters, sampling through, 299
Pulmonary fibrosis, 4
pressure volume curve for, 4, 5
Pulmonary function laboratory
infection control in, 58–59, 101–102
medications taken by patients tested in, 51r
Pulmonary function test cases
56-year-old woman
discussion, 133–134
flow-volume curves before/after administration of bronchodilator, 133
pulmonary function data before/after bronchodilator, 134r
for lung volumes and 95% confidence interval, 338
NHANES III, 337
for single-breath DL,CO, 339
Reference (predicted) values
for airway resistance, 340
specific conductance and, 340
in children aged 3 to 6, 269
for CPET system, 182
for DL,CO, 338, 340
for lung volumes, 337–338
for other tests, 340
for pulmonary function testing
general considerations, 334–336
selecting for laboratory, 336–337
variance in, 334
for Raw measurements in body box, 154
selecting, criteria values for, 101
for specific conductance, 340
for spirometry, 337
Refl ectance sensor, 320
Refractory period, exercise-induced
bronchoconstriction and, 213
Repeatability between maneuvers, evaluating, 33
Repeatability criteria, for preschool children, 268–269
Residual volume, 69, 70, 71
calculating, 72
determination of, 76
estimating, single-breath N₂ method for, 99
for obstructive, restrictive, and mixed obstructive
and restrictive lung diseases, 74
Resistance to airfl ow, 4, 7
Resistors, making, quality control and, 155, 155
Respiratory exchange ratio
calculation of, 178
defined, 168
Respiratory frequency, ventilatory response to exercise
and, 162, 162
Respiratory muscles, 2
composition of, 258
Respiratory rate, assessing, cardiopulmonary exercise
test and, 159
Rest measurements, CPET and, 176
Restrictive lung disease, lung volume compartments
and their status for, 74
Restrictive process in 64-year-old man
CPET case, 191–196
background, 191–193
cardiovascular and gas exchange responses, 196
interpretation, 194–196
ventilatory, cardiovascular, and gas exchange
measurements from final minute of rest
and maximal exercise, 194
ventilatory responses, 195

QMS. See Quality management system
Quality control
for blood gas analysis, 292–293
for body box system, 155–156
for CPET system, 181–182
for FRC₈₁ measurement, 93
for FRC measurement, 88
for FRC₈₅ measurement, 99
for six-minute walk test, 206–207
for spirometers, 22
Quality control, DL,CO system
collective components, 128–129
biological controls, 129
DL,CO simulator, 129
DL,CO with 3-liter syringe, 128–129
individual components, 127–128
gas analyzers, 127
other considerations, 128
timing device, 127
volume-measuring device, 127
Quality management blood gas laboratory, 312–315
inventory management, 315
operator training and competency certification, 315
policy and procedure manual, 312
proficiency testing, 313–314
quality control, 312–313
external or liquid, 313
internal or electronic, 312
system audits, 314
Quality management system, for laboratory, 312
Quanjer, P. H., 338
Race
lung volumes and, 334
pulmonary function values and, 105–107
reference values and, 334–335
selected for laboratory, 336–337
Racial adjustment factors, 336, 337
Radial artery
as puncture site, 296
puncture technique, description of, 297–298
Raw. See Airway resistance
Rebreathing technique, 113, 116
Recorder time sweep, for spirometers, 22
Red blood cells, 306
diffusion of gases and transfer of, 115
transport of carbon dioxide and, 291
Redelmeier, D. A., 207
Reference chamber, 118
Reference equations
choosing, DL,CO measurement and, 131
Index

Reversibility testing, 50–51. See also Spirometry

Revill, S. M., 182
RL. See Lung resistance
Roberts, C. M., 338
Roca, J., 338
Rosenthal dosimeter, newer model of, 220
Rossiter, C. E., 107
RTOT. See Total respiratory resistance
Running, as most asthmogenic form of exercise, 213, 213

RV. See Residual volume

S
Salmeterol, 51
withholding, for amount of time shown prior to
  mannitol challenge test, 244r
withholding, for amount of time shown prior to
  methacholine challenge test, 232r
withholding, prior to EIB test, 214, 214r
Saturation step-up procedure, 319
Scalene muscles, 2, 258
Sciurba, F., 203, 206
SEE. See Standard error of the estimate
SEM. See Standard of the mean
Sensors, transcutaneous monitoring and placement of, 322
Sensor technology, various configurations of, 323
sGaw. See Specific conductance of the airway
Sherrill, D. L., 207
Short-acting bronchodilators, 62
Shortness of breath in 62-year-old male case
  presentation, 324–325
  discussion, 325
Shuttle-walk test, six-minute walk test vs., 201–202
Single-breath carbon monoxide diffusing capacity,
  113–138
calculations, 123–127
  altitude and PAO2, 127
  alveolar volume, 126
  breath-hold time, 124–125
  carboxyhemoglobin, 126–127
  example, DL,CO, 123–124
  Hb concentration, 126
  inspired volume, 126
  single-breath DL,CO, 123
case presentations, 133–138
DL,CO instrumentation, 116, 118–119
  analyzers, 118, 119
  calibration, 119
  inspired gas composition, 119
  DL,CO testing techniques, 120–123
  basic maneuver, 120
  patient preparation, 120
  practical hints, 122–123
  recommendations for, 120–122
  first measurement of, 114
  interpretation, 130–132
  choosing reference equation, 131
  clinical applications and, 132
  examination of reference studies, 130–131, 131r
  physiology, 114–116
  diffusion of gases, 114–116
  measuring diffusing capacity, 116
  quality control, 127–129
  collective components, 128–129
  individual components, 127–128
  Single-breath carbon monoxide diffusing capacity test,
    70
  Single-breath DL,CO
    calculating, basic formula for, 123
    reference equations for, 339r
  Single-breath He (or other inert gas) test, static lung
    volume measurement with, 69
  Single-breath method, 113
    diffusing capacity measured with, 116
  Single-breath N2 method, uses for, 99
  Single breath N2 test, static lung volume measurement
    with, 69
  Singulair, 51
  withholding, for amount of time shown prior to
    mannitol challenge test, 244r
    methacholine challenge test, 232r
  witholding, prior to EIB test, 214, 214r
  witholding, for amount of time shown prior to
    SIRS. See Systemic inflammatory response syndrome
  Sitting height
  for pediatric pulmonary function testing, 264
  reference values and, 334–335
  SI units, Raw and sGaw expressed in, 151
  Shuttle-walk test, six-minute walk test vs., 201–202
  contraindications, 202
    absolute and relative, 203r
    indications, 202
  interpretation of, 207
  overview of, 201–202
  patient safety and, 202–203
  quality assurance and other issues, 206
    reporting results, 206–207
  testing technique, 203–206
    equipment/materials, 204
    patient preparation, 204
    procedure, 204–206
    walking course, 203
  62-year-old woman, 90-pack-year smoker
  CPET case, 190–191
  background, 190
cardiovascular and gas exchange responses, 193
interpretation, 190
ventilatory, cardiovascular, and gas exchange
measurements from final minutes of rest
and maximal exercise, 191
Slope of phase III, single-breath N\textsubscript{2} method and, 99
Slow, vital capacity
defined, 72, 73
expiratory, as expressed on volume-time spirogram, 75
FRC testing in children and use of, 271
in healthy and diseased patterns plotted as
percentage of total lung volume, 73
inspiratory, as expressed on volume-time spirogram, 75
measurement of, 74
obtaining, 72
Small airway disease, 52
Smith, D., 53
Smoke inhalation in house fire case presentation,
327–328
acid-base balance/oxygenation status, 327
background, 327
hemoximetry panel, 328
Soderholm, B., 338
Sodium cromoglycate, withholding, for amount of time
shown prior to mannitol challenge test, 244
Software errors, spirometers and, 23
Solubility coefficient, 282
Solway, S., 202
Sorensen, Soren, 287
Sourk, R. L., 53
Specific conductance
of the airway, 145, 151
determining, for each open- and closed-shutter
set, 148–149
methacholine challenge test taken by 32-year-old
female runner and, 249, 250, 251
reference values for, in body box, 154
airway resistance measurement in children and, 271
reference values for, 340
Specific resistance
of the airway, calculating, 145
airway resistance measurement in children and, 271
Specimen collection
indwelling vascular catheter and, 299
patient identification and, 295
Specimen handling, proper, 296
Sphygmomanometer, CPET and use of, 171
Spirette, ultrasonic flow measurement device, 17, 18
Spirometer circuit, with closed-circuit He dilution
technique, 90
Spirometers
closed-circuit bag-in-box system and, 117
evaluating, 24
infection control for, 58
with kymographs, FVC/FEV\textsubscript{1} calculations from, 39
for preschool children, 266
Spirometric results, examining, over time, 47–48
Spirometry. See also Forced spirometry
in children, age considerations, 265–266
forced expiratory maneuver during, 3
growth in, reasons for, 1–2
hyperresponsiveness and, 224
methacholine challenge test and, 235
reference values for, 337
scoring system for objective evaluation of
technologists performing, 23
special considerations, 55–56
patients who can’t, 56
patients who have difficulty following directions,
55–56
patients who won’t, 55
Spirometry instrumentation, 7–24
choosing, 22–24
quality control, 21
spirometer display, 18–21
volume-displacing spirometers, 7–13
Spirometry reference (predicted) values, 47
Spirometry reversibility testing
reporting bronchodilator therapy, 51
summary of key points for
Spirometry testing techniques, 24–35
acceptability criteria
summary of, 32
unacceptable spirometry because of early
termination of exhalation, 33
acceptable flow-volume loop, 36
acceptable spirometry, illustrated with volume-time
and flow-volume graphs, 34
coughing, 30–31
early termination, 31–32
explaining and demonstrating the maneuver, 26–29
coaching and encouragement during testing, 28
correct chin and neck positions for forced
spirometry, 26
good coaching during forced spirometry, 28
instructions, 27
oxygen use, 27
patient observation and feedback, 28–29
placing the mouthpiece, 27
summary of important points for procedure
explanation, 27
flow-volume loops, 34–35
T

Target heart rate, exercise-induced bronchoconstriction test and, 216

TAT. See Turnaround time

Temperature-corrected blood gases, 307

Temperature correction

ATPS to BTPS, 38r

forced spirometry and, 36–37

Terbutaline, 51r

withholding, for amount of time shown prior to methacholine challenge test, 232r

withholding, prior to EIB test, 214r

Terminal bronchioles, 2

Testing technique

for FRCm measurement, 92–93

equipment preparation and calibration, 92

patient preparation and instruction, 92

testing methodology, 92–93

for FRC measurement

equipment preparation and calibration, 84

patient preparation and instructions, 84

testing, 84–85

for FRCm measurement, 97–99

equipment preparation and calibration, 97

patient preparation and instruction, 97

testing, methodology, 97–99

TGV. See Thoracic gas volume

TGV during Raw maneuvers, calculating, 151
Transducers, ultrasonic flow measurement device, 17, 18
Transfer factor, 113
Transmittance sensor, 320
Transport, of blood gas analysis specimens, 295
Treadmill
  exercise-induced bronchoconstriction test and use of, 216
  motor-driven, CPET and, 170–171
  symptom-limited incremental exercise protocol and, 177
Treadmill running, as asthmogenic form of exercise, 213, 213
Troosters, T., 207
Trueness test, for blood gas analyzers, 293
Turbine or rotating flow-sensing device, 13, 17, 17
Turbines, CPET systems and, 173
TurboAire Challenger, 216
Turnaround time, laboratory, 296
TV. See Tidal volume
Twitchy airways, evaluation of, 223
Two-minute tidal breathing method, 228, 229
Two-way breathing valves, CPET and, 172, 172
U
Ultrasonic flow measurement device, 13, 17–18, 18
Umbilical artery catheters, sampling through, 299
Unacceptable spirometry
due to early termination of exhalation, 33
due to poor repeatability, 34
due to variable flow rates, 31, 31
Unconscious college freshman: case presentation and discussion, 324
Universal Precautions, 296
Upstream airways, 6, 6, 7
VA. See Alveolar volume
Valsalva maneuver, MEP test and, 258
Variable extrathoracic obstruction, flow-volume loop showing, 43, 46
Variable flow, spirometry testing and, 31, 32
Variable intrathoracic obstruction, flow-volume loop showing, 43, 46, 48
Variable-pressure body plethysmograph, 81
Variable-pressure box, 80, 81, 146
VAS. See Visual Analog Scale
Vascular catheter, indwelling, sampling through, 299–300
Vasopressors, transcutaneous monitoring and, 322
VC. See Vital capacity
VCO2, calculation of, 178
Index

VD/VT ratio, 164, 164
calculation of, 179
VE. See Minute ventilation
Ventilatory ceiling, 160, 162
Ventilatory equivalent for CO2, 164, 165
calculating, 178–179
Ventilatory equivalent for oxygen, calculating, 178
Ventilatory measurements, restrictive process in
64-year-old man, CPET case, 194
Ventilatory response
of asthmatic child, after 6 minutes of running, 212
for college student/cross-country runner, CPET case,
183, 185
to different types of exercise in groups of asthmatic
and normal subjects, 213
for dyspnea in 50-year-old man, CPET case, 187,
188
to exercise, 160–163
maximal respiratory flow-volume curve and
exercise tidal flow-volume curve within
maximal flow-volume curve, 163, 163
oxygen consumption, anaerobic metabolism and,
161
ventilatory ceiling, anaerobic metabolism and,
161
for restrictive process in 64-year-old man, CPET
case, 195
for 62-year-old woman, 90-pack-year smoker, CPET
case, 190, 191, 192
Ventilatory threshold, 16
Viljanen, A. A., 340
Vilzoni, D., 269
Viral infections, airway hyperresponsiveness and, 233
Visual Analog Scale, quantifying symptoms during
CPET with, 181
Vital capacity, 69, 70, 70
defined, 2
measurement of, 73–76
determining lung subdivisions, 76
repeatability and reporting, 74
for obstructive, restrictive, and mixed obstructive
and restrictive lung diseases, 74
performing, 72
testing children and measurement of, 271
two-step, on volume-time spirogram, 75
VO2 calculating, 177
Volatiles acids, 288
Volume adjustment technique, for isovolume FEF25%-75%
calculation, 42
Volume-displacing body plethysmograph (variable
volume), 83
Volume-displacement box, 82–83, 83, 146
Volume-displacing spirometers, 7–13
advantages/disadvantages with, 12
bellows, 7, 10, 10
characteristics of, summary, 13
diaphragm, 7, 10, 12
history behind, 7
manual, 36
manual calculation of FVC and FEV1 for, 37–38
rolling seal, 7, 8, 10
temperature correction and, 37
volume-time trace for proper calibration and leak
test of, 21
water seal, 7, 8, 8
Volume measuring devices
DLCO, quality control for, 127
DLCO, with 3-liter syringe, quality control for, 128
Volume-time curve display, 19
Volume-time display, for spirometers, 18, 19
Volume-time graphs
acceptable spirometry shown on, 34
of three acceptable forced spirometry efforts, 49
unacceptable spirometry due to early termination of
exhalation and, 33
Volume-time spirometry, examples of, in children, 268
Volume-time trace, proper and unacceptable calibration
and leak tests for volume-displacement spirometer with 3-liter calibration
syringe, 21
v-slope method, 168
VT, reported in BTPS, calculation for, 177
W
Walking, as asthmogenic form of exercise,
213, 213
Walking course, for six-minute walk test, 203
Wang, X., 269, 337
Washout volume, DLCO technique and, 122
Waste sample removal, indwelling vascular catheter
and, 299
Water-seal spirometers, 8, 8
Steal-Well's type, air moving in/out spirometer
bell, 9
Water-vapor pressure (PH2O), at different temperatures,
38f
Watt, 168
Index

Wedge spirometers, 10, 10
Weight, reference values and, 334–335
Weil, H., 107
Weisman, I. M., 162, 182
Weng, T. R., 338
White blood cells, 306
Whole blood components, cellular mass of, 306
Whole blood CO-oximetry, 316
Whole blood multiwavelength spectrophotometry, 316
Wise, R. A., 207
Women
MIP/MIP values in, 259, 260
pulmonary arterial hypertension and, 138
Work
alveolar-arterial oxygen gradient and, 164, 166
force, power and, 168
maximal O$_2$ consumption and, 164, 165
VCO$_2$ and, 164, 165
Wright nebulizers, output for, 229
Wright Respirometer, 17
Wubbel, C., 229
Z
Zafirlukast, 51
withholding, for amount of time shown prior to
mannitol challenge test, 244
withholding, for amount of time shown prior to
methacholine challenge test, 232
Zapletal, A., 269, 338
Zeballos, R. J., 162, 182

Z
Whole blood CO-oximetry, 316
Whole blood multiwavelength spectrophotometry, 316
Wise, R. A., 207
Women
MIP/MIP values in, 259, 260
pulmonary arterial hypertension and, 138
Work
alveolar-arterial oxygen gradient and, 164, 166
force, power and, 168
maximal O$_2$ consumption and, 164, 165
VCO$_2$ and, 164, 165
Wright nebulizers, output for, 229
Wright Respirometer, 17
Wubbel, C., 229

Z
Zafirlukast, 51
withholding, for amount of time shown prior to
mannitol challenge test, 244
withholding, for amount of time shown prior to
methacholine challenge test, 232
Zapletal, A., 269, 338
Zeballos, R. J., 162, 182