I LUNG FUNCTION ASSESSMENT AND THORACIC DIAGNOSTIC TECHNIQUES

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Although the history and physical examination are essential to the diagnostic process, pulmonary signs and symptoms often lack sufficient specificity to allow a definitive conclusion. Further information is often required, such as that acquired from assessments of physiologic function, imaging studies, and sampling procedures. Singly and in combination, these studies are important components of the clinical approach to respiratory disorders.

Assessment of Gas Exchange

The ultimate function of the lungs is to replenish the supply of oxygen in the blood and to eliminate the carbon dioxide produced by metabolic activity. Measurement of the partial pressure of oxygen and of carbon dioxide in arterial blood is central to the assessment of respiratory function. Arterial blood gases are obtained from a peripheral artery in a heparinized syringe. Care should be taken to avoid or expel air bubbles, and samples should be delivered to the laboratory on ice and should be processed promptly before cellular metabolism leads to an artifactual decrease in arterial oxygen tension (PaO2) and pH and an increase in arterial carbon dioxide tension (Paco2).

OXYGEN

Abnormalities in oxygen exchange are commonly described in relation to the alveolar Po2 (P(A)O2) or inspired oxygen concentration. Using the alveolar gas equation and assuming a normal resting respiratory exchange ratio (R) of 0.8 and that PaCO2 equals PacO2, PaO2 can be estimated as follows:

\[ P_{A}O_2 = P_{O_2} - (P_{A}CO_2 \times 1.2) \]

where PaO2 represents the inspired oxygen tension at body temperature, saturated with water.

The measured value of PacO2 is subtracted from the calculated value of PaO2 to give the alveolar-arterial difference in oxygen (A-aDo2). Normal values for A-aDo2 increase linearly with age because of a fall in PaO2 with essentially unchanged PacO2. Average values for A-aDo2 range from approximately 9 mm Hg at 20 years of age to 15 mm Hg at 70 years of age. The A-aDo2 is a commonly employed measure of the efficiency of oxygen exchange. However, even in the absence of changes in pulmonary gas exchanging function, it will change as a function of inspired oxygen fraction (FIO2), and it varies directly with cardiac output. The arterial-alveolar oxygen ratio, P(A)O2/PacO2, is somewhat more stable over varying inspired oxygen concentrations. The arterial-inspired oxygen ratio, P(A)O2/FIO2, is now widely used to quantitate abnormalities of oxygenation in critical care unit patients. A P(A)O2/FIO2 ratio of less than 250 indicates the presence of mild acute lung injury, and a P(A)O2/FIO2 ratio of less than 100 indicates a severe disorder.

Abnormalities of oxygen exchange [see Table 1] are most commonly caused by mismatching of pulmonary ventilation (V) and perfusion (Q) or by shunting. Impaired diffusion across the alveolar-capillary membrane generally does not cause abnormalities in oxygenation at rest but can cause abnormalities during exercise and at high altitudes. Abnormalities caused by diffusion impairment and V/Q mismatching can be corrected by increasing the FIO2 and can be completely abolished by 100% inspired oxygen. Hypoxemia caused by shunts, which may be pulmonary or intracardiac, is not corrected by the administration of 100% inspired oxygen. By contrast, other causes of hypoxemia, such as hypoventilation and low inspired O2 concentration, do not cause an increase in A-aDo2.

**Systemic Oxygen Transport**

The total amount of O2 delivered to the systemic circulation is the product of the cardiac output and the O2 content per unit of arterial blood (C(a)O2). The C(a)O2 is determined by the concentration and characteristics of hemoglobin and the arterial oxygen saturation (S(a)O2), as indicated by the following equation:

\[ C_{a}O_2 = Hgb \times S_{a}O_2 \times 1.39 \text{ ml O}_2/\text{g Hgb} \]

The last term in the equation reflects the amount of oxygen that is normally bound to fully saturated hemoglobin, the so-called carrying capacity of normal hemoglobin. The arterial O2 saturation refers to the percentage of the total O2 binding sites on hemoglobin that is actually occupied by O2. The S(a)O2 is in turn determined by the P(a)O2 and the physicochemical properties of hemoglobin, as reflected by the oxygen-hemoglobin dissociation curve [see Figure 1]. In the presence of acidaemia, fever, elevated concentrations of 2,3-diphosphoglycerate, and certain abnormal hemoglobin types (e.g., hemoglobin Kansas), the oxy-
right, so that at any given PaO₂, the hemoglobin saturation will be of certain abnormal hemoglobin types shifts the curve to the left or oxygen by hemoglobin. An alteration in pH or body temperature, a oxygen is shown by the oxygen-hemoglobin dissociation curve. The percentage of oxygen binding sites on hemoglobin that are saturated by monoxide, results in both a deformation of the shape of the dissoc-

Figure 1  The relation between arterial oxygen tension (P_{\text{a}}O₂) and the percentage of oxygen binding sites on hemoglobin that are saturated by oxygen is shown by the oxygen-hemoglobin dissociation curve. The sigmoidal shape of the normal curve reflects the cooperative binding of oxygen by hemoglobin. An alteration in pH or body temperature, a change in the concentration of 2,3-diphosphoglycerate, or the presence of certain abnormal hemoglobin types shifts the curve to the left or right, so that at any given P_{\text{a}}O₂, the hemoglobin saturation will be correspondingly increased or decreased. Carboxyhemoglobinemia, in which the oxygen binding sites of hemoglobin are occupied by carbon monoxide, results in both a deformation of the shape of the dissociation curve and a reduction in the maximum number of binding sites that are available to oxygen.

gen-hemoglobin dissociation curve shifts to the right, which gives a decreased affinity of hemoglobin for oxygen and increased availability of oxygen to tissues. Alkalemia, hypothermia, and other abnormal hemoglobin types (e.g., hemoglobin Chesapeake) have the opposite effect and shift the position of the curve to the left, reflecting an increased affinity of hemoglobin for oxygen and reduced availability of oxygen to tissues.

Anemia does not alter P_{\text{a}}O₂ or S_{\text{a}}O₂. Anemia does, however, reduce the value for C_{\text{a}}O₂ and will decrease \( \text{O}_2 \) delivery to the tissues if there is not a commensurate increase in cardiac output. A fixed change in P_{\text{a}}O₂ causes a considerably larger change in S_{\text{a}}O₂ over the steep portion of the oxygen-hemoglobin dissociation curve than it does over flatter portions of the curve. For instance, with a fall in P_{\text{a}}O₂ from 100 mm Hg to 90 mm Hg, S_{\text{a}}O₂ decreases from 97.4% to 96.8%, assuming that hemoglobin type is normal and physiologic conditions are standard—pH of 7.40 and body temperature of 37°C (98.6°F). In contrast, a 10 mm Hg decrement in P_{\text{a}}O₂ from 55 mm Hg to 45 mm Hg causes the S_{\text{a}}O₂ to decrease from 88.2% to 80.5%.

A profound reduction in arterial \( \text{O}_2 \) content may be observed without a significant change in P_{\text{a}}O₂ if \( \text{O}_2 \) binding to hemoglobin is acutely altered, as occurs in carbon monoxide intoxication. Because of the strong affinity of carbon monoxide for hemoglobin, an arterial carbon monoxide tension (P_{\text{a}}CO) of less than 1 mm Hg is sufficient to cause a 50% saturation of hemoglobin with CO. Under these conditions, P_{\text{a}}O₂ may be 100 mm Hg, but severe tissue hypoxia may be present because S_{\text{a}}O₂ and C_{\text{a}}O₂ values have been reduced by half.

**Oximetry**

Oxygenation can be monitored noninvasively by pulse oximetry. A pulse oximeter, placed on either a finger or an ear-lobe, measures the absorption of red (660 nM) and near infrared (940 nM) light through these tissue beds to estimate the ratio:

\[
\frac{\text{O}_2 \text{ Hb}}{\text{O}_2 \text{ Hb + reduced Hb}}
\]

By assuming the pulsatile portion of the signal represents arterial blood and by comparing the ratio of the pulsatile portion to the nonpulsatile component to a calibration curve of known mixtures of oxyhemoglobin and reduced hemoglobin, the pulse oximeter is capable of estimating S_{\text{a}}O₂. Oximetric estimates are accurate to within ±1% to 2% for true saturations above 90%. Accuracy deteriorates at saturations below 80%, with errors of ±5% to 8%. Pulse oximetry is commonly used in emergency and critical care settings, for in-hospital patient transportation, and for assessing oxygenation during sleep. Medicare guidelines allow the use of resting pulse oximetry for determination of qualification for long-term oxygen therapy, but arterial blood gas measurements are still necessary for exercise evaluations for adjudication of disability under Social Security Administration regulations. Accuracy of pulse oximetry is reduced by carboxyhemoglobin, methemoglobin, anemia, motion, bright ambient light, poor perfusion, nail polish, and darkly pigmented skin.

**Carbon Dioxide**

Physiologic mechanisms normally act to maintain the P_{\text{a}}CO₂ level within a narrow range (35 to 45 mm Hg) despite large changes in metabolic CO₂ production. Elevated P_{\text{a}}CO₂ levels (>45 mm Hg) are termed hypoventilation, and low P_{\text{a}}CO₂ values (<35 mm Hg) are termed hyperventilation. Corresponding alterations in P_{\text{a}}CO₂ are termed hypercapnia and hypocapnia, respectively. The P_{\text{a}}CO₂ level is directly proportional to the ratio of carbon dioxide production to alveolar ventilation:

\[
P_{\text{a}}\text{CO}_2 = K(V\text{CO}_2/V_A)
\]

where \( V\text{CO}_2 \) equals \( \frac{\dot{V}_E \times F\text{CO}_2}{\\text{B}} \) and represents the amount of CO₂ (in ml/min) produced by the body’s metabolism; and K is a constant (equal to 0.863) that reflects the fact that gas exchange occurs at normal body temperature under conditions of full saturation with water, assuming P_{\text{a}}CO₂ is equal to P_{\text{CO}_2}. Thus, for any given level of V\text{CO}_2, the alveolar (and arterial) P\text{CO}_2 is determined by the level of alveolar ventilation. Hypercapnia is categorized according to causes [\text{see Table 2}].

**Ventilation**

Alveolar ventilation (\( \dot{V}_A \)) is that portion of the minute ventilation (\( \dot{V}_E \)) that comes into equilibrium with alveolar gas and represents the difference between \( \dot{V}_E \) and dead space ventilation (\( \dot{V}_D \)). A decrease in \( \dot{V}_A \) results from either a reduction in \( \dot{V}_E \) or an increase in \( \dot{V}_D \).

Minute ventilation is the volume of gas that moves in and out of the lung. The minute ventilation can be calculated by multiplying the respiratory frequency (f) and the tidal volume (\( V_T \)), which is the volume of air expired with each breath. Typical resting values in the adult are as follows: respiratory frequency,
Regional deficits in perfusion rather than excessive ventilation. Although in most disease states, the mismatch is caused by lung regions having greater ventilation than perfusion. The excess distribution of alveolar ventilation and perfusion. Certain conditions, dead space ventilation can be caused by inequalities in the ratio of ventilation to perfusion (V/Q) is significantly greater than 1.

A fixed volume of gas from each breath is required to fill the anatomic dead space. For any V_{E}, fast and shallow breathing wastes a greater percentage of the minute ventilation because the anatomic dead space is proportionately greater as tidal volume decreases. Conversely, the alveolar ventilation at any V_{E} is greatest when breathing is slow and deep [see Figure 2]. Additionally, dead space ventilation can be caused by inequalities in the distribution of alveolar ventilation and perfusion. Certain lung regions have greater ventilation than perfusion. The excess of regional ventilation to blood flow can be thought of as wasted, although in most disease states, the mismatch is caused by regional deficits in perfusion rather than excessive ventilation.

Dead space can be assessed by measuring the fractional concentration of CO₂ in exhaled gas (FECO₂) and by estimating the fractional concentration of CO₂ in alveolar gas (FACO₂). The FACO₂ is estimated by assuming ideal alveolar air conditions, in which PₐCO₂ values are equal to PₐCO₂ values. V_{D}/V_{T}, the so-called dead space fraction, is calculated as follows:

\[
\frac{(F_{ACO2} - F_{ECO2})}{F_{ACO2}}
\]

The normal value for V_{D}/V_{T} is less than 0.4. The increased work demands imposed by a high V_{D}/V_{T} contribute significantly to dyspnea and often to respiratory failure in clinical lung disease.

### Pulmonary Function Tests

Pulmonary function testing is used to categorize the nature and severity of pathophysiologic disturbances, to follow the progression of known cardiopulmonary disorders, and to measure the response to therapy. Pulmonary function is often used as the basis for the definition of disability for insurance purposes. Lung resection is the only indication for preoperative pulmonary function testing for which a consensus currently exists. Otherwise, such testing offers little additional benefit over clinical parameters in assessing the risk for postoperative pulmonary complications, and prohibitive thresholds cannot be reliably established. A review reported that abnormal pulmonary function predicted a significantly increased relative risk for postoperative pulmonary complications in only four of 11 studies.

The most commonly used pulmonary function tests are based on the forced vital capacity maneuver, measurements of lung volumes, and pulmonary diffusion capacity. Recording of the forced vital capacity maneuver produces a record of volume versus time, flow versus volume, or both during a forced exhalation from total lung capacity (TLC) to residual volume (RV). Forced vital capacity (FVC) is measured with a spirometer and is the most basic and useful lung function test. The test is simple and highly reproducible. However, valid values require maximal efforts by the patient, and these efforts may be compromised by pain or debilitation. The forced vital capacity maneuver shows whether obstruction is present and, if present, quantitates the severity. If there is no obstruction, a reduced vital capacity indicates restriction. In the absence of obstruction, the severity of restriction is defined by comparing vital capacity with the value predicted according to the patient’s height, sex, age, and race.

#### Lung Volumes

The balance between the physical properties of the lung and chest wall and the action of inspiratory and expiratory muscles determines lung volume. TLC is determined by the action of inspiratory muscles, chiefly the diaphragm, against the elastic recoil of the lung and of the chest wall. RV is determined by expiratory muscles opposing the outward recoil of the lung and chest wall at low lung volumes (in older persons, RV may be increased by airway closure). At the end of each tidal breath (expiration), the respiratory muscles are quiet and the lungs are expanded approximately one third of the way from RV. Functional residual capacity (FRC) is the mechanical resting position of the respiratory system and is determined by the balance of elastic recoil of the lung, which reduces respiratory system volume, and elastic recoil of the chest wall, which increases respiratory system volume. In obstructive lung diseases, FRC may be elevated above the lung–chest wall elastic balance volume if inspiration is initiated before that volume is reached. This is so-called dynamic hyperinflation (or air trapping). The vital capacity (VC) is the largest breath a person can take. The tidal volume at rest is the volume of air that is inspired and expired during normal quiet breathing. A person who has just exhaled a tidal breath (to reach FRC) can either inhale to the top of his or her lung volume (the TLC) or exhale further to the bottom of his or her lung volume (the RV). The inspiratory capacity (IC) is the volume from FRC to TLC, and the expiratory reserve volume (ERV) is the volume from FRC down to RV.

### Table 2: Categorization of Hypercapnia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
<th>P_{a}CO₂</th>
<th>V̇_E</th>
<th>V_{D}/V_{T}</th>
<th>A-aDO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective central control of breathing</td>
<td>Drug overdose</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>Amyotrophic lateral sclerosis</td>
<td>↑</td>
<td>↓</td>
<td>Normal or ↑</td>
<td>Normal or ↓</td>
</tr>
<tr>
<td>Chest wall disease</td>
<td>Kyphoscoliosis</td>
<td>↑</td>
<td>↓</td>
<td>Normal or ↑</td>
<td>Normal or ↑</td>
</tr>
<tr>
<td>Primary lung disease</td>
<td>Chronic obstructive pulmonary disease</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

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RESPIRATORY MEDICINE: Lung Function Assessment–3
ry reserve volume (IRV) is the volume from the end of an in-
spired breath up to TLC. Most of these lung volumes are measured with a spirometer.

In the forced expiratory maneuver, the patient breathes quietly
until the tidal volume is stable, inhales to TLC, and then per-
forms a maximal expiration followed immediately by a full in-
spiration to TLC. The lung volumes and capacities are deter-
mained from a mechanical or electronic record of the volume
changes [see Figure 3]. The RV cannot be measured by spirome-
try. Instead, the FRC is measured indirectly by one of several
methods. Once the FRC is known, the ERV is subtracted from
the FRC to give the RV.

**Plethysmography**

In the body plethysmograph, the patient breathes quietly at
normal tidal volumes. At the end of a tidal breath (at FRC), a
shutter occludes the airway. The individual pants against the
occluded airway and, in so doing, expands the volume of gas
in the chest with each inspiratory effort and compresses the vol-
ume of gas with each expiratory effort. The initial volume (FRC)
can be calculated by the use of Boyle's law (V₁P₁ = V₂P₂).5

**Gas Dilution**

There are two gas dilution methods for measuring FRC: the
open-circuit nitrogen washout technique and the helium dilu-
tion method.

With the open-circuit nitrogen washout technique, the pa-
tient breathes quietly at normal tidal volumes. At the end of
a tidal breath, the inhaled gas is changed from air to 100% O₂. The
amount of nitrogen in each subsequent exhalation decreases as O₂
replaces the resident air in the lung until the exhaled gas con-
tains only O₂ and CO₂. The nitrogen in each breath is measured,
and the nitrogen measurements of all the exhalations are then
summed to give the total volume of nitrogen exhaled after the
switch to pure O₂. The initial volume of gas required to provide

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**Figure 2** The effect of varying the respiratory frequency (f) and the tidal volume (VT) on the alveolar ventilation (VA) and the dead space ventilation (VD) is shown. Two different breathing patterns (a and b) in a normal person weighing 150 lb are shown; both patterns achieve a minute ventilation (VE) of 9 L/min. For each breath, the dead space volume (VD) remains constant; its value in milliliters is estimated to be equal to the lean body weight in pounds, or 150 ml. In frame a, the person breathes rapidly and shallowly at a frequency of 30 breaths/min and a VT of 300 ml. With each breath, 150 ml of the inspired air goes to filling the dead space; the remaining 150 ml equilibrates with the gas exchange areas of the lung. Thus, VD equals 150 ml/breath × 30 breaths/min, or 4.5 L/min; and VA equals 150 ml/breath × 30 breaths/min, or 4.5 L/min. The ratio of dead space volume to tidal volume, VD/VT, which represents the portion of the total ventilation that is not involved in gas exchange, is 0.50. In contrast, in frame b, breathing is slower and deeper, with a VT of 900 ml and a frequency of 10 breaths/min. VD remains constant at 150 ml; however, because 900 ml of air is now being taken in with each breath, the remaining 750 ml of air is available for gas exchange. Therefore, VD equals 150 ml/breath × 10 breaths/min, or 1.5 L/min; and VA equals 750 ml/breath × 10 breaths/min, or 7.5 L/min. The value of VD/VT in this example is 0.17.

**Figure 3** Most lung volumes and capacities can be measured by spirometry. Inspired and expired volumes during normal quiet breathing are shown here.
O2 is added to the system to replace that consumed. The initial luminal gas velocity equals the local wave speed. Data from the pressures; choke points occur only when and where local intra-flows. All airway segments have a wave speed at all transmural have a lower wave speed and therefore allow lower maximal flow. Smaller, floppier airways stiffness. Larger, stiffer airways have higher wave speed and speed). Wave speed is directly proportional to airway area and the speed of wave propagation in the airway wall (i.e., wave forms) when and where gas velocity within the airway equals airway pressure. In points downstream (mouthward) some point or points in the airways, pleural (outside) pressure the airways because of frictional (resistive) losses, so that at flow limitation is described by the wave-speed theory. During a forced expiratory vital capacity, and FEF25-75 is forced expiratory flow between 25% and 75% of vital capacity.

The volume exhaled is plotted on the ordinate against time on the abscissa. Spirometry illustrates distinctive patterns for normal breathing (a), obstructive diseases (b), and restrictive diseases (c). FEV1 is forced expiratory volume in 1 second, FVC is forced vital capacity, and FEF25-75 is forced expiratory flow between 25% and 75% of vital capacity.

Obstructive and restrictive disorders produce distinctive patterns on spirometry [see Figure 4]. A normal spirogram rises rapidly, with 95% of the vital capacity exhaled within the first 3 seconds. In obstruction, the rise is slower, and a considerable portion of the vital capacity is exhaled after 3 seconds; the spirogram fails to reach a plateau. Obstruction is identified also by an absolute reduction in the forced expiratory volume in 1 second (FEV₁) as well as the ratio with the forced vital capacity (FEV₁/FVC). A low FVC with a high FEV₁/FVC is typical of restrictive processes, such as pulmonary fibrosis, neuromuscular diseases, and chest wall deformities (e.g., kyphoscoliosis).

Flow-Volume Loop Patterns

Obstructive lung diseases reduce maximum expiratory air-flow by decreasing elastic recoil pressure (e.g., emphysema), narrowing peripheral airways (e.g., chronic bronchitis and asthma), or both. Flow is reduced when airway obstruction is caused by parenchymal lung disease. As the lung empties during forced exhalation, flow rates decrease and become progressively lower than normal as volume decreases. Consequently, the curve acquires a scooped-out appearance [see Figure 5]. Flow rates become extremely low at the end of the FVC maneuver. In restrictive diseases, the peak flow is somewhat decreased. The total exhaled volume is small, and the flow-volume curve is horizontally compressed [see Figure 5]. Flow from the top of the vital capacity to the bottom decreases in a linear manner, as it does in normal lungs, and does not have the scooped-out appearance seen in airway obstruction caused by parenchymal lung disease. Variable intrathoracic airway obstruction, such as that caused by tracheomalacia, limits expiratory flow, so that the expiratory limb of the flow-volume loop is flat. During inspiration, the posterior membranous portion of the trachea billows outward in response to negative intrathoracic pressure, permitting greater flow. During expiration, pleural pressure is greater than the pressure in the intrathoracic airway, which causes a narrowing of the airway at the site of the obstruction.

The term variable indicates that the relation of intraluminal pressure to surrounding pressures [see Figure 5] determines flow. Variable extrathoracic airway obstruction is most common at the larynx and occurs as a result of vocal cord paralysis or tracheomalacia of the extrathoracic trachea. It causes inspiratory limitation. Because of the Bernoulli effect from laryngeal narrowing, the pressure in the extrathoracic upper airway during inspiration is less than the surrounding tissue pressure. As a
result, the airway tends to collapse, which aggravates any structural narrowing.\(^9\)

Maximal inspiratory flow rates less than 2 L/sec suggest severe upper airway obstruction. A fixed airway obstruction such as stenosis of either the intrathoracic or the extrathoracic trachea causes equal and symmetrical flattening of the limbs of the curve that represent severe flow during inspiration and expiration [see Figure 5]. Lesions in either intrathoracic or extrathoracic locations may produce a fixed obstructive pattern.

**DIFFUSING CAPACITY**

The pulmonary diffusing capacity is physiologically determined by the surface area and thickness of the alveolar capillary membrane, by the volume of blood circulating in the alveolar capillary bed, and by the reaction rate of the test gas with hemoglobin. In actualty, the pulmonary diffusing capacity reflects the overall efficiency of gas transfer at each step from the mouth to pulmonary capillary hemoglobin. Because the process involves much more than just diffusion, the term transfer factor is more appropriate, but the term diffusing capacity remains in common use in North America.

The transfer factor of any gas is calculated by dividing the volume of gas taken up by the difference between the alveolar concentration and the mixed capillary concentration (\(P_{\text{A}}CO\)). Carbon monoxide is usually used for measuring the transfer factor. The affinity of CO for hemoglobin is so high that the hemoglobin takes up almost all the CO entering the blood. The partial pressure in plasma remains so low that the value for mixed capillary PCO can be omitted from the calculation. Thus, the diffusing capacity for CO is expressed as the volume of CO taken up per minute per mm Hg of \(P_{\text{A}}CO\) and can be calculated by using the following equation:

\[
D_{\text{LCO}} = \frac{V_{\text{CO}}}{P_{\text{A}}CO}
\]

Diffusing capacity is most commonly measured by the single-breath technique. The patient takes a vital capacity breath of a gas mixture containing 0.3% CO and 10% helium. After a 10-second breath hold, the patient exhales. The first portion of exhaled gas, which is contaminated with dead space ventilation, is discarded. The next liter is collected and analyzed. The helium is needed to calculate the amount of dilution of the inspired sample so that the initial alveolar CO can be calculated.

**Figure 5**  Flow is depicted on the ordinate with expiration above and inspiration below the intercept. Volume is shown on the abscissa going left to right from TLC to RV. (a) A normal expiratory flow-volume curve is shown. (b) In variable intrathoracic obstruction, the expiratory flow-volume curve shows a scooped-out appearance as a result of progressive decreases in flow as lung volume becomes smaller. Obstruction is volume dependent. Flow rates at any given lung volume (isovolumic flow) are reduced. Because of air trapping, the entire curve may be shifted to a higher lung volume (leftward). This pattern is typical of chronic obstructive pulmonary disease or asthma. (c) The expiratory flow-volume curve shows a decreased flow that is the same at all lung volumes. Obstruction, which is not dependent on lung volume, is caused by upper airway obstruction, not by disease of the lung parenchyma. (d) Disproportionate reduction of inspiratory airflow is indicative of variable extrathoracic upper airway obstruction. (e) Fixed airway obstruction, the site of which is undetermined, shows volume-independent reduction of flow in both inspiration and expiration. (f) An expiratory flow-volume curve in a patient with a restrictive disorder is shown. Isovolumic flow rates are increased, whereas the volume axis is compressed and shifted toward lower volume (rightward).
Interpretation of Pulmonary Function Tests

The results of pulmonary function tests are interpreted in comparison with predicted normal values that have been defined for various populations. Pulmonary function studies should be performed with carefully calibrated equipment that meets uniform standards, with the use of approved techniques in patients who are well coached to ensure a maximal effort and reproducible results. Interpretive errors can be minimized by adhering to the standards published by the American Thoracic Society (ATS) in 1994.7 Newer standards are now being prepared jointly by the ATS and European Respiratory Society (http://www.thoracic.org). Results that are within the 95% confidence limits for the reference population are considered to be normal.

Pulmonary function tests seldom confirm a specific diagnosis. Rather, they show certain patterns, each of which may be consistent with a number of different diseases. Once a specific diagnosis has been made by combining the pulmonary function results with other clinical information, the quantitative results help in assessing the severity of the physiologic impairment caused by the disease. Vital capacity, FEV1, and FEV1/FVC are the basic spirometric parameters used for pulmonary function interpretation to make an assessment of normality or to define patterns of abnormality. TLC and DLco provide important additional information and may provide independent evidence of a pattern of physiologic abnormality.

Obstruction

An obstructive defect is defined as reduction in maximal expiratory flows and FEV1/FVC. Although the earliest evidence of obstruction can be found in a reduction in the instantaneous flow after 75% of a vital capacity has been exhaled (FEF75) or in average midflow rates (FEF25–75), these are nonspecific findings of uncertain clinical significance.

When the presence of obstruction has been determined, its severity is best assessed with the FEV1 as a percentage of the predicted value. Although there is some variability in interpretative schemes, an FEV1 less than 50% of predicted is generally considered to be severe, a value between 50% and 70% of predicted is moderate impairment, and higher values of FEV1 with a reduced FEV1/FVC are considered to be mild disturbance. Obstruction with normal lung volumes and DLco suggests airway disease with preservation of pulmonary parenchyma. These findings are consistent with mild asthma or chronic bronchitis.

Hyperinflation is defined by an elevated TLC, and air trapping is defined by an increased RV/TLC ratio. Obstruction with hyperinflation and air trapping is characteristic of more severe airway disease. Vital capacity may be reduced; the concave shape of the expiratory flow-volume curve and the flattened spirogram may provide indirect evidence of air trapping as the cause of the reduction of vital capacity, but lung volume measurements are often necessary to confirm the impression. Hyperinflation in the presence of a normal diffusing capacity for carbon monoxide indicates preservation of the alveolar capillary bed and may be suggestive of chronic obstructive bronchitis or chronic severe asthma. A low DLco in a patient with obstruction and hyperinflation suggests that emphysema is the cause of the obstruction. In this disorder, the obstruction occurs as a result of the loss of lung parenchyma, which ordinarily attaches to the outside of the small airways and, by radial traction, helps maintain the airway diameter during expiration. Loss of this supporting tissue allows the airways to collapse during expiration. Loss of elastic recoil also reduces expiratory flow. As the lung parenchyma is destroyed, the capillary bed is also lost, causing a low diffusing capacity for carbon monoxide.

Restriction

A restrictive pattern is defined by a reduced TLC, although presence of a restrictive pattern may be inferred by a reduced VC in the presence of a normal or elevated FEV1/FVC. A restrictive defect may be caused by parenchymal lung disease, by chest wall disorders, or by neuromuscular disorders. Patients whose vital capacity and residual volume are reduced by about the same amount have symmetrical reduction in lung volumes. These patients often have fibrotic diseases that shrink the lungs, such as pulmonary fibrosis and sarcoidosis. Destruction of the lung parenchyma results in reduced volume of the capillary bed and a lower DLco. Patients with neuromuscular diseases often show a pattern in which the vital capacity is reduced but the residual volume is normal or even slightly increased. Weak inspiratory muscles limit the size of a maximal breath. Weak expiratory muscles, especially a weak rectus abdominis muscle, prevent complete emptying. Muscle weakness does not affect the lung parenchyma, and the DLco is normal when corrected for the lung volume. Patients with chest wall abnormalities caused by kyphosis and scoliosis have a similar pattern.

Isolated Low Diffusion

If the patient is not anemic or does not have an elevated carboxyhemoglobin level, isolated low diffusion suggests loss of the pulmonary capillary bed, either because of pulmonary vascular disease (e.g., pulmonary emboli or pulmonary hypertension) or because of an early interstitial lung disorder that has not yet reduced the lung volumes or of early emphysema that has not yet produced airflow obstruction.

Muscle Function

Assessment of respiratory function is frequently performed in the intensive care unit (ICU), often to help determine reasons for prolonged ventilator dependence. The diaphragm is the chief inspiratory muscle. Abnormalities in diaphragmatic function generally manifest as exertional dyspnea accompanying reductions in VC and TLC with a preserved DLco. Patients with weakness or paralysis of one or both hemidiaphragms typically experience more dyspnea when they are supine than when they are seated or in an upright position (orthopnea). On physical examination, the abdominal wall may retract with inspiration (abdominal paradox), which indicates that the diaphragm is neither performing active inspiratory work nor providing a pressure barrier between the abdominal and pleural compartments.

In any severe obstructive or restrictive ventilatory disorder, the muscles of breathing carry a heavy workload in providing
ventilation, even at rest. High respiratory muscle loads elicit reflex responses that manifest as a rapid, shallow breathing pattern. High inspiratory workloads may also cause the appearance of abdominal paradox. These two findings, once thought to reflect respiratory muscle fatigue, are nonspecific indicators of respiratory muscle load and may be seen before diaphragmatic fatigue is actually present. Continuous loads can lead to the development of inspiratory muscle fatigue, defined as the loss of contractile strength despite maximal stimulation. Diaphragmatic function can be assessed in the laboratory by several techniques. In patients with significant diaphragmatic weakness or paralysis, vital capacity may decline by 20% or more in the supine position compared with the upright position. Muscle strength can be assessed by having the patient perform maximal inspiratory and expiratory efforts against a closed system and measuring the static pressures that are generated.

A young, healthy adult can generate negative pressures in excess of −100 cm \( \text{H}_2\text{O} \) on inspiration and positive pressures in excess of +120 cm \( \text{H}_2\text{O} \) on maximal expiratory effort. In certain clinical settings, serial measurements of muscle strength may be of particular value. Examples include progressive neuromuscular disorders, such as Guillain-Barré syndrome, in which it is important to identify respiratory muscle weakness or paralysis early in its course (before the development of overt respiratory failure) and disorders that are characterized by fluctuating periods of muscle weakness, such as myasthenia gravis.

**Nonroutine Pulmonary Function Tests**

**Lung Elasticity**

The elastic properties of the lung can be assessed by measuring the static transpulmonary pressure as a function of lung volume. Transpulmonary pressure is defined as the pleural pressure minus the oral pressure, and static denotes that the measurements are made at a time when no airflow is occurring. When the mouth is open, oral pressure is equal to atmospheric pressure, and pleural pressure can be approximated from intraesophageal pressure. Measurements of intraesophageal pressure require that the patient swallow a balloon-tipped catheter; thus, it is not a routine procedure in most clinical pulmonary function laboratories.

The static transpulmonary pressure, measured at various volume intervals during deflation of the lung, can be plotted against the percentage of the predicted total lung capacity [see Figure 6]. The change in lung volume divided by the change in pressure, measured over the volume interval extending from 500 ml above FRC to FRC, is known as the static compliance. Normal values for the static compliance range from 0.1 to 0.4 L/cm \( \text{H}_2\text{O} \). Pressure-volume curves can also be plotted for obstructive and restrictive disorders and can be modeled mathematically for further analysis. The static compliance is abnormally high in emphysema and abnormally low in interstitial fibrosis.

**Bronchial Provocation**

One of the defining characteristics of asthma is an increase in the responsiveness of the airways to a number of stimuli. If lung function is normal but the history suggests the presence of asthma, the demonstration of bronchial hyperresponsiveness to one of several constrictor challenges can be useful in establishing a diagnosis.

Methacholine, carbacholine, and histamine aerosol challenges are common means of bronchial provocation. Because droplet size and the amount of drug delivered vary among aerosol-generating devices and because great care must be taken to monitor responses to avoid provoking severe obstructive episodes, such aerosol challenges should be performed only in laboratories with extensive experience in utilizing these techniques. In addition to the issue of safety, such laboratories have a large database on the distribution of airway responsiveness in a broad population, which allows a more reasonable assessment of the response measured.

Another alternative constrictor challenge is 4 or 5 minutes of either exercise or voluntary hyperventilation with cold, dry air. Such approaches appear to be as valuable as drug challenges, and they avoid the problems of variations in aerosol delivery and the dangers of inadvertent overdose with a potent constrictor agent. Results of bronchoprovocation challenges are normally expressed as the provocative dose (PD) of a stimulus that produces a defined level of response in a pulmonary function parameter, most often the FEV\(_1\) (e.g., PD\(_{20}\)FEV\(_1\), is the dose that produces a 20% decrease in FEV\(_1\)) [see Figure 7]. The lower the PD\(_{20}\), the greater the degree of responsiveness.

**Exercise Testing**

Measurements of cardiovascular and respiratory performance at several levels of exercise are useful for the objective evaluation of patients for disability. Cardiopulmonary exercise tests can also be used to evaluate patients with unexplained dyspnea. The tests quantify the severity of the abnormality and may give clues to the etiology of the dyspnea.

Another use of exercise testing is to document the occurrence and severity of hypoxemia during exertion. Assessment of oxy-
During exercise, anaerobic glycolysis is initiated, which can be identified by the increase in lactic acid and the onset of anaerobic glycolysis. This is termed the anaerobic threshold. Common patterns include the increase in lactic acid and signals the onset of anaerobic glycolysis.

Minute ventilation and tidal volume, heart rate, blood pressure, and other medical parameters are continuously monitored and correlated with the patient's perceived level of dyspnea on a visual analogue scale. Maximum oxygen uptake ($V_{O2max}$) is reached when there is no further increase in $V_{O2}$ with increasing work output. Anaerobic metabolism, reflecting a disproportionate increase in $CO_2$ output and ventilation with increasing $V_{O2}$, occurs as a result of buffering the increase in lactic acid and signals the onset of anaerobic glycolysis; it is termed the anaerobic threshold. Common patterns of findings of exercise testing have been correlated with heart disease, obstructive and restrictive pulmonary diseases, pulmonary vasculopathies, and deconditioning.

For severely disabled patients who are candidates for lung transplantation or lung volume reduction surgery, exercise capacity can be determined with the 6-minute-walk distance, a very simple test that requires only oximetry, a timepiece, and a measured distance. The 6-minute-walk distance test has been standardized and shown to be repeatable.

### Polysomnography

The term polysomnography is used to describe a collection of measurements made during sleep to assess sleep-associated respiratory and neurologic disturbances. These are discussed in detail elsewhere [see 14:VI Ventilatory Control during Wakefulness and Sleep and 11:XIII Disorders of Sleep].

### Imaging Studies

#### Standard Chest Radiograph

In patients with a pulmonary disorder, the relative lack of specificity of respiratory tract symptoms and the relatively poor reliability of the pulmonary physical examination make radiologic imaging techniques essential to the diagnostic process [see Table 3]. For this reason, the chest roentgenogram (posteroanterior and lateral) is the single most commonly utilized radiologic technique, accounting for some 40% of all radiologic procedures.

Standard radiographic imaging techniques depend on large differences in the densities of the various body components to discern structure and detect abnormalities. Four distinct densities—gas, water (solid tissues), fat, and metal (bones)—can be identified. Radiographic imaging brings the thoracic cage and mediastinal structures into sharp contrast with the adjacent gas-containing lung, and any lesion within the lung is made apparent by this same contrast in densities. Several technically sophisticated diagnostic imaging techniques are also employed in the assessment of diseases of the thorax. These techniques include perfusion scans, ventilation scans, pulmonary angiography, computed tomography, magnetic resonance imaging, and ultrasonography.

#### Radionuclide Scans

**Ventilation Scans**

Ventilation scans are used either to assess the distribution of pulmonary ventilation or to improve the diagnostic reliability of radionuclide perfusion scans performed for the diagnosis of pulmonary embolic disease. Ventilation scans can be performed with radioactive gases (usually xenon) or with a fine aerosol of particles labeled with technetium-99m ($^{99m}$Tc). When a gas is used, images are made after a wash-in phase (at equilibrium) and during a timed wash-out phase. Regions of lung that are poorly ventilated retain radioactivity. If a radioactive aerosol is used, multiple views can be obtained for comparison with the perfusion scan.

**Perfusion Scans**

Perfusion scanning is employed to assess the distribution of blood flow to the lung, either as a diagnostic tool for the evaluation of pulmonary embolic disease [see 1:LVIII Venous Thromboembolism] or to quantitate regional pulmonary blood flow for the assessment of physiologic operability for surgical pul-

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RESPIRATORY MEDICINE: I Lung Function Assessment—9
99mTc, are attached to macroaggregated human albumin or to al-
monary resection. Isotopes that emit gamma rays, most often
0.99 and a negative predictive value of 0.97, suggesting that ac-
probability of pulmonary emboli. If a region with no perfusion
increased likelihood of pulmonary embolic disease. However, if
hypothesis has been shown to have a positive predictive value of
ation with perfusion scans and are most useful in assessing the
radiolabeled particles are then injected into a peripheral
ment correlates well with pulmonary hemodynamics in acute pulmonary embolism, but less so in chronic pulmonary hypertension because of the presence of vascular remodeling.
According to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (which used pulmonary angiography as the standard), two or more large segmental mismatches, two or more moderate segmental mismatches and one large defect, or at least four moderate mismatches define a high probability scan that indicates an 80% or greater likelihood of pulmonary embolism. A nonsegmental perfusion defect, a perfusion defect much smaller than corresponding opacity on an accompanying chest roentgenogram, or three or fewer small matched defects in the presence of a normal chest film define a low-probability scan. A single moderate-sized mismatch or a moderate and a large defect, more than three matched defects in a lung zone or four in a whole lung, or a pattern that is neither high nor low probability defines an indeterminate scan. The positive predictive value of the ventilation-perfusion scan increases as the number and volume of mismatched defects increases. Two segmental mismatches carry an 80% positive predictive value for embolism.5 As opposed to a completely normal study, 11% (8/75) of patients with a nearly normal ventilation-perfusion scan were subsequently found to have positive angiograms for pulmonary embolism. The PIOPED II study, which is currently under way, is assessing helical (spiral) CT in relation to pulmonary angiography, ventilation-perfusion scans, digital subtraction angiography, and lower extremity venous compression ultrasonography and contrast venography. PIOPED II is likely to generate new sensitivity and specificity data for these techniques. This study will be completed in 2004.57

<table>
<thead>
<tr>
<th>Technique</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posteroanterior and lateral roentgenogram*</td>
<td>Wide variety of pulmonary disorders</td>
<td>—</td>
<td>Technique dependent; specificity and sensitivity are observer dependent and vary with disease process and clinical setting</td>
</tr>
<tr>
<td>Contrast angiography*</td>
<td>Pulmonary thromboembolic disease</td>
<td>Contrast sensitivity, renal insufficiency, left bundle branch block</td>
<td>Gold standard for diagnosis of pulmonary embolism; used for evaluation of pulmonary vasculature; indicated when other studies are inconclusive and when treatment is invasive, hazardous, or contraindicated</td>
</tr>
<tr>
<td>Digital subtraction angiography*</td>
<td>Pulmonary thromboembolic disease</td>
<td>—</td>
<td>Used to assess distribution of pulmonary ventilation and blood flow and in assessment of physiologic suitability for pulmonary resection</td>
</tr>
<tr>
<td>Radionuclide scanning*</td>
<td>Pulmonary thromboembolic disease</td>
<td>Reports of complications, anecdotal only</td>
<td></td>
</tr>
<tr>
<td>Ventilation Perfusion</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computed tomography*</td>
<td>Emphysema, pulmonary nodules, infectious processes, parenchymal pulmonary disorders</td>
<td>Obesity (&gt; 300 lb), inability to hold breath, contrast sensitivity</td>
<td>CT reconstructions provide sagittal sections of 10 mm thickness; increased sensitivity compared with plain film but with 100 x radiation exposure, especially suited for evaluation of mediastinal anatomy and the pleura and for staging malignancies Spiral CT shortens breath-hold time; can be used for three-dimensional reconstructions of airway anatomy and lung masses 1–2 mm slices allow resolution of secondary pulmonary lobules by high-resolution CT</td>
</tr>
<tr>
<td>Spiral CT*</td>
<td>Pulmonary thromboembolism</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>High-resolution CT*</td>
<td>Parenchymal pulmonary disorders, bronchiectasis</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Disorders of the chest wall, mediastinum, and soft tissues</td>
<td>Presence of any ferrometallic objects, claustrophobia</td>
<td>No radiation exposure; provides coronal as well as sagittal reconstructions; resolves soft tissue anatomy</td>
</tr>
<tr>
<td>MR angiography*</td>
<td>Pulmonary thromboembolic disorders</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Positron emission tomography*</td>
<td>Moderate to large focal pulmonary lesions</td>
<td>—</td>
<td>Accuracy uncertain for lesions smaller than 1 cm</td>
</tr>
<tr>
<td>Ultrasoundography</td>
<td>Pleural effusions</td>
<td>—</td>
<td>May help localize subpleural pulmonary nodules</td>
</tr>
</tbody>
</table>

*Radiation exposure requires caution for women of childbearing age.
Unfortunately, in more than 60% of cases, results of ventilation-perfusion scanning can neither confirm nor exclude pulmonary embolism. In a patient with normal D-dimer levels, an equivocal scan can reliably exclude pulmonary embolism. In patients with an equivocal scan and elevated D-dimer levels, further clinical evidence is required [see 1:XVIII Venous Thromboembolism]. There are four indications for the use of pulmonary angiography in patients who may have pulmonary thromboembolic disease: (1) to confirm the diagnosis when anticoagulation carries significant risks to the patient or when a younger patient may face prolonged anticoagulation; (2) when aggressive therapy such as thrombolysis, vena caval interruption, or surgical clot extraction is contemplated; (3) to provide a definitive diagnosis when the clinical suspicion of thromboembolism is high, but less invasive studies are inconclusive; and (4) in the evaluation of pulmonary hypertension. If leg vein studies are negative and the clinical probability of pulmonary embolism is great, a pulmonary angiogram should be done because it is currently the only way to positively exclude pulmonary embolism. Pulmonary angiography as currently practiced is safe. Mortality is less than 1%. Major complications, such as hypotension, myocardial infarction, and renal failure, occur in 1.5%, and minor complications, particularly contrast nephrotoxicity, occur in 4.8%. Most cases of renal failure occur in critically ill patients. Other risks include allergy to contrast media (0.1%), transient right bundle branch block, and nonsustained ventricular tachyarrhythmias. Pulmonary arterial pressure rises by an average of 4 mm Hg, linearly dependent on the size of the injectate. The rise in pulmonary arterial pressure is independent of the presence of pulmonary embolism. Most angiographic defects in pulmonary embolism are found in segmental or larger vessels. Reproducibility of interpretation is reduced in the 17% of patients with defects in subsegmental vessels. When angiography is unavailable, excessively risky, or contraindicated, alternative imaging techniques may be considered.

**Digital Subtraction Angiography**

In digital subtraction angiography (DSA), images are taken before and after the injection of intravenous contrast medium, and a computer then subtracts the plain image from the contrast image. This enhances the resolution of the contrast image. DSA has been shown to be sufficiently sensitive to confidently exclude pulmonary embolism. Twelve-month follow-up of 54 patients with negative DSA examinations showed no indications of a missed diagnosis of pulmonary embolism, whether in the form of subsequent clinical events, positive angiograms, or positive scans. The PIOPED II study (see above) will provide data on the utility of DSA in relation to other techniques.

**Computed Tomography**

CT scanning utilizes standard radiographic signals that are processed by computer to provide detailed cross-sectional images of desired contrast. Although CT scanning offers significantly better visualization of anatomic structures than does standard radiography, a thoracic CT examination involves a radiation exposure equivalent to 100 standard chest radiographs. Risks and benefits must always be taken into consideration when ordering CT examinations.

CT scanning distinguishes gradations of density ranging from air (−1,000 Hounsfield units [HU]) to bone (+1,000 HU). Normal tissue has the density of water, 0 HU. Intravenous contrast media in modest doses allow CT scanning to be used to assess the intrapulmonary-versus-extrapulmonary location of a pulmonary lesion, the vascularity of lesions, and tracheobronchial pathology; to diagnose bronchiectasis; and to identify major vascular structures in regions of abnormality. The technique is employed to locate and characterize mediastinal masses and lymph nodes, intrapulmonary lesions, and pleural processes. CT scanning is now considered integral to the staging of most cases of lung cancer and to the evaluation of most mediastinal masses. CT scanning before bronchoscopy for suspected lung cancer increases the bronchoscopic yield from 71% to 90%.

**High-Resolution Computed Tomography**

In high-resolution CT (HRCT), the thickness of the tomographic section is reduced from about 1 cm to 1 to 3 mm. Modified software improves resolution and shows fine morphologic detail. The technique is most useful for evaluating diffuse lung disease, and usually, only three to six scans are performed. Resolution of structures down to 200 μm can be achieved, so that secondary pulmonary lobules and even thickened intralobar septa can be visualized.

HRCT is a good screening test for interstitial lung disease, especially in patients with dyspnea whose chest roentgenogram is normal and whose lung volumes and diffusing capacity are in the low normal range or are mildly reduced. Negative results on HRCT are evidence against significant interstitial lung disease, although open lung biopsy specimens may still show evidence of abnormality in some cases. HRCT may be useful in assessing drug-induced lung damage; air-space abnormalities can be seen even when the chest roentgenogram is normal.

Certain patterns have been recognized and closely correlated with specific pathologic processes [see 14:V Chronic Diffuse Infiltrative Lung Disease]:

1. A ground-glass pattern correlates with active alveolitis. A higher proportion of ground-glass density in relation to septal thickening or honeycombing patterns suggests a more favorable prognosis in usual interstitial pneumonia.

2. Active tuberculosis is characterized on HRCT by ground-glass densities and centrilobular and poorly marginated nodules, whereas nontuberculous Mycobacterium infections frequently present as bronchiectasis associated with parenchymal nodules.

3. Idiopathic pulmonary fibrosis is characterized by crescentic subpleural reticular densities that are most dense in the posterior basal segments of the lower lobes. Scans taken with the patient in the prone position can ensure that such densities are not a result of increased perfusion of dependent zones. In advanced disease, reticular interstitial densities, regions of fibrosis, and cystic spaces are found throughout the lung. These changes are not specific to idiopathic pulmonary fibrosis but are seen in end-stage fibrotic lung disease from any cause.

4. Lymphangitic cancer has a rather characteristic appearance, with thickening of bronchovascular bundles and intralobar

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should replace ventilation-perfusion scanning in the standard
tions; most of these patients had cancer. Whether spiral CT
embolism if combined with other clinical and laboratory data.
Whether this point needs confirmation from PIOPED II (see
basis for withholding anticoagulation for suspected pulmonary
is significantly reduced compared with ventilation-perfusion
linear banding, and increase in the size of affected arteries. Be-
ventricular dilatation, pleural-based wedge-shaped infiltrates,
and ancillary findings of pulmonary embolism, such as right
scanning. Spiral CT may be sufficiently sensitive to be used as a
cause of these advantages, the number of indeterminate studies
between inspiration and expiration.
the rapidity of image acqui-
mized. Reconstructions can be constituted at any level of the
thorax, decreasing the likelihood that a small lesion in between
tomographic cuts could be missed. The rapidity of image acqui-
sion allows a correlation of lung anatomy and physiology be-
tween inspiration and expiration.
Spiral CT is capable of resolving second- to fourth-generation
pulmonary arterial branches. It has been shown to be a highly
sensitive and specific tool in the diagnosis of central pulmonary
embolism that, in most studies, offers performance superior to
that of radionuclide imaging [see Figure 8]. A major advantage
of spiral CT is its ability to demonstrate alternative diagnoses
and ancillary findings of pulmonary embolism, such as right
ventricular dilatation, pleural-based wedge-shaped infiltrates,
linear banding, and increase in the size of affected arteries.
Because of these advantages, the number of indeterminate studies
is significantly reduced compared with ventilation-perfusion
scanning. Spiral CT may be sufficiently sensitive to be used as a
basis for withholding anticoagulation for suspected pulmonary
embolism if combined with other clinical and laboratory data.
However, this point needs confirmation from PIOPED II (see
above). Unsuspected pulmonary embolism has been reported
as an incidental finding in 5% of inpatient spiral CT examina-
tions; most of these patients had cancer. Whether spiral CT
should replace ventilation-perfusion scanning in the standard
workup of pulmonary embolism has not been definitively re-
olved24 and is currently being assessed in PIOPED II.
Three-dimensional reconstruction is possible from spiral CT
data and has been used to create accurate virtual bronchoscopic
examinations of the airways. Although these reconstructions do
not identify subtle bronchial wall abnormalities, they may
prove useful in identification of sites suitable for transbronchial
needle sampling of lymphadenopathy and in the assessment of

Spiral Computed Tomography

Helical, or spiral, CT differs from conventional CT imaging
by continuously acquiring imaging data while the patient
moves through the CT gantry at a constant rate. Spiral CT has
become the standard approach for thoracic imaging in many
institutions because imaging time is substantially reduced, often
to less than 1 minute. Contrast requirements are also mini-
mized. Reconstructions can be constituted at any level of the
thorax, decreasing the likelihood that a small lesion in between
tomographic cuts could be missed. The rapidity of image acqui-
sion allows a correlation of lung anatomy and physiology be-
tween inspiration and expiration.

HRCT helps localize the distribution and severity of emphy-
sema. This may be of importance in the evaluation of patients
for lung volume reduction surgery. HRCT can clarify the extent
and pattern of intrathoracic disease; if patterns are typical, they
can be used in lieu of an open biopsy technique to establish a
specific diagnosis of interstitial disease.23

Figure 8  A large filling defect is seen in the right pulmonary artery in
this contrast-enhanced study. Note accompanying pleural effusion.

MAGNETIC RESONANCE IMAGING

MRI reveals tissue properties by using physical principles
different from those used and revealed in standard chest
roentgenograms and CT. Because MRIs of the chest can be
degraded by motion, thoracic MRIs are usually gated to the heart
rate by ECG. MRI produces sagittal and coronal images that are
3 to 10 mm in thickness. Advantages of MRI are its increased
soft tissue contrast, multiplanar capability, sensitivity to blood
flow, and lack of ionizing radiation. Because of its ability to dif-
fentiate between tissues of varying compositions, MRI is par-
ticularly suited to evaluation of soft tissue processes. Disadvan-
tages of MRI include inferior spatial resolution, degradation of
image with respiratory motion, and the necessity of eliminating
metallic objects from the imaging environment, making the
method unsuitable for ventilated patients as well as those with
metallic implants of any sort. The ability of MRI to differentiate
contiguous structures makes it a useful technique for evaluating
intrathoracic malignancies in relation to vascular and mediasti-
nal structures. CT and MRI are comparable in accuracy for the
evaluation of nodal spread of bronchogenic carcinoma.

MAGNETIC RESONANCE ANGIOGRAPHY

The advent of rapid imaging techniques has made magnetic
resonance angiography (MRA) an attractive technology to sup-
plement or supplant pulmonary angiography in the evaluation
of pulmonary vascular disorders. MRA has been compared
with pulmonary angiography in the diagnosis of pulmonary
embolism. For segmental and larger pulmonary embolism,
MRA is quite specific and sensitive. In limited studies, magnetic
resonance venography has shown high sensitivity and specifici-
fity for diagnosis of deep vein thrombosis and may prove an
important diagnostic modality.24

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) utilizing 18-fluo-
rrodeoxyglucose as the positron emitter (to indicate active glu-
cose metabolism) appears to be an accurate noninvasive test for
the diagnosis of moderate sized and larger pulmonary focal le-
was visualized and biopsies performed as hypoechoic or nonechoic regions. Pleural lesions in suspected variety of pleuropulmonary disorders. Pleural effusions present dimensional ultrasonography, but in the presence of consolidations. A meta-analysis.26

Fewer data exist for lesions smaller than 1 cm. A sensitivity of 96.8% and a specificity of 77.8% have been reported from a meta-analysis.26

ULTRASONOGRAPHY

The normal air-containing lung is poorly visualized by two-dimensional ultrasonography, but in the presence of consolidation, ultrasonography may prove useful in the evaluation of a variety of pleuropulmonary disorders. Pleural effusions present as hypoechoic or nonechoic regions. Pleural lesions in suspected malignant effusion were visualized and biopsies performed with 100% specificity and 88% sensitivity in one study.26 Consolidation is seen as hypoechoic regions that move with the patient’s breathing. Air bronchograms are hyperechoic, whereas liquid-filled airways associated with atelectasis or endobronchial obstruction are hypoechoic. Abscesses are seen as irregularities in density in an otherwise homogeneous region, and tumors may be distinguished within a consolidated area by their relatively homogeneous consistency and by their regular borders. The specificity and sensitivity of the method are insufficient to permit ultrasonography to replace CT or other radiologic methods, but it may be viewed as a complementary technique.

Sampling Techniques

Several techniques are available for obtaining material for microscopic examination or, in the case of infectious agents, growing in culture media. Some sampling techniques are clearly superior in terms of yield, specificity, ease of performance, and safety. In any clinical setting, however, the local experience with, and availability of, specific sampling techniques will dictate the best choice in a given situation. In general, it is advisable to start with the least invasive approaches.

FIBEROPTIC BRONCHOSCOPY

Fiberoptic bronchoscopy has become the standard procedure for exploring the tracheobronchial tree. The fiberoptic bronchoscope possesses excellent optics, is flexible and easily manipulated, and has a small diameter. Topical anesthesia provides adequate comfort, and endotracheal intubation is generally not needed. These factors contribute to ease of performance and the excellent level of patient acceptance associated with this technique. From a diagnostic standpoint, the fiberoptic bronchoscope has virtually replaced the rigid bronchoscope, except in cases involving examination of the tracheobronchial tree during active massive hemoptysis or for extraction of aspirated foreign bodies [see Table 4].

In addition to allowing excellent visualization of the bronchi, the fiberoptic bronchoscope provides samples that can be used for smear, culture, cytologic study, and histologic examination.

Direct Vision

Contemporary fiberoptic bronchoscopes allow viewing of the first six generations of the airways from the posterior oropharynx and nasopharynx and the larynx to sub-subsegmental bronchi. Although this corresponds only to the inner third of the lung fields on a chest roentgenogram, a significant proportion of pathologic processes, including many lung tumors, aspirated foreign bodies, inhalation and aspiration injuries, and Kaposi sarcoma, occur in the proximal airways and are amenable to direct inspection. Localization of the source of hemoptysis is made by direct visualization, although it should be noted that in massive hemoptysis, a rigid bronchoscope may be preferable for its superior visualization and ability to maintain a clear airway.

Washings

Washings from the tracheobronchial tree using isotonic saline are useful for cytologic and microbiologic examination. Bronchial washing is particularly helpful in the diagnosis of sputum smear-negative tuberculosis, in which 40% of smokers and up to 95% of cultures may be positive.

Bronchoalveolar lavage If the endoscopist wedges the bronchoscope in a segmental or subsegmental orifice before instilling and aspirating saline, the distal airways and air spaces may be sampled. Bronchoalveolar lavage (BAL) has proved extremely useful in the assessment of opportunistic infections in AIDS patients. The sensitivity of BAL for Pneumocystis carinii approaches 95% when compared with open lung biopsy and may exceed that of transbronchial biopsy. The yield for other opportunistic infections may be somewhat lower. Culture of BAL specimens has a sensitivity for tuberculosis of up to 88%. BAL has also been used in the evaluation of interstitial lung diseases and in the identification and assessment of rejection of lung transplants. The total number of cells recovered and the differential cell count help categorize alveolitis as neutrophilic or lymphocytic in nature and to gauge its intensity. BAL may be

<table>
<thead>
<tr>
<th>Table 4 Common Indications and Contraindications for Fiberoptic Bronchoscopy</th>
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<tbody>
<tr>
<td><strong>COMMON INDICATIONS</strong></td>
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<tr>
<td>Inspection of Tracheobronchial Tree</td>
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<tr>
<td>Search for source of bleeding in patient with mild to moderate hemoptysis</td>
</tr>
<tr>
<td>Suspected endobronchial lesion (e.g., in patient with lobar collapse)</td>
</tr>
<tr>
<td>Search for occult cancer in patient with malignant cells in sputum but normal chest radiograph</td>
</tr>
<tr>
<td>Assessment of intractable cough</td>
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<tr>
<td>Staging of known lung cancer</td>
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<td>Sampling from Lower Respiratory Tract</td>
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<tr>
<td>Microbiologic</td>
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<tr>
<td>Pulmonary infiltrate in immunocompromised host</td>
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<td>Complicated pneumonia in immunocompetent host</td>
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<td>Cytologic and histologic</td>
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<td>Suspected pulmonary neoplasia</td>
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<td>Diagnosis of unexplained pulmonary infiltrates</td>
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<td>Aspiration of paratracheal or parabronchial lymph nodes</td>
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<td>Cell count and differential</td>
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<td>Assessing activity of chronic interstitial pneumonia (investigational)</td>
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<td><strong>THERAPEUTIC INTERVENTIONS</strong></td>
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<tr>
<td>Suctioning mucous plugs</td>
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<td>Guided intubation</td>
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<tr>
<td>Removal of foreign bodies (infrequent)</td>
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<td>Placement of endobronchial stents</td>
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<tr>
<td>Endobronchial brachytherapy</td>
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<tr>
<td><strong>CONTRAINDICATIONS</strong></td>
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<tr>
<td>Uncooperative patient</td>
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<tr>
<td>Uncorrectable hypoxemia or hypercapnia</td>
</tr>
<tr>
<td>Uncorrectable bleeding diathesis</td>
</tr>
<tr>
<td>Severe asthma</td>
</tr>
</tbody>
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diagnostic for eosinophilic granuloma when Langerhans cells are recovered in the washings. Milky BAL fluid indicates alveolar proteinosis; such fluid stains positively with the periodic acid–Schiff (PAS) reaction.

**Brushings**

Specimens obtained from the stiff bristles of a wire brush that can be passed through the bronchoscope may contribute to the cytologic diagnosis of pulmonary malignancies. Bronchial brushings have a much higher diagnostic yield for endobronchially visible proximal lesions but may be positive in 20% to 40% of peripheral lesions when the brushing is fluoroscopically guided. Lesions larger than 2 cm in diameter and lesions located more centrally tend to have higher cytologic yields, as do lesions that directly involve the bronchial tree. Bronchial brushing may contribute material for microbiologic smears and cultures but is unlikely to provide the sole positive result of a diagnostic evaluation.

**Biopsy**

Bronchoscopic biopsy forceps produce 2 to 3 mm specimens of lung tissue by tearing tissue away from the lung or bronchus. The biopsy is not painful for the patient. It is, however, associated with bleeding, which is usually minor but is occasionally significant or even life threatening.

**Endobronchial**

Endobronchial biopsy of visible lesions through the bronchoscope was shown to be quite sensitive when compared with the aggregate yield of all other available diagnostic modalities, including bronchial brushings and washings, surgical biopsies, bronchoscopic and nonbronchoscopic needle biopsies, pleural fluid cytology, and biopsy of metastases. False negative results are sometimes encountered because a lesion has an overlying necrotic surface or because the process is more than 2 to 3 mm below the mucosal surface. Negative results in a patient who is strongly suspected of having a bronchogenic carcinoma should lead to a repeat procedure and biopsy attempt. CT scanning before the procedure improves the yield (see above).

**Transbronchial**

Transbronchial lung biopsies provide small specimens of lung parenchyma that can be examined histologically and cultured. This technique is commonly used to sample focal and diffuse lesions beyond the range of direct vision. Under fluoroscopic guidance, the biopsy forceps are advanced to a region of interest, and samples are obtained. Usually, four to six individual biopsies provide acceptable diagnostic sensitivity. Transbronchial biopsy for diffuse parenchymal pulmonary disorders is helpful in the diagnosis of granulomatous disorders, such as sarcoidosis, and in infections or metastatic malignancy. However, its value in the evaluation of the nonlymphocytic alveolitides, such as idiopathic interstitial pulmonary fibrosis, is a subject of considerable debate. Chest radiographs are routinely obtained after transbronchial forceps biopsy procedures because pneumothorax complicates 5% to 10% of these cases. Approximately half of patients who experience pneumothorax after transbronchial lung biopsy require chest tube drainage.

**Microbiologic Sampling**

Quantitative culture methods using bronchoalveolar lavage or a protected catheter brush are useful for documenting bacterial pneumonia and providing guidance for antimicrobial therapy. Careful technique must be observed. Recovery of 10⁷ organisms/ml by protected catheter brush, recovery of 10⁶ organisms/ml from the fluid obtained from bronchoalveolar lavage, or the presence of intracellular organisms in more than 2% of alveolar cells usually indicates pneumonia, except in patients with chronic bronchitis or bronchiectasis. In an ICU patient, quantitative cultures are reliable if there has been no change in antibiotics for 48 to 72 hours, and they can be used to prove or exclude significant lung infection when infiltrates and fever of uncertain origin are present. The use of invasive techniques for the diagnosis of bacterial pneumonia remains highly controversial, however; there is no evidence that these procedures improve outcome in severe hospital-acquired pneumonia.

Because appropriate management of community-acquired bacterial pneumonia depends on the rapid (and usually empirical) administration of appropriate antibiotics, these techniques have only limited utility for the diagnosis of pneumonia in this setting. In practice, an invasive and expensive procedure, such as bronchoscopy with quantitative culture, is seldom done before first initiating a trial of antibacterial therapy.

**Transbronchial Needle Aspiration**

Lesions in the pulmonary parenchyma and in the mediastinum may be accessible to bronchoscopic sampling by transbronchial needle aspiration. A 1.3 cm, 22-gauge cytology needle or a 19-gauge cutting needle may be advanced through the sampling channel of a bronchoscope and passed through the bronchial wall to obtain cytologic or histologic material from tumors or adjacent lymph nodes. Transbronchial needle aspiration is particularly useful for the nodal evaluation of intrathoracic malignancy and for pulmonary nodules that are neither central nor peripheral in location. Correlation of endobronchial anatomicity with CT findings is advisable before transbronchial needle aspiration is attempted. Percutaneous transthoracic needle aspiration is still better suited for small peripheral nodules, especially when there is a substantial likelihood of a benign diagnosis.

**Complications of Fiberoptic Bronchoscopy**

When reasonable precautions are taken, the complication rate of fiberoptic bronchoscopy is quite low, and those complications that do occur tend to be minor. Deaths resulting from bronchoscopy are extremely rare. Major complications—chiefly pneumothorax or severe hemorrhage—occur in 0.5% of routine bronchoscopies and about 7% of transbronchial biopsies. Minor complications, including bronchospasm, laryngospasm, epistaxis, and vasovagal syncope, occur in 0.8%. Fever may result when liquid instilled into airways activates alveolar macrophages to release interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α. Significant hypoxemia, occasionally leading to respiratory failure, may be seen in immunocompromised patients, especially those undergoing BAL for AIDS-related opportunistic infections. Myocardial ischemia has been objectively demonstrated to occur in elderly patients who undergo prolonged bronchoscopies. Careful monitoring and attention to oxygenation are needed in such patients. Because of its favorable safety profile, fiberoptic bronchoscopy is routinely performed as an outpatient procedure.

**PERCUTANEOUS TRANSTHORACIC NEEDLE ASPIRATION**

Cutting or cytologic needles may be passed through the chest wall under local anesthesia and fluoroscopic, CT, or ultrasound guidance to obtain tissue samples from the lung, mediastinum,
pleura, chest wall, and hila [see Figure 9]. Percutaneous transthoracic needle aspiration (PTNA) should be considered when fiberoptic bronchoscopy has been unsuccessful in obtaining diagnostic tissue or when a patient is inoperable or refuses thoracotomy for diagnosis. The major risks of both needle procedures are pneumothorax, severe hemoptysis, and air embolism. The risk of pneumothorax is considerably higher in patients with chronic obstructive pulmonary disease and varies directly with the amount of pulmonary parenchyma that must be traversed to reach the lesion in question. Pneumothorax occurs in 25% to 45% of cases, but only 4% to 15% require chest tube placement. Hemoptysis is seen in 2% to 16% of cases. Because bleeding originates from noncompressible sites, coagulopathy remains an absolute contraindication to PTNA or transbronchial needle aspiration. PTNA should not be attempted in patients with pulmonary hypertension, suspected arteriovenous malformations, or echinococcal cysts.

Depending on their design, percutaneous needles can be used either to aspirate a lesion—thereby providing samples for cytologic examination, smear, and culture—or to obtain a core of tissue that can provide material for histologic examination; their use carries a risk of pneumothorax. PTNA has been reported to have an 88% sensitivity and a 99% specificity for malignant lung lesions and to have a 95% sensitivity and an 81% specificity for benign lesions.32

**THORACENTESIS**

Thoracentesis, the aspiration of liquid from the pleural space, is a standard diagnostic technique. A pleural effusion without known cause should be sampled by thoracentesis for diagnostic purposes. The aspirated liquid can be analyzed for the number of red and white blood cells and the white blood cell differential; concentrations of glucose, lactate dehydrogenase, and total protein; appropriate cultures and smears; and, if indicated, cytologic examination of the aspirated liquid. Pleural liquid pH is useful in evaluating parapneumonic effusions. A pH of less than 7.29 (or less than 7.22 in the setting of low probability and higher risk) is associated with a complicated effusion that may require drainage.33 pH paper should not be used; pH should be determined from an aliquot of pleural liquid placed in a heparinized syringe.

The most common complications of thoracentesis are bleeding and pneumothorax. The use of catheter-based thoracentesis kits has led to an increase in the incidence of retained catheters. The risk of complication from thoracentesis is a function of the experience of the operator and may be increased in certain settings, such as in patients with chronic obstructive lung disease or those who have undergone previous radiation therapy. If a single pass is required for the tap, if no air leak is encountered, and if the operator feels the procedure is uncomplicated, the rate of pneumothorax is less than 1%, and a postthoracentesis chest roentgenogram is not necessary.

**PLEURAL BIOPSY**

In contrast to thoracentesis, pleural biopsy should be performed by a specialist. The technique is employed in the evaluation of patients with unexplained exudative pleural effusions. The technique is performed using a large-bore needle with a cutting edge; small (2 to 3 mm) tissue samples are obtained blindly from the parietal pleura. Some pleural liquid must be present to ensure proper placement of the needle in the pleural space and to minimize the risk of lung puncture. Only 40% of submitted closed pleural biopsy specimens actually contain pleural tissue. It is advisable to submit tissue from at least six separate passes to obtain optimal diagnostic sensitivity. Its value is greatest in establishing the diagnosis of postprimary tuberculosis involvement of the pleura: with an adequate number of biopsies submitted for microbiologic and histologic examination, closed pleural biopsy has a sensitivity of 87% for the diagnosis of tuberculous pleurisy (60% culture, 80% histology).34 The diagnostic yield of biopsy in confirming malignant invasion of the pleura is only slightly greater than that obtained through cytologic examination of the aspirated liquid.

The major contraindication for these techniques is a bleeding disorder, because it is impossible to apply pressure to a pleural bleeding site without performing an open surgical procedure.

**THORACOSCOPY**

Thoracoscopy is currently employed in the diagnosis of pleural and mediastinal disorders, for the introduction of talc pleurodesis in the management of malignant pleural effusion or recurrent spontaneous pneumothorax, and for the evacuation of partially loculated empyema. Thoracoscopy has been successfully applied as an alternative to open lung biopsy in the evaluation of diffuse interstitial lung disease, for solitary pulmonary nodules, and for lung volume reduction surgery for advanced emphysema.35 The technique requires access to the pleura through one or more small intercostal incisions, induction of artificial pneumothorax, and examination through a rigid thoracoscope (medical thoracoscopy) or via telescope attached to a video camera (video-assisted thoroscopic surgery, or VATS). Medical thoracoscopies can be performed in an endoscopy suite under local anesthesia and conscious sedation, whereas VATS usually requires general anesthesia and double-lumen intubation in the operating room. Complication rates are higher than for mediastinoscopy, and hospital stays are longer.

Thoracoscopy should be undertaken for mediastinal disorders only when lesions are inaccessible to the mediastinoscope.

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Mortality from medical thoracoscopy is reported to be 1% to 5%. Thoracoscopy has a 2% to 3% rate of complications, including prolonged air leak and pleural effusion. Empyema, significant bleeding, and tumor seeding of incisions are also reported. Approximately 10% of thoracoscopies require conversion to open thoracotomy to manage unexpected findings. For this reason, most experts recommend that all thoracoscopic procedures be performed by a thoracic surgeon.

MEDIASTINOSCOPY

Mediastinoscopy and anterior mediastinal exploration through a limited superior parasternal incision (mediastinotomy) are surgical procedures used for diagnostic biopsy of mediastinal masses and the staging of carcinoma of the lung. Mediastinoscopy is performed under general anesthesia and requires a small transverse incision just above the suprasternal notch. Blunt dissection along the pretracheal fascial plane is performed, and paratracheal lymph nodes can be sampled. Mediastinoscopy is especially suited for evaluation of the superior and anterior mediastinum. Mediastinoscopic access to posterior, subcarinal, and some para-aortic nodes is difficult and often necessitates an open exploration through a left-sided second intercostal space incision, the so-called Chamberlain procedure.

Mediastinoscopy is indicated in the nodal staging of lung cancer for superior sulcus tumors; for small cell cancer being considered for resection; for patients with poor ventilatory reserve in whom CT results are discordant with the expected likelihood of nodal metastasis; in evaluation of the superior vena cava syndrome (previously thought to be an absolute contraindication); and in settings of clinical uncertainty.

OPEN LUNG BIOPSY

Noninvasive diagnostic studies are subject to sampling error because of the size of the sample and the frequent nonhomogeneity of the pathologic process of interest. Samples may be crushed or distorted, leading to difficulty in pathologic interpretation. Biopsy by open thoracotomy provides the best obtainable specificity and sensitivity but at the cost of the risk of the open procedure and a painful intercostal incision. Histologic diagnoses are possible in 85% to 95% of cases. New or unexpected diagnoses may be made in almost half of these cases. Surgical mortality is reported in the range of 0% to 13% in immunocompetent patients but as high as 25% to 65% in immunocompromised and mechanically ventilated patients. Mortalitv is higher when open lung biopsy is performed on an emergent rather than an elective basis. Significant morbidity may occur in another 25% to 50% of patients.

Open biopsy should be considered when the overall prognosis is good, when less invasive modalities have failed to provide a useful diagnosis, and when an empirical therapeutic trial has not resulted in clinical improvement. Decisions for open lung biopsies, however, should give considerable weight as to whether a definitive diagnosis will change therapy and whether that therapy can be expected to lead to improvement in survival. An Israeli study of open lung biopsy in diffuse lung disease reported an 18% benefit, as defined above, at the cost of 13% mortality in immunocompetent patients. For immunocompromised patients, the benefit was 46% but at the cost of 39% operative mortality.

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