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**Chapter 19**

**HYPOXEMIA AND HYPERCAPNIA**

Over the course of an average ICU stay, about 125 laboratory measurements are performed on each patient, requiring an average of 550 mL of blood per patient (enough to drop the hemoglobin level by 3 g/dL) (1). The most frequently performed laboratory test in the ICU is the arterial blood gas measurement (the simultaneous measurement of P02' $PC0_2$, and pH in arterial blood) (2). This chapter focuses on two abnormalities in the blood gas measurement: a low arterial $P0_2$ (hypoxemia) and an elevated arterial $PC0_2$ (hypercapnia). The first part of the chapter describes the relationship between arterial blood gases (P02 and $PC0_2$) and pulmonary gas exchange, and the second part of the chapter presents a physiological approach to identify the sources of hypoxemia and hypercapnia in the individual patient.

**PULMONARY GAS EXCHANGE**

The adequacy of gas exchange in the lungs is determined by the balance between pulmonary ventilation and capillary blood flow (3-5). This balance is commonly expressed as the ventilation-perfusion (V /Q) ratio. The influence of V /Q ratios on pulmonary gas exchange can be described using a schematic alveolar-capillary unit, as shown in Figure 19.1. The upper panel shows a perfect match between ventilation and perfusion (V /Q = 1). This is the reference point for defining the abnormal patterns of gas exchange.

*Dead Space Ventilation*

A V /Q ratio above 1.0 (Fig. 19.1, middle panel) describes the condition where ventilation is excessive relative to capillary blood flow. The excess ventilation, known as *dead space ventilation,* does not participate in gas exchange with the blood. There are two types of dead space ventilation.

*Anatomic dead space* is the gas in the large conducting airways that does not come in contact with capillaries (approximately 50% of the anatomic dead space is in the pharynx).

*Physiologic dead space* is the alveolar

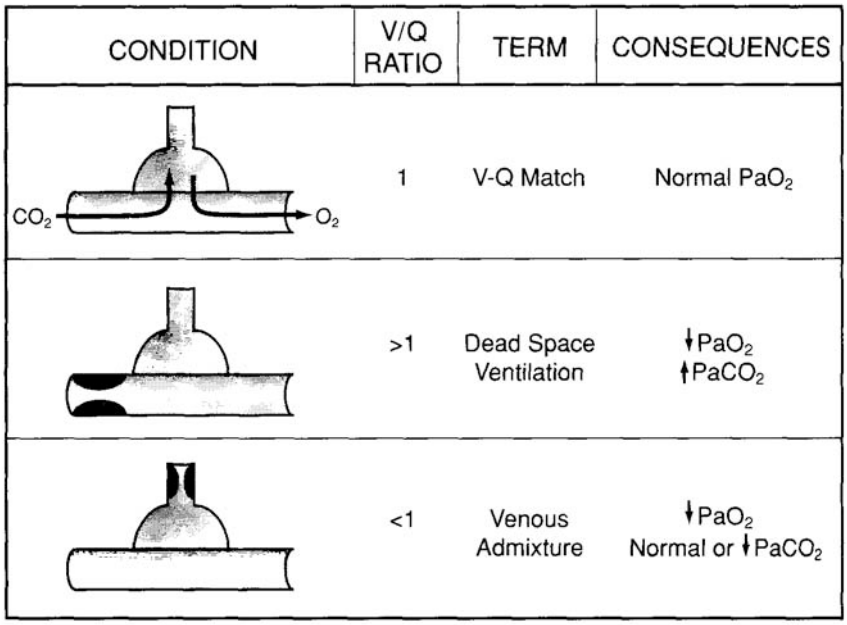


**FIGURE 19.1** Ventilation–perfusion ($V/Q$) relationships and associated blood gas abnormalities.

gas that does not equilibrate fully with capillary blood. In normal subjects, dead space ventilation (V D) accounts for 20 to 30% of the total ventilation ($V_T$), so $VD/V_T$ = 0.2 to 0.3 (3,5).

*Pathophysiogy*

Dead space ventilation increases when the alveolar-capillary interface is destroyed (e.g., emphysema), when blood flow is reduced (e.g., low cardiac output), or when alveoli are overdistended (e.g., positive-pressure ventilation).

*Arterial Blood Gases*

An increase in V *D/V* T above 0.3 results in both hypoxemia and hypercapnia (analogous to what would happen if you held your breath). The hypercapnia usually appears when the V *D/V* T rises *above* 0.5 (5).

Intrapulmonary Shunt

A V *IQ* ratio below 1.0 (Fig. 19.1, lower panel) describes the condition where capillary blood flow is *excessive* relative to ventilation. The excess blood flow, known as *intrapulmonary shunt,* does not participate in pulmonary gas exchange. There are two types of intrapulmonary shunt. *True shunt* indicates the total absence of exchange between capillary blood and alveolar gas (V *IQ* = 0), and is equivalent to an anatomic shunt

between the right and left sides of the heart. *Venous admixture* represents the capillary flow that does not equilibrate completely with *alveolar* gas ($0 < V\ IQ < 1$). As the venous admixture increases, the V *IQ* ratio decreases until it reaches true shunt conditions ($V / Q = 0$).

The fraction of the cardiac output that represents intrapulmonary shunt is known as the *shunt fraction.* In normal subjects, intrapulmonary shunt flow (Qs) represents less than 10% of the total cardiac output (Qt), so the shunt fraction *(Qs/Qt)* is less than 10% (3,4,6).

*Pathophysiology*

Intrapulmonary shunt fraction increases when small airways are occluded (e.g., asthma), when alveoli are filled with fluid (e.g., pulmonary edema, pneumonia), when alveoli collapse (e.g., atelectasis), or when capillary flow is excessive (e.g., nonemboli2ed regions of lung in pulmonary embolism).

*Arterial Blood Gases*

The influence of shunt fraction on arterial oxygen and carbon dioxide tensions ($Pa0_2$, $PaC0_2$, respectively) is shown in Figure 19.2. The $Pa0_2$ falls progressively as shunt fraction increases, but the $PaC0_2$ remains constant until the shunt fraction exceeds 50% (6). The $PaC0_2$ is often below normal in patients with increased intrapulmonary shunt as a result of hyperventilation triggered by the disease process (e.g., sepsis) or by the accompanying hypoxemia.

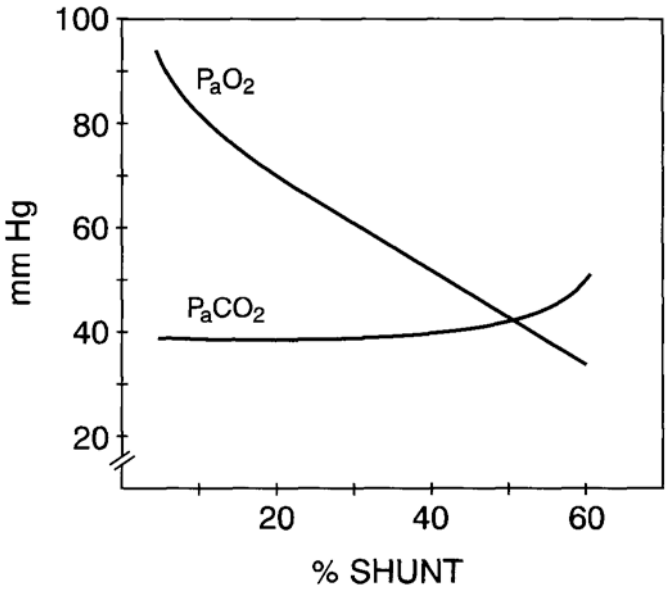


**FIGURE 19.2** The influence of shunt fraction on arterial $PO_2$ ($PaO_2$) and arterial $PCO_2$ ($PaCO_2$). (From D'Alonzo GE, Dantzger DR. Mechanisms of abnormal gas exchange. Med Clin North Am 1983;67:557–571.)

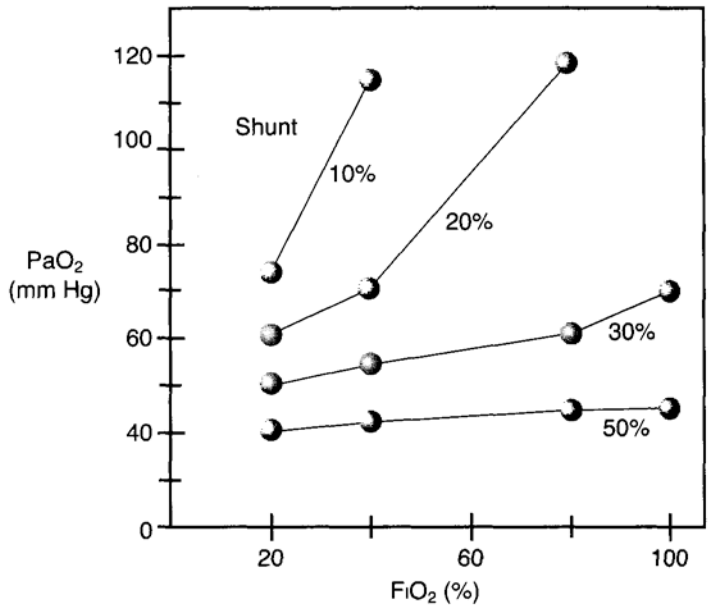


**FIGURE 19.3** The influence of shunt fraction on the relationship between the inspired oxygen ($FIO_2$) and the arterial $PO_2$ ($PaO_2$). (From D'Alonzo GE, Dantzger DR. Med Clin North Am 1983;67:557–571.)

*Inhaled Oxygen*

The shunt fraction also determines the influence of inhaled oxygen on the arterial $P0_2$. This is shown in Figure 19.3 (6). As intrapulmonary shunt increases from 10 to 50%, an increase in fractional concentration of inspired oxygen ($Fi0_2$) produces less of an increment in the arterial $P0_2$. When the shunt fraction exceeds 50%, the arterial $P0_2$ is independent of changes in Fr02' and the condition behaves like a true (anatomic) shunt. This means that, *in conditions associated with a high shunt fraction* (e.g., acute respiratory distress syndrome), *the FI02 can often be lowered to non-toxic levels ($FI0_2$ below 50%) without further compromising arterial oxygenation.* This can be a valuable maneuver for preventing pulmonary oxygen toxicity.

**QUANTITATIVE MEASURES**

The following derived variables are used to determine the presence and severity of gas exchange abnormalities in the lungs.

*Dead Space Ventilation*

The calculation of dead space ventilation (VD / V *T)* is based on the difference between the $PC0_2$ in exhaled gas and end-capillary (arterial)

blood. In the normal lung, the capillary blood equilibrates fully with alveolar gas, and the exhaled $PCO_2$ ($PECO_2$) is equivalent to the arterial $PCO_2$ ($PaCO_2$)' As dead space ventilation ($VD/V_T$) increases, the $PECO_2$ decreases relative to the $PaCO_2$. The Bohr equation shown below (derived by Christian Bohr, father of Neils Bohr) is based on this principle.

*Vd/Vt = PaC02 – PEC02 / PaC02*

Thus, when the $PECO_2$ decreases relative to the $PaCO_2$' the calculated V D/V T rises. The $PECO_2$ is measured in a random sample of expired gas (mean exhaled $PCO_2$)' and is not measured at the end of expiration (endtidal *PCO2)'*

**Intrapulmonary Shunt Fraction**

The intrapulmonary shunt fraction (Qs/Qt) is derived by the relationship between the *02* content in arterial blood $(CaO_2)'$ mixed venous blood ($CvO_2$)' and pulmonary capillary blood $(CcO_2)'$

Qs/Qt = CcO2- CaO / CcO2– Cv02

The problem with this formula is the inability to measure the pulmonary capillary *02* content $(CcO_2)$ directly. As a result, pure oxygen breathing (to produce 100% oxyhemoglobin saturation in pulmonary capillary blood) is recommended for the shunt calculation. *However* in this situation, Qs/Qt measures only true shunt.

**The A-a *PO2* Gradient**

The *PO2* difference between alveolar gas and arterial blood $(PAO_2$ $PaO_2)$ is an indirect measure of ventilation-perfusion abnormalities (7-9). The $PAO_2$ - $PaO_2$ (A-a *p02)* gradient is determined with the alveolar gas equation shown below.

$PAO_2 = PIO_2$ - (PaCO2/RQ) (19.3)

This equation defines the relationship between the *PO2* in alveolar gas $(PAO_2)'$ the *PO2* in inhaled gas $(PIO_2)'$ the $PCO_2$ in arterial blood ($PaCO_2$)' and the respiratory quotient (RQ). The RQ defines the relative rates of exchange of *02* and *CO2* across the alveolar-capillary interface:

RQ = VCO2/$VO_2$' The $PIO_2$ is determined using the fractional concentration of inspired oxygen (FIO2), the barometric pressure (P B) and the partial pressure of water vapor (P $H_2O$) in humidified gas:

*PIO2 = FIO2* (PB- PH20) (19.4)

TABLE 19.1 Normal Arterial Blood Gases

| Age (years) | $Pa0_2$ (mm Hg) | $PaC0_2$ (mm Hg) | A-a $P0_2$ (mm Hg) |
|---|---|---|---|
| 20 | 84-95 | 33-47 | 4-17 |
| 30 | 81-92 | 34-47 | 7-21 |
| 40 | 78-90 | 34-47 | 10-24 |
| 50 | 75-87 | 34-47 | 14-27 |
| 60 | 72-84 | 34-47 | 17-31 |
| 70 | 70-81 | 34-47 | 21-34 |
| 80 | 67-79 | 34-47 | 25-38 |

All values pertain to room air breathing at sea level.
From the Intermountain Thoracic Society Manual of Uniform Laboratory
Lake Citv. 1984:44-45.

If equations 19.3 and 19.4 are combined (for the alveolar p02), the A - a PO2 gradient can be calculated as follows:

$$\text{A-a } PO2 = [FIO_2 (P_B - PH20) - (PaCO/RQ)] - PaO_2$$

In a healthy subject breathing room air at sea level, $FIO2 = 0.21$, $P_B = 760$ mm Hg, $PH20 = 47$ mm Hg, $PaO_2 = 90$ mm Hg, $PaCO_2 = 40$ mm Hg, and $RQ = 0.8$:

A-a PO2 = [0.21 (760 - 47) - *(40/0.8)]* - 90 = 10 mm Hg 09.6) This represents an idealized rather than normal A-a $P0_2$ gradient, because the A-a PO2 gradient varies with age and with the concentration of inspired oxygen.

*Influence of Age*
As shown in Table 19.1, the normal A-a PO2 gradient rises steadily with advancing age (8). Assuming that most adult patients in an lCU are 40 years of age or older, the normal A-a PO2 gradient in an adult leU patient can be as high as 25 mm Hg when the patient is breathing room air. *However,* few lCU patients breathe room air and the A-a PO2 gradient is increased further when oxygen is added to inhaled gas.

*Influence of Inspired Oxygen*
The influence of inspired oxygen on the A-a PO2 gradient is shown in Figure 19.4 (9). The A-a PO2 gradient increases from 15 to 60 mm Hg as the *PlO2* increases from 21 % (room air) to 100%. According to this relationship, the normal A-a *PO2* gradient increases 5 to 7 mm Hg for every 10% increase in FIO2. This effect is presumably caused by the loss of regional hypoxic vasoconstriction in the lungs. Hypoxic vasoconstriction in poorly ventilated lung regions diverts blood to more adequately ventilated regions, and this helps to preserve the normal V *IQ* balance.

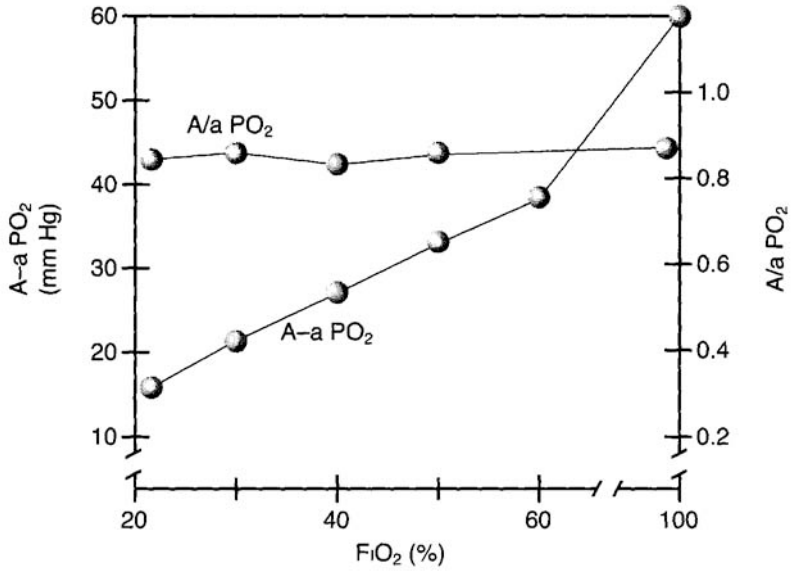


**FIGURE 19.4** The influence of $FiO_2$ on the alveolar-arterial $PO_2$ gradient (A-a $PO_2$) and the arterial–alveolar $PO_2$ ratio (a/A $PO_2$) in normal subjects. (From Reference 9.)

Loss of regional hypoxic vasoconstriction during supplemental oxygen breathing maintains blood flow in poorly ventilated lung regions, and this increases intrapulmonary shunt fraction and increases the A-a *PO2* gradient.

*Positive-Pressure Ventilation*

Positive-pressure mechanical ventilation elevates the pressure in the airways above the ambient barometric pressure. Therefore, when determining the A-a *PO2* gradient in a ventilator-dependent patient, the mean airway pressure should be added to the barometric pressure (10). In the example presented previously, a mean airway pressure of 30 cm *H2O* would increase the A-a *PO2* gradient from 10 to 16 mm Hg (a 60% increase). Thus, neglecting the contribution of positive airway pressure during mechanical ventilation will underestimate the degree of abnormal gas exchange.

The a/ A *PO2* Ratio

Unlike the A-a *PO2* gradient, the a/A *PO2* ratio is relatively unaffected by the *FIO2.* This is demonstrated in Figure 19.5. The independence of the a/ A *PO2* gradient in relation to the $FIO_2$ is explained by the equation below.

a/ A *PO2* = 1 - (A-a *PO2*) /$PaO_2$

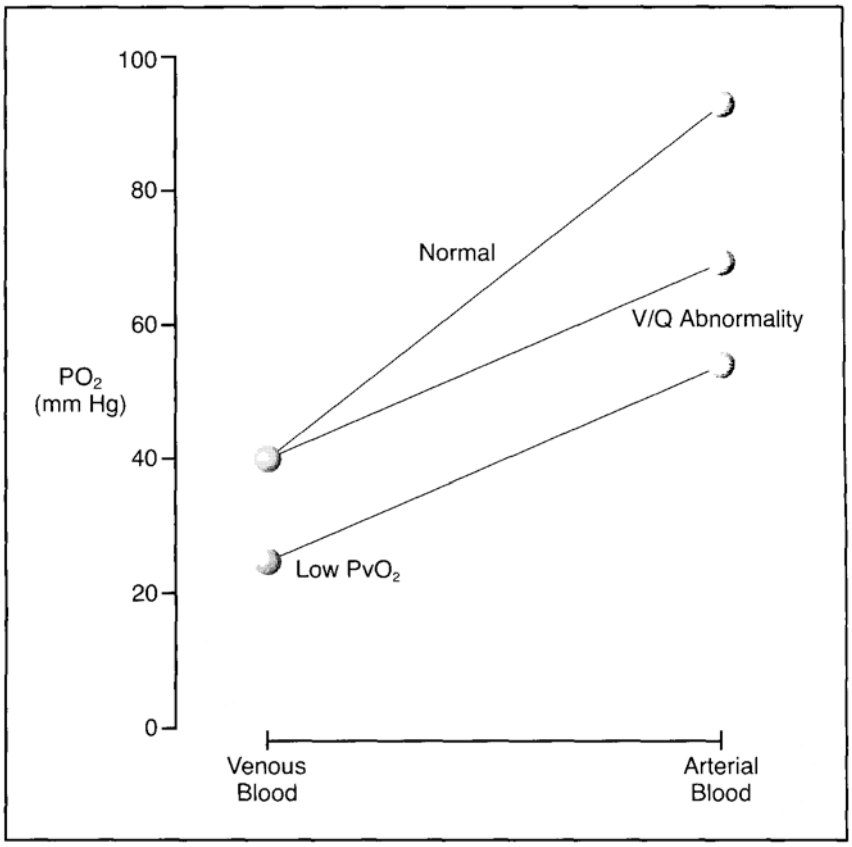


**FIGURE 19.5** The influence of a V/Q abnormality on the transition from venous to arterial $PO_2$ and the added effect of a low mixed venous $PO_2$ ($PvO_2$).

Because the alveolar *P02* is in both the numerator and denominator of the equation, the influence of *FIO2* on the $PaO_2$ is eliminated. Thus, the alA $P0_2$ ratio is a mathematical manipulation that eliminates the influence of $FIO_2$ on the A-a *p02* gradient. The normal a/A PO2 ratio is 0.74 to 0.77 when breathing room air, and 0.80 to 0.82 when breathing 100% oxygen (9).

The $PaO/FIO_2$ Ratio

The $PaO/FIO_2$ ratio is used as an indirect estimate of shunt fraction. The following correlations have been reported (1).

| $PaO/FI0_2$ | Qs/Qt |
|---|---|
| <200 | >20% |
| >200 | <20% |

TABLE 19.2 Spontaneous Blood-Gas Variability

| Variation | $Pa0_2$ | $PaC0_2$ |
|---|---|---|
| Mean | 13 mm Hg | 2.5 mm Hg |
| 95th Percentile | +/-18 mm Hg | +/- 4 mm Hg |
| Range | 2-37 mm Hg | 0-12 mm Hg |

Represents variation over a 1-hour period in 26 ventilator-dependent trauma were clinically stable.
From Hess D, Agarwal NN. Variability of blood gases, pulse oximeter end-tidal carbon dioxide pressure in stable, mechanically ventilated trauma J Clin Monit 1992:8: 111.

The major limitation of the $PaO/FIO_2$ ratio is the variability of the $FIO_2$ when supplemental oxygen is delivered through nasal prongs or a face mask (see Chapter 21). This limitation also applies to the A-a PO2 gradient.

**BLOOD GAS VARIABILITY**

Arterial blood gases can *vary* spontaneously without a change in the clinical condition of the patient. This is demonstrated in Table 19.2, which shows the spontaneous variation in arterial PO2 and $PCO_2$ *over* a onehour period in a group of clinically stable trauma victims (2). Note that the arterial PO2 varied by as much as 36 mm Hg, while the arterial $PCO_2$ varied by as much as 12 mm Hg. This *variability* has also been observed in patients in a medical ICU (3). Because arterial blood gases can vary spontaneously without a change in the clinical condition of the patient, routine monitoring of arterial blood gases can be misleading and is not justified.

**HYPOXEMIA**

The causes of hypoxemia can be separated into 3 groups based on the physiological process involved (14,15). Each group of disorders can be distinguished by the A-a *PO2* gradient and/ or the mixed venous PO2' as shown in Table 19.3.

TABLE 19.3 Sources of Hypoxemia

| Source | A-a $P0_2$ | $pv0_2$ |
|---|---|---|
| Hypoventilation | Normal | Normal |
| *V/Q* mismatch | Increased | Normal |
| DO2/V02 imbalance | Increased | Decreased |

TABLE 19.4 Alveolar Hypoventilation in the leu

*Brainstem respiratory depression*

1. Drugs (e.g., opiates)
2. Obesity-hypoventilation syndrome

*Peripheral neuropathy*

1. Critical illness polyneuropathy
2. Guillain-Barre syndrome

*Muscle weakness*

1. Critical illness myopathy
2. Hypophosphatemia
3. Magnesium depletion
4. Myasthenia gravis

**Hypoventilation**

Alveolar hypoventilation causes both hypoxemia and hypercapnia as a result of a decrease in the total volume of air inhaled (and exhaled) each minute. There is no V /Q imbalance in the lungs, so the A-a *PO2* gradient is not elevated. The common causes of alveolar hypoventilation are listed in Table 19.4. Most cases of hypoventilation in the ICU are the result of drug-induced respiratory depression or neuromuscular weakness. Obesity-related hypoventilation (Pickwickian syndrome) is present in uR to one third of morbidly obese patients (body mass index >35 kg/m) (6), and this disorder is likely to become much more common as the ranks of the obese continue to grow steadily in number.

*Respiratory Muscle Weakness*

Most cases of respiratory muscle weakness in the lCU are the result of an idiopathic polyneuropathy and myopathy that is specific to lCU patients, particularly those with sepsis, prolonged mechanical ventilation, and prolonged neuromuscular paralysis (7). (This is described in Chapter 51). The standard method of evaluating respiratory muscle strength is to measure the *maximum inspiratory pressure* (PImax), which is the maximum pressure recorded during a maximum inspiratory effort against a closed valve. The normal PImax varies with age and gender, but most healthy adults can generate a negative PImax of at least 80 cm H2O (8). A PImax that does not exceed -25 cm *H2O* is considered evidence of respiratory muscle failure (9). (See Chapter 51 for more information on neuromuscular weakness syndromes in the ICU.)

V /Q Abnormality

Most cases of hypoxemia are the result of a V/Q mismatch in the lungs. Virtually any lung disease can be included in this category, but the

common ones encountered in the ICU are pneumonia, inflammatory lung injury (acute respiratory distress syndrome), obstructive lung disease, hydrostatic pulmonary edema, and pulmonary embolism. The A-a PO2 gradient is almost always elevated in these conditions, but the elevation can be minimal in patients with severe airways obstruction (which behaves like hypoventilation).

**$DO/VO_2$ Imbalance**

As explained in Chapter 2, a d,~crease in systemic *O2* delivery (DO2) is usually accompanied by an increase in *O2* extraction from capillary blood, and this serves to maintain a constant rate of *O2* uptake ($VO_2$) into the tissues. The increased *O2* extraction from capillary blood results in a decrease in the p02 of venous blood, and this can have a deleterious effect on arterial oxygenation, as explained below.

*Mixed Venous p02*

The oxygen in arterial blood represents the sum of the oxygen in mixed venous (pulmonary artery) blood and the oxygen added from alveolar gas. When gas exchange is normal, the p02 in alveolar gas is the major determinant of the arterial p02, However when gas exchange is impaired, the contribution of the alveolar p02 declines and the contribution of the mixed venous p02 rises (20). The greater the impairment in gas exchange, the greater the contribution of the mixed venous *p02* to the arterial p02, (If there is no gas exchange in the lungs, the mixed venous *p02* would be the sole determinant of the arterial *p02.)*

The diagram in Figure 19.5 demonstrates the influence of mixed venous p02 on the arterial p02 when gas exchange is impaired. The curves in the graph represent the transition from mixed venous p02 to arterial p02 in the lungs. The slope of each curve reflects the efficiency of gas exchange in the lungs. Note that the curve representing the V/Q abnormality results in a lower arterial p02 because the slope is decreased (indicating impaired oxygen exchange in the lungs) when compared to the normal curve. If this curve begins at a lower mixed venous PO" as indicated, the *curve* shifts downward, resulting in a further decreas-e in arterial pal' This illustrates how a decrease in mixed venous p02 can aggravate the hypoxemia caused by a V /Q abnormality. It also indicates that, in the presence of a V /Q abnormality, the mixed venous p02 is an important consideration in the evaluation of hypoxemia.

The relationship between *O2* delivery ($DO_2$)' *O2* uptake (V02) and the mixed venous p02 ($PvO_2$) is shown below (k is the proportionality constant).

$$PvO_2 = k \times (DO/VO_2)$$

Thus, any condition that reduces $DO_2$ (e.g., low cardiac output, anemia) or increases V02 (e.g., hypermetabolism) can decrease the $PvO_2$ and aggravate the hypoxemia caused by abnormal gas exchange in the lungs.

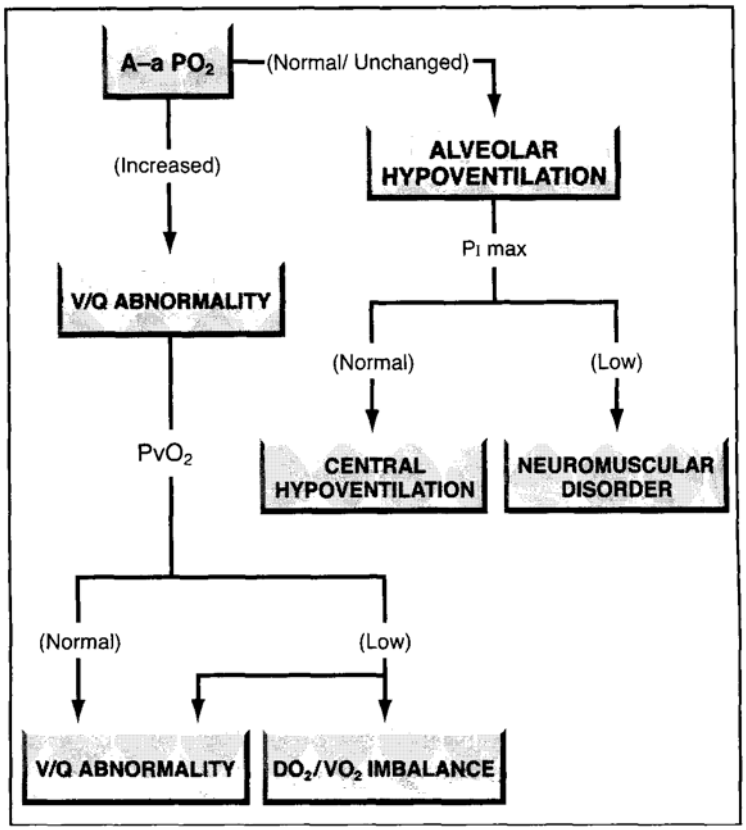


**FIGURE 19.6** Flow diagram for the evaluation of hypoxemia.

## Diagnostic Evaluation

The evaluation of hypoxemia can proceed according to the flow diagram in Figure 19.6. This approach uses three measures: A-a *p02* gradient, mixed venous p02, and maximum inspiratory pressure. The p02 in superior vena cava blood (central venous *p02)* can be used as the mixed venous *O2* when there is no indwelling pulmonary artery catheter.

### *Step I : A-a p02 Gradient*

The first step in the approach involves a determination of the A-a PO2 gradient. After correcting for age and $FIO_2$' the A-a *p02* gradient can be interpreted as follows:
*Normal A-a PO2:* Indicates a hypoventilation disorder rather than a cardiopulmonary disorder. In this situation, the most likely problems are drug-induced respiratory depression and neuromuscular weakness. The latter condition can be uncovered by measuring the maximum inspiratory pressure (PImax). This measurement is described in the upcoming section on hypercapnia.

*Increased A-a PO2:* Indicates a Y /Q abnormality (cardiopulmonary disorder) and/or a systemic DO/V02 imbalance. The mixed venous (or central venous) *p02* will help to differentiate between these two disorders.

*Step* 2: *Mixed Venous PO 2*
When the A-a gradient is increased, the *p02* should be measured in a blood sample taken from a central venous catheter or the distal port of a pulmonary artery catheter.

*Normal venous PO2:* If the venous p02 is 40 mm Hg or higher, the problem is solely a V /Q mismatch in the lungs.

*Low venous PO2:* If the venous p02 is below 40 mm Hg, there is a $DO/VO_2$ imbalance adding to the hypoxemia created by a Y /Q mismatch in the lungs. The source of this imbalance is either a decreased $DO_2$ (from anemia or a low cardiac output) or an increased VO2 (from hypermetabolism).

*Spurious Hypoxemia*
Spurious hypoxemia is a rarely reported phenomenon that is characteri2ed by hypoxemia in an arterial blood sample without corresponding hypoxemia in circulating blood (as measured by pulse oximetry) (21). This phenomenon seems to occur only in patients with hematologic malignancies who have marked leukocytosis (WBC > 100,000) or thrombocytosis (platelet count> 1,000,000). The reduced *p02* in the blood sample has been attributed to *O2* consumption by activated leukocytes in the sample; a process that has been called *leukocyte larceny* (22). While this is the prevailing explanation, it doesn't explain why marked thrombocytosis can also produce spurious hypoxemia because platelets are not oxygengu22lers like activated leukocytes. Regardless of the mechanism, there is no accepted method of preventing spurious hypoxemia (rapid cooling of blood samples has had inconsistent results), so you should be aware of the phenomenon and the value of pulse oximetry for validating in vitro *p02* measurements (pulse oximetry is described in the next chapter).

**HYPERCAPNIA**
Hypercapnia is defined as an arterial $PCO_2$ above 46 mm Hg that does not represent compensation for a metabolic alkalosis (23). The causes of hypercapnia can be identified by considering the determinants of arterial $PC0_2$ ($PaC0_2$). The $PaCO_2$ is directly related to the rate of *CO2* production ($VCO_2$) in the body, and is inversely related to the rate of *CO2* elimination by alveolar ventilation (VA) (3,18). Therefore, $PaCO_2 = k \times (VCO\ 2/V_A)$, where *k* is a proportionality constant. Alveolar ventilation is the portion of the total ventilation (V E) that is not dead space ventilation ($Vo/V_r$); that is, $VA = V_E\ O - VD/V_r$). Combining these relationships yields Equation 19.8, which identifies the determinants of $PaCO_2$:

$$PaCO_2 = k \times [VCO2 /VE( 1 - VD/V_T)]$$

This equation identifies three major sources of hypercapnia: (a) increased $CO_2$ production ($VC0_2$), (b) hypoventilation 1/VE), and (c) increased dead space ventilation (VD/VT)'

*Hypoventilation*
Hypoventilation was discussed briefly in the last section on hypoxemia, and Table 19.4 shows the common causes of hypoventilation. Because hypoxemia is so common in ICU patients, hypercapnia may be the first sign of hypoventilation from neuromuscular weakness or drug-induced respiratory depression in the ICU. This is also the case in obesity-hypoventilation syndrome, where hypercapnia while awake is often the first evidence of daytime hypoventilation. On the other hand, hypercapnia is a relatively late sign in neuromuscular disorders, and does not appear until the maximum inspiratory pressure (described in the hypoxemia section) falls to levels below 50% of normal (9).

**V / Q Abnormality**
As mentioned earlier, hypercapnia is not a feature of increased intrapulmonary shunt until late in the process (which is why hypercapnia is not a feature of pulmonary edema or other infiltrative lung processes until they are far advanced). Hypercapnia is more a feature of increased dead space ventilation (such as occurs in *advanced* emphysema, where there is destruction of the alveolar-capillary interface), and the $PaCO_2$ usually begins to rise when dead space ventilation accounts for more than 50% of total ventilation (VD/ VT > 0.5).

*Increased CO2 Production*
An increase in *CO2* production is usually related to oxidative metabolism, but non-metabolic *CO2* production is possible when extracellular acids generate hydrogen ions that combine with bicarbonate ions and generate *CO2'* Whatever the source, increased *CO2* production is normally accompanied by an increase in minute ventilation, which eliminates the excess *CO2* and maintains a constant arterial $PCO_2$. Therefore, excess *CO2* production does not normally cause hypercapnia. However when *CO2* excretion is impaired (by neuromuscular weakness or lung disease), an increase in *CO2* production can lead to an increase in $PaC0_2$. Thus, increased *CO2* production is an important factor in promoting hypercapnia only in patients with a reduced ability to eliminate *CO2'*

*Overfeeding*
Overfeeding, or the provision of calories in excess of daily needs, is a recogni2ed cause of hypercapnia in patients with *severe* lung disease and acute respiratory failure (24). Nutrition-associated hypercapnia occurs predominantly in ventilator-dependent patients, and can delay weaning from mechanical ventilation. Overfeeding with carbohydrates is particularly problematic because *oxidative* metabolism of carbohydrates

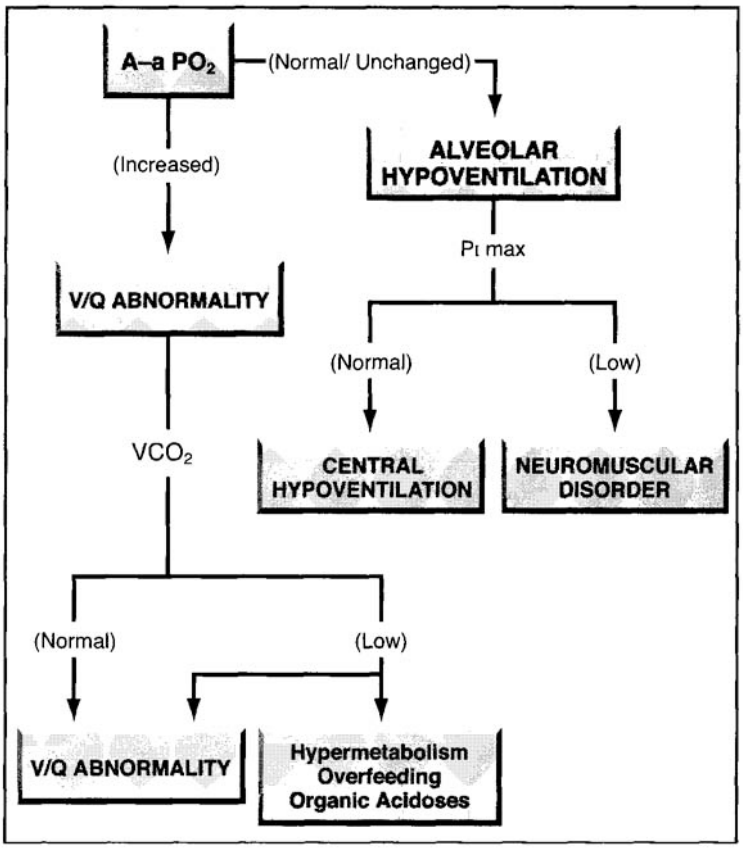


**FIGURE 19.7** Flow diagram for the evaluation of hypercapnia.

generates more carbon dioxide than the other nutrient substrates (lipids and proteins).

**Diagnostic Evaluation**

The bedside evaluation of hypercapnia is shown in Figure 19.7. The evaluation of hypercapnia, like hypoxemia, begins with the A-a *p02* gradient (25). A normal or unchanged A-a *p02* gradient indicates that the problem is alveolar hypoventilation (the same as described for the evaluation of hypoxemia). An increased A-a p02 gradient indicates a V /Q abnormality (an increase in dead space ventilation) that mayor may not be accompanied by an increase in *CO2* production.

*Measuring C02 Production*

The rate of $CO_2$ production ($YCO_2$) can be measured at the bedside with speciali2ed metabolic carts that are normally used to perform nutritional

assessments. These carts are equipped with infrared devices that can measure the *CO2* in expired gas (much like the end-tidal *CO2* monitors described in Chapter 20), and can determine the volume of *CO2* excreted per minute. In steady-state conditions, the rate of CO, excretion is equivalent to the $VCO_2$. The normal $VC02_2$ is 90 to 130 L/minute/$m^2$, which is roughly 80% of the $V0_2$. As mentioned earlier, an increased $YC0_2$ is evidence for one of the following conditions: generalized hypermetabolism, overfeeding (excess calories), or organic acidoses.

**A FINAL WORD**

The measurement of arterial blood gases ($P0_2$ and $PC0_2$) enjoys a popularity that is undeserved, and this is particularly true for the arterial p02, **It** is important to remember that the arterial *p02* is not a useful measure for determining the amount of oxygen in the blood (this requires the hemoglobin concentration and the percent saturation of hemoglobin with oxygen, as described in Chapter 2). Instead, the $Pa0_2$ (along with the $PaCO_2$) can be useful for evaluating gas exchange in the lungs. A more useful measurement for evaluating the oxygenation of blood is the pulse oximeter measurement of arterial oxyhemoglobin saturation (described in the next chapter).

**REFERENCES**

**Chapter 20**

**OXIMETRY AND CAPNOGRAPHY**

The noninvasive detection of blood gases *(P02, $PCO_2$)* using optical and colorimetric techniques (1,2) is the most significant and useful advance in critical care monitoring in the last quarter century. This chapter describes the monitoring techniques that have become an integral part of daily patient care in the ICU (and in most other areas of the hospital as well). Despite the popularity of these techniques, surveys reveal that 95% of ICU staff members have little or no understanding of how the techniques work (3).

**OXIMETRY**

All atoms and molecules absorb specific wavelengths of light (this is the source of color in the lighted world). This property is the basis for an optical technique known as *spectrophotometry,* which transmits light of specific wavelengths through a medium to determine the molecular composition of the medium. The absorption of light as it passes through a medium is proportional to the concentration of the substance that absorbs the light and the length of the path that the light travels (this is known as the Lambert-Beer Law). The application of this principle to the detection of hemoglobin in its different forms is known as *oximetry.*

*Optical Recognition of Hemoglobin*

Hemoglobin (like all proteins) changes its structural configuration when it participates in a chemical reaction, and each of the configurations has a distinct pattern of light absorption. The patterns of light absorption for the different forms of hemoglobin are shown in Figure 20.1. Four different forms of hemoglobin are represented in the figure: oxygenated hemoglobin *($HbO_2$)* deoxygenated hemoglobin (Hb), methemoglobin (met Hb) and carboxyhemoglobin (COHb). Comparing the oxygenated and deoxygenated forms of hemoglobin *($HbO_2$* and Hb) shows that, in the red region of the light spectrum (660 nm), *$HbO_2$* does not absorb light

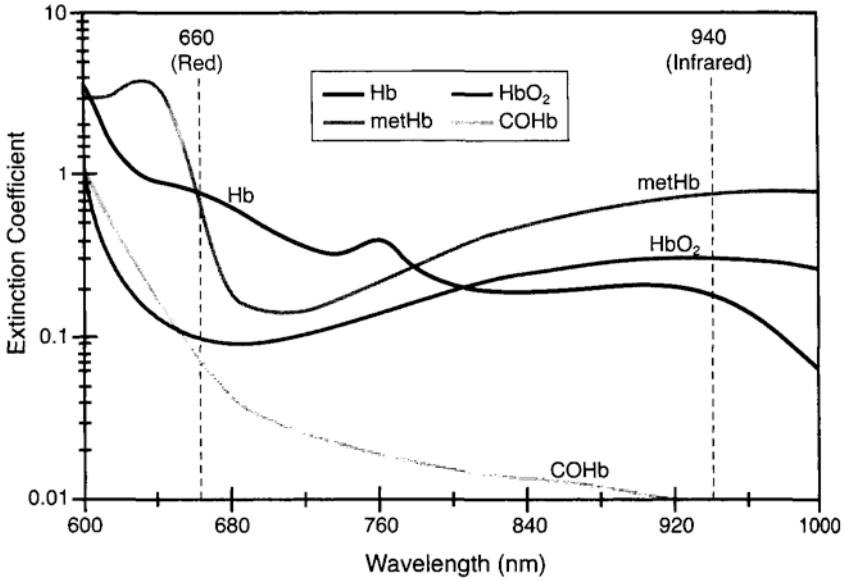


**FIGURE 20.1** The absorption spectrum for the different forms of hemoglobin: oxygenated hemoglobin ($HbO_2$), deoxygenated hemoglobin (*Hb*), carboxyhemoglobin (*COHb*), and methemoglobin (*metHb*) The vertical lines represent the two wavelengths of light (660 nm and 940 nm) used by pulse oximeters. (Adapted from Barker SJ, Tremper KK. Pulse oximetry: applications and limitations. Internat Anesthesiol Clin 1987;25:155)

as well as Hb (this is why oxygenated blood is more intensely red than deoxygenated blood), while in the infrared region (940 nm), the opposite is true, and $HbO_2$ absorbs light more effectively than Hb.

Because methemoglobin (metHb) and carboxyhemoglobin (COHb) make up less than 5% of the total hemoglobin pool in most situations (2-4), the transmission of light at 660 nm through a blood sample is determined by the amount of $HbO_2$ in the sample, while light transmission at 940 nm is determined by amount of Hb in the sample. The amount of $HbO_2$ can then be compared to the total amount of hemoglobin ($HbO_2$ + Hb) to express the fraction of the hemoglobin pool that is in the oxygenated form. This is known as % *saturation,* and is derived in Equation 20.1 below.

$$\% \text{ Saturation} = (HbO/HbO_2 + Hb) \times 100 \qquad (20.1)$$

This is how most bedside oximeters operate, using two wavelengths of light (660 and 940 nm), and expressing the oxygenated hemoglobin as a percentage of the total hemoglobin.

### *Early Oximeter s*

The first bedside oximeters used probes that were clamped onto an earlobe. A light emitting device on one side of the probe sent red and

infrared light through the earlobe to a photodetector on the other side, which amplified the transmitted light. The intention was to measure the oxygenated hemoglobin in the small arterioles within the earlobe. These devices suffered from two shortcomings: (1) the transmission of light was affected by factors other than hemoglobin (e.g., skin pigments), and (2) it was not possible to distinguish between oxyhemoglobin saturation in arteries and veins.

*Pulse Oximetry*

The introduction of pulse oximetry in the mid-1970s eliminated many of the problems that plagued the early oximeters. The basic operation of a pulse oximeter is shown in Figure 20.2. The probes on pulse oximeters are shaped like sleeves that are placed around a finger. One side of the probe has a photo transmitter that emits monochromatic light at wavelengths of 660 and 940 nm. The light travels through the tissues of the finger to reach a photodetector on the other side. The unique feature of pulse oximeters is the photodetector, which amplifies only light of alternating intensity. (This is analogous to an AC amplifier, which amplifies only alternating-current impulses.) Light that strikes a pulsating artery will develop phasic changes in intensity and will be amplified by the photo detector, while light that passes through non-pulsatile tissue will be blocked by the photodetector. This allows pulse oximeters to detect only the hemoglobin in pulsating arteries, and it reduces or eliminates errors created by light absorption in non-pulsatile structures like connective tissue and veins.

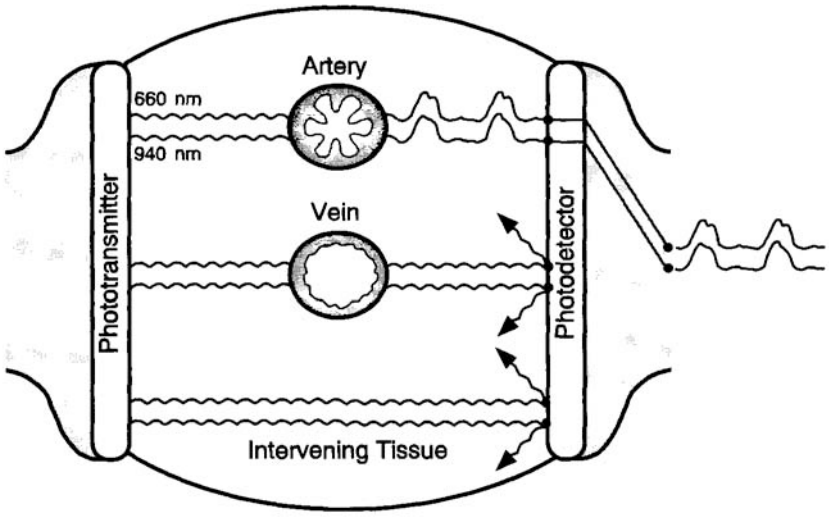


**FIGURE 20.2** The principle of pulse oximetry. The photodetector senses only light of alternating intensity (analogous to an AC amplifier).

TABLE 20.1 Variability in Oximetry and Capnometry Recordings

| Study Parameters | Sp02* | $Sv0_2$** | $PETC0_2$* |
|---|---|---|---|
| Time period | 60 min | 120 min | 60 min |
| Mean variation | 1% | 6% | 2 mm Hg |
| Range of variation | 0-5% | 1-19% | 0-7 mm Hg |

Clinically stable patients. 95% of measurements obtained during mechanical

*Accuracy*

At clinically acceptable levels of arterial oxygenation *(SaO2* above 70%), the *02* saturation recorded by pulse oximeters (SpO2) differs by less than 3% from the actual *SaO2* (4,5). SpO2 also shows a high degree of precision (consistency of repeated measurements). This is demonstrated in Table 20.1 (6), which shows that SpO2 varies by <=2% in most patients who are clinically stable.

*Carbon Monoxide Intoxication*

Carbon monoxide displaces oxygen from the iron binding sites in hemoglobin, so carbon monoxide intoxication will increase carboxyhemoglobin (COHb) levels and decrease oxyhemoglobin ($HbO_2$) levels. This should be evident as a decreased arterial *02* saturation (SaO2)' However, as demonstrated in Figure 20.1, light absorption at 660 nm is similar for carboxyhemoglobin (COHb) and oxygenated hemoglobin (HbO). This means that pulse oximeters will mistake COBb for *$HbO_2$'* and the SpO will be higher than the actual *SaO2.* The difference between the *SpO2* and the *SaO2* (SpO2 - *SaO2)* the *pulse oximetry gap,* is equivalent to the COHb level (7).

Because the *SpO2* overestimates the SaO2 when COHb levels are elevated, pulse oximetry is unreliable for detecting hypoxemia in carbon monoxide intoxication. When carbon monoxide intoxication is suspected, an arterial blood sample should be sent to the clinical laboratory for a direct measurement of the COHb level. (Clinical laboratories have multiple-wavelength spectrophotometers that can more precisely measure the different forms of hemoglobin in the blood.)

*Methhemoglobinemia*

The oxidized iron moieties in methemoglobin do not carry oxygen effectively, so accumulation of methemoglobin (metHb) will decrease the *SaO2.* Pulse oximetry overestimates the *SaO2* (SpO2 > *SaO2),* and the SpO2 rarely falls below 85% in methemoglobinemia despite much lower levels of *SaO2* (8). Thus, pulse oximetry should not be used when methemoglobinemia is suspected. Accurate measurements of metHb, and *SaO2* require the more sophisticated spectrophotometers in clinical labora tories.

*Hypotension*
Although pulse oximetry is based on the presence of pulsatile blood flow, SpO2 is an accurate reflection of *SaO2* down to blood pressures as low as 30 mm Hg (9). Damped pulsations also do not affect the accuracy of fingertip SpO2 recordings taken distal to a cannulated radial artery (10).
For situations where fingertip SpO2 recordings may be problematic because of severely reduced peripheral blood flow, specialized oximeter sensors are available that can be placed on the forehead. These sensors differ from the fingertip sensors because they record light that is reflected back to the skin surface (reflectance spectrophotometry). Forehead sensors respond much more rapidly to changes in spO2 than fingertip sensors (11), and they should gain popularity as a suitable alternative to the traditional fingertip sensors.

*Anemia*
In the absence of hypoxemia, pulse oximetry is accurate down to hemoglobin levels as low as 2 to 3 g/ dL (12). With lesser degrees of anemia (Hb between 2.5 and 9 g/ dL), *SpO2* underestimates *SaO2* by only 0.5% (12).

*Pigments*
The effects of dark skin pigmentation on the SpO2 has varied in different reports. In one study, the spa? was spuriously low in patients with dark skin (13), while in another study, the SpO2 was spuriously high *(SpO2 SaO2* = 3.5%) when the *SaO2* was less than 70% (14). Fingernail polish has a small effect on the SpO2 when the color is black or brown (spO2 2% less than *SaO2)'* but this effect can be eliminated by placing the probes on the side of the finger (15). The largest pigment effect is produced by methylene blue, which can produce a 65% decrease in SpO2 when injected intravenously (4). Because methylene blue is used to treat methemoglobinemia, this is another reason to avoid pulse oximetry in patients with methemoglobinemia.

*Detecting Hypoventilation*
Clinical studies have shown that the *SpO2* can be a sensitive marker of inadequate ventilation (a low $PaO_2$) when patients are breathing room air, but not when they are breathing supplemental oxygen (16). This is explained by the shape of the oxyhemoglobin dissociation curve. When *SpO2* (or *SaO2)* exceeds 90% ($PaO_2$ > 60 mm Hg), the curve begins to flatten, and larger changes in $PaO_2$ are accompanied by smaller changes in SpO2. Breathing supplemental oxygen will push the *SpO2* further out onto the flat part of the oxyhemoglobin dissociation curve (the *SpO2* is often >98% during supplemental *02* breathing), where relatively large changes in $PaO_2$ are accompanied by minor changes in the spO2'
There is a tendency to use supplemental oxygen routinely in the ICU (and the postanesthesia recovery unit) even when the spO2 exceeds 90%. Because there is no documented benefit to increasing the *SaO2* far above 90%, supplemental 02 can be safely withheld **if** the Sp02 is

92% or higher on room air. This practice will limit unnecessary oxygen administration (to limit the toxic effects of oxygen), and will preserve the sensitivity of pulse oximetry in detecting inadequate ventilation.

### *When to Use Pulse Oximetry*

Considering that the spO2 has been called the *fifth vital sign,* it might be more appropriate to consider when *not* to use pulse oximetry. In short, pulse oximetry is indicated in any situation where monitoring arterial oxygenation is considered important. In critically ill patients, at least 15 clinical studies have shown that continuous monitoring of Sp02 with pulse oximetry is superior to periodic blood gas measurements for detecting episodes of significant hypoxemia (4). The combination of pulse oximetry and end-tidal *CO2* monitoring (described next) should largely replace the more expensive and painful method of arterial blood gas measurements.

## Venous Oximetry

The *O2* saturation in the superior vena cava or pulmonary artery can be monitored contim,lOusly with specialized catheters that emit red and infrared light from the catheter tip and record the light reflected back from the hemoglobin in circulating erythrocytes (see Figure 20.3) (17). This technique of *reflectance spectrophotometry* is a variant of the *transmission spectrophotometry* used by fingertip probes for pulse oximetry. Most venous oximetry systems process and display the venous *O2* saturation every 5 seconds.

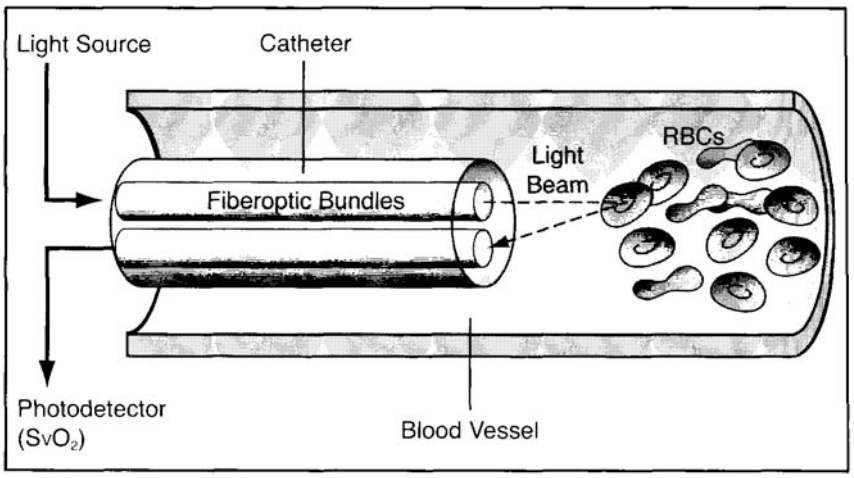


**FIGURE 20.3** Continuous measurement of $O_2$ saturation of hemoglobin in mixed venous blood ($SvO_2$) using reflectance spectrophotometry.

*Mixed Venous* **02** *Saturation*

The interpretation of mixed venous *02* saturation (svO) is described in Chapter 11. The *Sv02* is measured in pulmonary artery blood, and is a marker of the balance between whole-body *02* delivery (DO) and *02* consumption (VO): *Sv02 = DO/VO$_2$'* A decrease in Sv02 below the normal range of 70 to 75% identifies a state of inadequate **O,** delivery relative to *02* consumption that could be the result of a decreased *DO2* (from low cardiac output, anemia, or hypoxemia) or an increased *VO2* (from hypermetabolism). (The determinants of *DO2* and *VO2* are described in Chapter 2.)

The continuous measurement of Sv02 using specialized pulmonary artery catheters is accurate to within 1.5% of the *Sv02* measured in the clinical laboratory (18). Despite this acceptable accuracy, *Sv02* can vary considerably without an apparent change in hemodynamic status. The spontaneous variability of Sv02 is shown in Table 20.1. The average variation over a 2-hour period is 6%, but can be as high as 19% (19). As a general rule, a greater than 5% variation in Sv02 that persists for longer than 10 minutes is considered a significant change (20).

*Central Venous* **02** *Saturation*

Continuous monitoring of the central venous *02* saturation (scv$O_2$) is achieved with specialized central venous catheters placed in the superior vena cava. The scv$O_2$ tends to be slightly lower than the Sv02' and this difference is magnified in the presence of circulatory shock (17). Single measurements of scv$O_2$ can differ from Sv02 by as much as 10%, but the difference is reduced (to within 5%) when multiple measurements are obtained (21). The *ScvO$_2$* seems most valuable in identifying *trends* in the balance between *DO2* and *VO2'*

Central venous oximetry is gaining popularity over mixed venous oximetry because of the cost and morbidity associated with pulmonary artery catheters. Recent guidelines for the early management of patients with severe sepsis and septic shock includes an *ScvO$_2$* of greater than 70% as a therapeutic end-point (22).

*Dual Oximetry*

The predictive value of Sv02 or *ScvO$_2$* can be increased by adding the *SaO2* measured by pulse oximetry (SpO). This provides a continuous measure of *(SaO2* - svO), which is equivalent to the *02* extraction from capillary blood (23). The determinants of the (SaO2 - *Sv02)* can be derived using the determinants of *DO2* and *VO2* (which are described in Chapter 2):

(SaO2 - Sv02) = VO/Q X Hb (20.2)

An increase in *(SaO2* - Sv02) above the normal range of 20 to 30% can be the result of increased *VO2* (hypermetabolism), a reduced Q (low cardiac output) or a reduced Hb (anemia). The *(SaO2* - *Sv02)* may be

more valuable as a marker of tissue dysoxia (defined as a state of oxygen-limited metabolism) or impending dysoxia. For example, in the presence of anemia or a low cardiac output, an increase in (SaO2 - *Sv02)* to its maximum level of 50 to 60% indicates that the tissues are no longer able to compensate for further reductions on Hb or cardiac output, which means there is a risk for tissue anaerobiasis. Thus, in a patient with progressive anemia, an *(SaO2 - Sv02)* of 50 to 60% could be used as an indication for transfusion (transfusion trigger).

**CAPNOMETRY**

Capnometry is the measurement of *CO2* in exhaled gas. This can be achieved with a colorimetric technique, or with infrared spectrophotometry. Both methods are described below.

*Colorimetric CO2 Detection*

The colorimetric detection of *CO2* in exhaled gas is a quick and simple method of determining if an endotracheal tube has been placed in the lungs (24,25). This is recommended as a standard practice following attempted intubation because auscultation for breath sounds is an unreliable method of determining if an endotracheal tube is in the esophagus or lungs (26).

The most popular colorimetric *CO2* detector in clinical practice is illustrated in Figure 20.4. This device has two ports for attachment: one to the endotracheal tube and the other end to an inflatable resuscitation bag. The central area of the device contains filter paper that is impregnated with a pH-sensitive indicator that changes color as a function of pH. When exhaled gas passes over the filter paper, the *CO2* in the gas is hydrated by a liquid film on the filter paper, and the resulting pH is detected by a color change. The outer perimeter of the chemical reaction area contains color-coded sections indicating the concentrations of exhaled *CO2* associated with each color change. A purple color indicates *<0.5% CO2* in exhaled gas, a tan color indicates 0.5 to <2.0% *CO2* in exhaled gas, and a yellow color indicates 2.0 to 5.0% *CO2* in exhaled gas. (The normal exhaled *CO2* is 5%, which is equivalent to a $PCO_2$ of 40 mm Hg.)

*Predictive Value*

The accuracy of this colorimetric device for predicting the success of endotracheal intubation is shown in Table 20.2 (24). For patients who are not in cardiac arrest, the absence of a color change from purple (exhaled *CO2* < 0.5% or exhaled $PCO_2$ <4 mm Hg) always means the tube is in the esophagus, and the presence of a color change from purple almost always means the tube is in the trachea. However in cardiac arrest victims, the absence of a color change from purple (indicating little or no *CO2* in exhaled gas) is not reliable for predicting if the tube is in the esophagus or trachea. This is explained by the fact that exhaled *CO2*

TABLE 20.2 Performance of Colorimetric $CO_2$ Detector[t]

| | Color on $CO_2$ Detector | |
|---|---|---|
| | Purple | Tan or Yellow |
| Patient Group | ($C0_2$ < 0.5%) | ($C0_2$ > = 0.5%) |
| No cardiac arrest (n = 83) | Tube in esophagus in 100% of cases. | Tube in trachea in 99% of cases. |
| Cardiac arrest (n = 144) | Tube in trachea in 77% of cases and tube in esophagus in 23% of cases. | Tube in trachea in 1 00% of cases. |

t From Ornato JP, et al. Multicenter study of a portable, hand-size, colorimetric $CO_2$ detection device. Ann Emerg Med 1992;21:518.

decreases when cardiac output is reduced, and thus a very low level of exhaled *CO2* in a cardiac arrest victim can be the result of a very low cardiac output rather than esophageal intubation. Therefore, during cardiac arrest, the lack of a color change from purple on the colorimetric $CO_2$

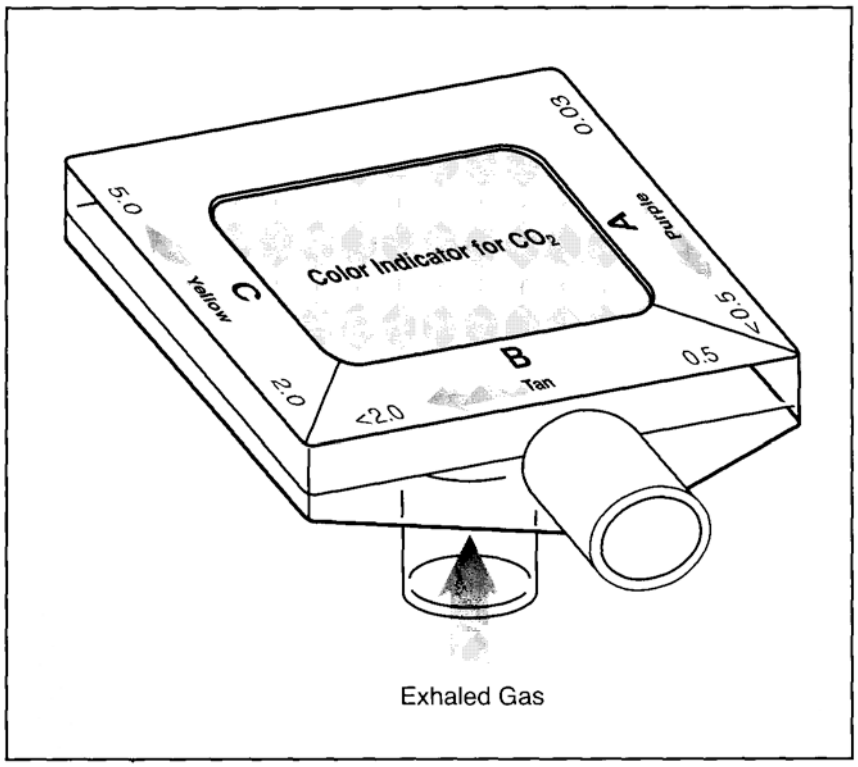


**FIGURE 20.4** A disposable device (*Easy Cap II*, Nellcor, Pleasanton, CA) for the colorimetric detection of $CO_2$ in exhaled gas.

detector (indicating little or no $CO_2$ in exhaled gas) is not evidence of failure to intubate the lungs.

*Feeding Tube Placement*

The colorimetric *CO2* detector has been used to detect improper placement of feeding tubes. In one study (27), placement of feeding tubes in the upper airways was always associated with a color change from purple, while placement of feeding tubes in the upper GI tract was never associated with a color change from purple. (See reference 27 for a description of how to attach the *CO2* detector to the feeding tube.) If these results are corroborated, colorimetric *CO2* detection could replace chest films for evaluating the placement of feeding tubes.

*Infrared Capnography*

Carbon dioxide absorbs light in the infrared spectrum, and this property is the basis for the use of infrared capnography to measure the $PC0_2$ in exhaled gas (28). This provides a more quantitative measure of exhaled *CO2* than the colorimetric method. Figure 20.5 shows an infrared $CO_2$ probe that has an airway attachment (which is placed in series with the expiratory tubing during mechanical ventilation) and a fitted transducer. When in place, the probe emits a continuous infrared light beam that travels through the exhaled gas. The photo detector has a rapid response,

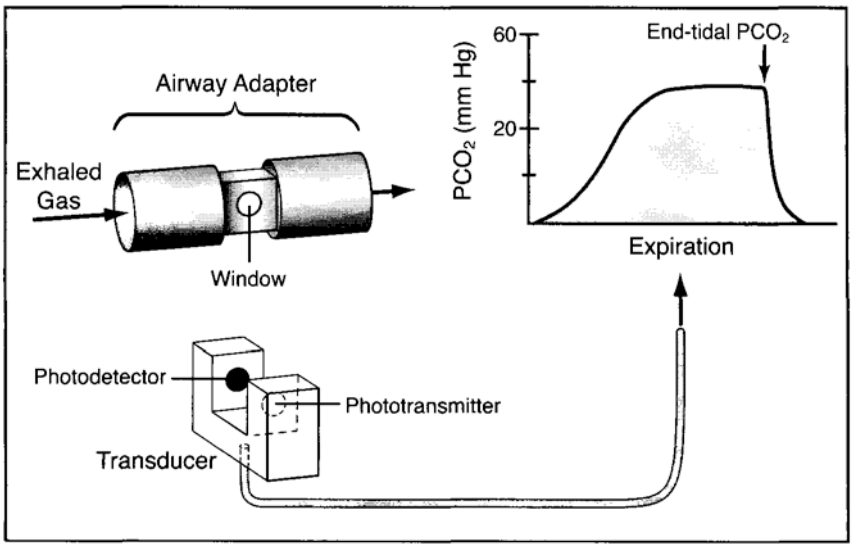


**FIGURE 20.5** Infrared capnography. The airway adapter and fitted transducer on the left allow for a steady beam of infrared light to pass through exhaled gas. The photodetector records changes in $PCO_2$ during each exhalation, as shown in the capnogram on the right.

and can measure changes in $PCO_2$ during a single exhalation to produce a capnogram like the one shown in Figure 20.5.

*Capnography*
The shape of the normal capnogram has been described as "the outline of a snake that has swallowed an elephant" (29). The $PCO_2$ at the onset of expiration is negligible because the gas in the upper airways is first to leave the lungs. As exhalation proceeds, gas from the alveoli begins to contribute to the exhaled gas, and the $PCO_2$ begins to rise steadily. The rate of rise eventually declines, and the exhaled $PCO_2$ reaches a plateau near the end of expiration. When gas exchange is normal, the $PCO_2$ at the very end of expiration (called the *end-tidal* $peO_2$) is equivalent to the $PCO_2$ in end-capillary (arterial) blood.

*End- Tidal Versus Arterial* $PC0_2$
When pulmonary gas exchange is normal, the end-tidal $PCO_2$ ($PETCO_2$) is only 2 to 3 mm Hg lower than the arterial $PCO_2$ (2,28). However, when gas exchange in the lungs is impaired, $PETC0_2$ decreases relative to $PaC0_2$, and the ($PaCO_2$ - $PETCO_2$) difference exceeds 3 mm Hg.
This occurs in the following conditions:

Increased anatomic dead space:
Open ventilator circuit Shallow breathing
Increased physiologic dead space:
Obstructive lung disease Low cardiac output:
Pulmonary embolism
Excessive lung inflation (e.g., PEEP)

Although uncommon, the end-tidal $PCO_2$ can be higher than arterial $PCO_2$ (30). This is possible in the following situations: when $CO2$ production is high and there is a low inspired volume or a high cardiac output, or at high concentrations of inhaled $O2$ (the $O2$ displaces $CO2$ from Hb).

**Nonintubated Patients**
End-tidal $PCO_2$ can be monitored in patients who are not intubated using a modified nasal cannula. These are commercially available (Salter divided nasal cannula, DRE Medical, Louisville, KY), or a nasal cannula can be modified as shown in Figure 20.6 (31). The tubing between the two nasal prongs must be occluded (either with a cotton ball inserted through one of the nasal prongs or with a small screw clamp). This allows one nasal prong to be used for oxygen inhalation while the other nasal prong is used to transmit exhaled gas. A 14-gauge intravascular catheter (2 inches long) is inserted into the exhalation side of the nasal cannula to transmit gas to the $CO2$ detector. A sidestream $CO2$ detector (i.e., one that applies

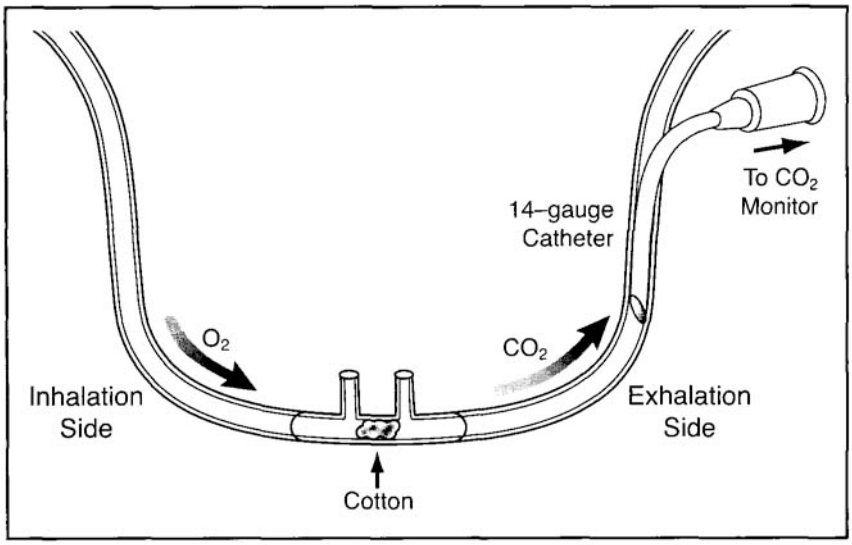


**FIGURE 20.6** A modified nasal cannula to measure end-tidal $PCO_2$ during spontaneous breathing.

suction to draw gas from the tubing) is best suited for this application. If one of these is not available, a mainstream infrared *CO2* detector (such as the one shown in Fig. 20.5) can be used with a suction pump to draw gas samples from the cannula (at 150 mL/minute). The respiratory therapy department should help with this modification.

**Clinical Applications**

The end-tidal $PCO_2$ can be used in a number of ways in the ICD. The following are some possible applications.

*Monitoring Arterial $PCO_2$*

The end-tidal $PCO_2$ is most often used as a noninvasive method of monitoring the arterial $PCO_2$. The continuous (breath-by-breath) measurement of end-tidal $PCO_2$ provides a real advantage over the traditional method of measuring arterial blood gases periodically. When gas exchange in the lungs is abnormal and the $PETCO_2$ is lower than the arterial $PCO_2$, it is still possible to monitor *changes* in end-tidal $PCO_2$ as a measure of *changes* in arterial $PCO_2$. The arterial $PCO_2$ should be measured simultaneously with the end-tidal $PCO_2$ to establish the PaCO2-$PETCO_2$ gradient. This gradient should remain the same as long as no other process intervenes to disturb pulmonary gas exchange. Changing ventilator settings will affect the *PaCO2-$PETCO_2$* gradient (32), so the arterial $PCO_2$ should be measured after each change in ventilator settings to establish the new PaCO2-$PETCO_2$ gradient.

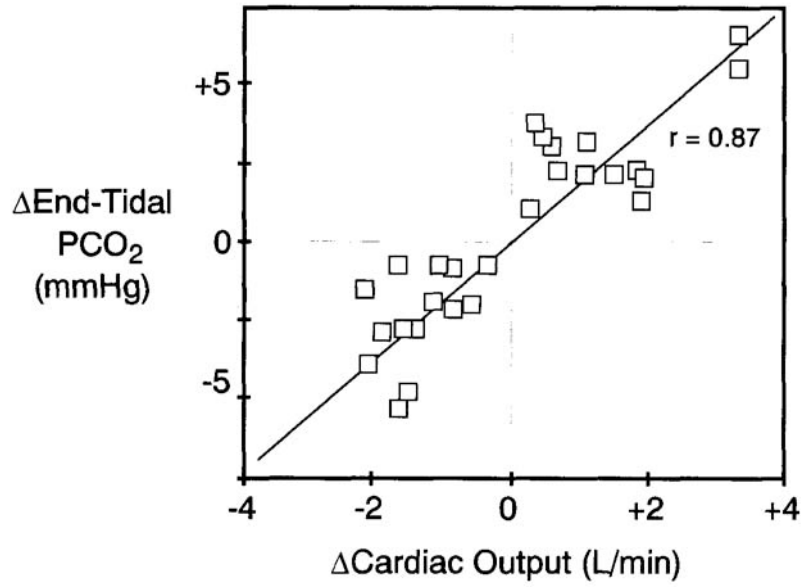


**FIGURE 20.7** Relationship between changes in end-tidal $PCO_2$ and changes in cardiac output in a group of postoperative patients. Correlation coefficient indicated as *r*. (From Reference 33.)

*Cardiac Output*

There is a close correlation between changes in $PETCO_2$ and changes in cardiac output, as demonstrated in Figure 20.7 (33). This is the basis for the use of end-tidal $PCO_2$ to evaluate the effectiveness of chest compressions during CPR, as described in Chapter 15 (see Fig. 15.5). This relationship can also be used to detect changes in cardiac output resulting from aggressive diuresis or short-term volume loading.

*Early Detection of Nosocomial Disorders*

A decrease in $PETCO_2$ accompanied by an increase in the $PaCO_2$ - $PETCO_2$ gradient can be an early manifestation of any of the following conditions:

Overdistention of alveoli from high tidal volumes or PEEP Migration of an endotracheal tube into a main-stem bronchus (34) Acute pulmonary embolism (35)
Pneumonia
Pulmonary edema

An increase in the $PaCO_2$ - $PETCO_2$ gradient can thus serve as an early warning signal for any of these conditions. The use of the $PaCO_2$ - $PETCO_2$ gradient to detect overdistention of alveoli may be particularly useful in light of the discovery that high tidal volumes, which are common during mechanical ventilation, can be damaging to

the lungs (see Chapters 22 and 24 for information on ventilator-induced lung injury).
The end-tidal $PCO_2$ has become a popular measurement in the evaluation of suspected pulmonary embolism. A normal $PaCO_2$ - $PETCO_2$ gradient, combined with a normal D-dimer assay, can be used to exclude the diagnosis of acute pulmonary embolism (35). The value of this approach in the ICU (where patients often have an elevated $PaCO_2$ - $PETCO_2$ gradient) is unclear.

*Ventilator Weaning*
During weaning from mechanical ventilation, end-tidal CO2 monitoring can serve several purposes (36). In uneventful weaning (e.g., following surgery), it serves as a noninvasive measure of $PaCO_2$. In difficult or complicated weaning, it can help determine the success or failure of the wean attempt. For example, a progressive rise in $PETCO_2$ can signal an increase in the work of breathing (a sign of wean failure), whereas a decline in $PETCO_2$ with a increase in the $PaCO_2$ - $PETC0_2$ gradient can signal respiratory muscle weakness with shallow breathing (another sign of wean failure).

*Controlled Hyperventilation*
When induced hyperventilation is used to reduce intracranial pressure (e.g., in patients with closed head injuries), monitoring the end-tidal *CO2* is useful for maintaining the $PaCO_2$ at the desired level (which is usually 25 mm Hg). In this setting, the $PaCO_2$ - $PETCO_2$ gradient must be checked periodically to maintain the PETCO, at a level that corresponds to the
target $PaCO_2$.

TRANSCUTANEOUS $PC0_2$
The latest in noninvasive *CO2* monitoring is a cutaneous *CO2* electrode (TOsCA, Linde Medical Sensors, Basel, Switzerland) that is placed on the earlobe and measures the $PCO_2$ in the underlying arterioles. The electrode (which is combined with a pulse oximeter sensor) heats the underlying skin to 42°C to dilate surface arterioles and promote the diffusion of *CO2'* One study of this device in ICU patients showed a good correlation between transcutaneous $PCO_2$ and arterial $PCO_2$ over a wide range of arterial $PCO_2$ values (from 25 to 100 mm Hg) (37). If proven reliable, the transcutaneous $PCO_2$ should be more accurate than the end-tidal $PCO_2$ for monitoring arterial $PCO_2$ in patients with abnormal pulmonary gas exchange (where end-tidal $PCO_2$ is lower than arterial PCO).

**A FINAL WORD**
Pulse oximetry is the single most useful monitoring technique that has been introduced in my 25 years of service to critical care medicine. Besides being safe, inexpensive, easy to use, and remarkably reliable, the

SpO2 measurement is valuable because it provides information about the state of arterial oxygenation (which the $PaO_2$ does not). In fact, if the SpO2 is combined with a measurement of the hemoglobin concentration in blood, it is possible to calculate the concentration of oxygen in arterial blood (see Chapter 2, Equation 2.5), which is the parameter that *should* be used (instead of the $PaO_2$ or SaO2) to evaluate the state of arterial oxygenation.

**REFERENCES**

**Chapter 21**

**OXYGEN INHALATION THERAPY**

*For* as a *candle burns out much faster* in *dephlogisticared than* in *common air,* so *we might,* as *may be said, live out too fast ...* in *this pure* kind ofair.
*Joseph Priestley*

One of the rare sights in any ICU is a patient who is *not* receiving supplemental oxygen to breathe. The overzealous use of oxygen is often without justification (without evidence of impaired tissue oxygenation) and is even more often without consideration of the toxic effects of oxygen. This chapter begins by highlighting the shortcomings in the indications and end-points of supplemental oxygen administration. This is followed by a brief description of the methods used to provide supplemental oxygen. The final section of the chapter focuses on the dark side of oxygen; i.e., the tendency for oxygen to produce widespread and lethal cell injury.

**THE NEED FOR SUPPLEMENTAL OXYGEN**

Oxygen inhalation should be used to prevent or correct tissue hypoxia, but in most cases it seems to be a knee-jerk response to the mere presence of a serious illness. This is supported by a survey showing that over 50% of hospitalized patients were receiving supplemental oxygen without a written order 0). This section will briefly examine the need for supplemental oxygen.

*Tissues are Normally Hypoxic*
The care of critically ill patients is dominated by the fear of tissue hypoxia. However, the tissues of the human body normally operate in a lowoxygen environment. As described in Chapter 2, oxygen does not dissolve readily in water, which is why we need hemoglobin to transport

TABLE 21.1 Total Volume of Oxygen in Tissues

| | Interstitial Fluid | Intracellular Fluid |
|---|---|---|
| $P0_2$ | 15 mm Hg | 5 mm Hg |
| $O_2$ Content* | 0.45 mL/L | 0.15 mL/L |
| Total Volume† | 16 L | 23 L |
| Volume of $O_2$ | 9.6 mL | 3.5 mL |

*Based on solubility coefficient for $O_2$ in water at 37°C = 0.03 mL/L/mm Hg.
†Volume estimates based on total body water (TBW) = 42 liters, intracellular 55% of TBW, and interstitial volume = 0.38% of TBW.

oxygen to the tissues. The concentration of (dissolved) oxygen in tissues is determined by the *pa02* in the tissues and the solubility coefficient of oxygen in water. This is shown in the equation below (which is similar to Equation 2.2 in Chapter 2).

$$\text{Dissolved } O_2 \text{ (mL/ dL)} = 0.003 \times P0_2 \qquad 21.1$$

where 0.003 is the solubility coefficient of $O_2$ in water (expressed as mL *O2* per 100 mL blood per mm Hg $P0_2$) at a body temperature of 37°C. Experimental observations show that the intracellular $P0_2$ is about 5 mm Hg (1) and the tissue (interstitial) *p02* is about 15 mm Hg (2). This corresponds to an $O_2$ concentration of 0.15 mL/L inside cells and 0.45 mL/L in the interstitial fluid. Using the estimated volume of the body fluid compartments shown in Table 21.1, the total volume of oxygen in the tissues of the human body is only about 13 mL. This demonstrates that the tissues of the human body normally operate in an oxygen deficient environment.

### *Tolerance to Arterial Hypoxemia*

The standard indications for supplemental oxygen are an arterial *pa2* ($Pa0_2$) less than 60 mm Hg or an arterial $O_2$ saturation (SaO) less than 90% (4). However, clinical observations show that severe degrees of hypoxemia are tolerated without evidence of inadequate tissue oxygenation (5-7). This is demonstrated in Table 21.2, which shows the arterial *pa2* and corresponding blood lactate level in seven patients with severe hypoxemia ($Pa0_2 < 40$ mm Hg) due to acute exacerbation of chronic obstructive lung disease (5). The normal blood lactate levels «4 mmollL) show no evidence of a switch to anaerobic metabolism in any of the patients with severe hypoxemia, even at arterial $P0_2$ levels as low as 22 mm Hg. This observation has been corroborated in patients with acute respiratory distress syndrome (6).

The available evidence is stated best in the study shown in Table 21.2:

**In the resting patient, even the most severe clinical hypoxemia due to pulmonanary insufficiency does not itself lead to generalized tissue anaerobiasis** *(5).*

TABLE 21.2 Severe Hypoxemia without Evidence of Anaerobic Metabolism

| Patient | Arterial $P0_2$ (mm Hg) | Blood Lactate (mmol/L) |
|---|---|---|
| 1 | 22 | 0.90 |
| 2 | 30 | 0.25 |
| 3 | 32 | 0.86 |
| 4 | 33 | 1.57 |
| 5 | 34 | 2.03 |
| 6 | 37 | 2.08 |
| 7 | 39 | 1.12 |

Data from Reference 5.

Remember this statement when considering the use of supplemental oxygen based on measures of arterial oxygenation.

**THE END-POINT OF OXYGEN INHALATION**

The standard end-point of supplemental oxygen inhalation is a satisfactory increase in the $Pa0_2$ or $Sa0_2$ (what is satisfactory seems to differ with individual physicians). The problem with this approach is demonstrated in Figure 21.1. The graphs in this figure show the discrepancy between changes in arterial $P0_2$ and changes in systemic oxygen transport during supplemental oxygen administration (8). Note that arterial $P0_2$ increases from 61 to 83 mm Hg (36% change, $P < 0.01$) while the rate of oxygen transport decreases from 12.8 to 12.1 mL/minute/kg (5% change, not significant). Thus, an increase in arterial $P0_2$ during oxygen inhalation should not be used as evidence for an increase in tissue oxygen availability (8,9). This is consistent with the observation that oxygen inhalation does not protect against myocardial ischemia.

*OXYGEN and Systemic Blood Flow*

The lack of improvement in systemic oxygen transport during oxygen inhalation is explained by the tendency for oxygen to reduce systemic blood flow. There are two mechanisms for this effect. First, oxygen acts as a vasoconstrictor in all vascular beds except the pulmonary circulation (where it acts as a vasodilator) 01,12). Second, oxygen inhalation is often associated with a decrease in cardiac output (8,9,13). Although this is caused partly by reversal of the cardiac stimulatory effects of hypoxemia, oxygen also has negative inotropic effects on the heart, and oxygen inhalation can reduce cardiac output in the absence of hypoxemia (3). The ability of oxygen to reduce systemic blood flow emphasizes the need to adopt measures other than the $Pa0_2$ and $Sa0_2$ to evaluate the success of oxygen inhalation.

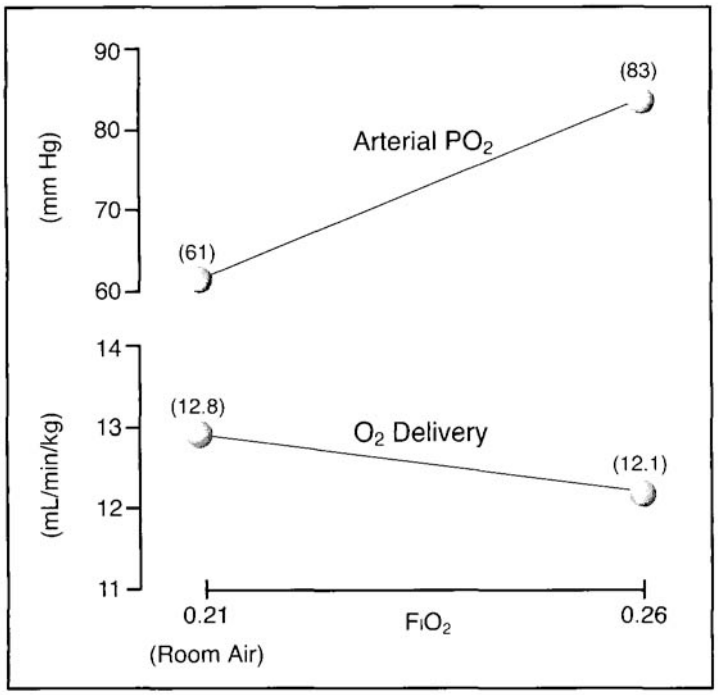


**FIGURE 21.1** Effects of oxygen inhalation ($FiO_2 = 0.26$) on arterial oxygenation and systemic oxygen transport. Points on the graph represent mean values for the group of patients studied. (Data from DeGaute JP et al. Oxygen delivery in acute exacerbation of chronic obstructive pulmonary disease. Effects of controlled oxygen therapy. Am Rev Respir Dis 1981;124:26.)

## METHODS OF OXYGEN INHALATION

Oxygen delivery systems are classified as low-flow or high-flow systems **(4)**. Low-flow delivery systems, which include nasal prongs, face masks, and masks with reservoir bags, provide a reservoir of oxygen for the patient to inhale. When the patient's minute ventilation exceeds the flow rates of these devices, the oxygen reservoir is drained, and room air is inhaled to meet the patient's additional needs. The final concentration of inhaled oxygen ($FI0_2$) is determined by the size of the oxygen reservoir, the rate at which the reservoir is filled, and the ventilatory demands of the patient. In contrast to the variable $FI0_2$ with low-flow systems, highflow oxygen delivery systems provide a constant $FI0_2$" This is achieved by delivering oxygen at flow rates that exceed the patient's peak inspiratory flow rate, or by using devices that entrain a fixed proportion of room air.

### *Nasal Prongs*

Nasal prongs deliver a constant flow of oxygen to the nasopharynx and oropharynx, which acts as an oxygen reservoir (average capacity = 50 mL,

TABLE 21.3 Low-Flow Oxygen Inhalation Systems

| Device | Reservoir Capacity | Oxygen Flow (L/min) | Approximate ($FI0_2$)* |
|---|---|---|---|
| Nasal cannula | 50 mL | 1 | 0.21-0.24 |
| | | 2 | 0.24-0.28 |
| | | 3 | 0.28-0.34 |
| | | 4 | 0.34-0.38 |
| | | 5 | 0.38-0.42 |
| | | 6 | 0.42-0.46 |
| Oxygen face mask | 150-250 mL | 5-10 | 0.40-0.60 |
| Mask-reservoir bag: | 750-1250 mL | | |
| Partial rebreather | | 5-7 | 0.35-0.75 |
| Nonrebreather | | 5-10 | 0.40-1.0 |

'Estimated value based on a tidal volume of 500 mL, a respiratory rate of 20 and an inspiratory: expiratory time ratio of 1
From Reference 14

or about one-third of the anatomic dead space) (5). The relationship between the oxygen flow rate and the $FI0_2$ in normal subjects is shown in Table 21.3 (5). As the oxygen flow rate increases from 1 to 6 L/min, the $FI0_2$ increases from 0.24 to 0.46. This relationship varies with changes in the patients' minute ventilation: when minute ventilation increases and exceeds the flow rate of $O_2$, the excess ventilation is drawn from room air, and the $FI0_2$ begins to decline. This is demonstrated below, which shows the relationship between minute ventilation (V E) and the $FI0_2$ at a constant flow rate through the nasal cannula (6).

| 02 Flow | $V_E$ | FI02 |
|---|---|---|
| 6 L/min | 5 L/min | 0.60 |
| 6 L/min | 10 *L/min* | *0.44* |
| 6 L/min | 20 L/min | 0.32 |

In this case, a fourfold increase in minute ventilation above the $O_2$ flow rate provided by the nasal cannula resulted in a 48% reduction in $FI0_2$. This demonstrates the limitations of $O_2$ delivery through nasal prongs in patients who have high ventilatory demands.

*Advantages and Disadvantages*

Nasal prongs are easy to use and well tolerated by most patients. The major disadvantage of nasal prongs is the inability to achieve high concentrations of inhaled $O_2$ in patients who have a high minute ventilation.

*Low-Flow Oxygen Masks*

Face masks add 100 to 200 mL to the capacity of the oxygen reservoir. These devices fit loosely on the face, which allows room air to be inhaled, if needed. Standard face masks deliver oxygen at flow rates between 5 and 10 L/min. The minimum flow rate of 5 L/min is needed to clear exhaled gas from the mask. Low-flow oxygen masks can achieve a maximum $Fr0_2$ of approximately 0.60.

*Advantages and Disadvantages*

Standard face masks can provide a slightly higher maximum $Fr0_2$ than nasal prongs. However, this difference can be small and insignificant. In general, face masks are considered to have the same drawbacks as nasal prongs.

Masks with Reservoir Bags

The addition of a reservoir bag to a standard face mask increases the capacity of the oxygen reservoir by 600 to 1000 mL (depending on the size of the bag). If the reservoir bag is kept inflated, the patient will inhale only the gas contained in the bag. There are two types of mask-reservoir bag devices. The one shown in Figure 21.2 is a partial rebreathing system. This device allows the gas exhaled in the initial phase of expiration to return to the reservoir bag. As exhalation proceeds, the expiratory flow rate declines, and when the expiratory flow rate falls below the oxygen flow rate, exhaled gas can no longer return to the reservoir bag. The initial part of expiration contains gas from the upper airways (anatomic dead space), so the gas that is rebreathed is rich in oxygen and largely devoid of $CO_2$, Partial rebreather devices can achieve a maximum $Fr0_2$ of 70 to 80%.

The modified device in Figure 21.3 is a nonrebreathing system. This device has a one-way valve that prevents any exhaled gas from returning to the reservoir bag. Nonrebreather devices permit inhalation of pure oxygen ($Fr0_2 = 1.0$).

*Advantages and Disadvantages*

The principal advantage of the reservoir bags is the greater ability to control the composition of inhaled gas. However, because the masks must create a tight seal on the face, it is not possible to feed patients by mouth or nasoenteral tube when these devices are in use. Aerosolized bronchodilator therapy is also not possible with reservoir bag devices.

*High-Flow Oxygen Masks*

High-flow oxygen inhalation devices provide complete control of the inhaled gas mixture and deliver a constant $Fl0_2$ regardless of changes in ventilatory pattern. The operation of a high-flow oxygen mask is shown in Figure 21.4 (7). Oxygen is delivered to the mask at low flow rates, but at the inlet of the mask, the oxygen is passed through a narrowed

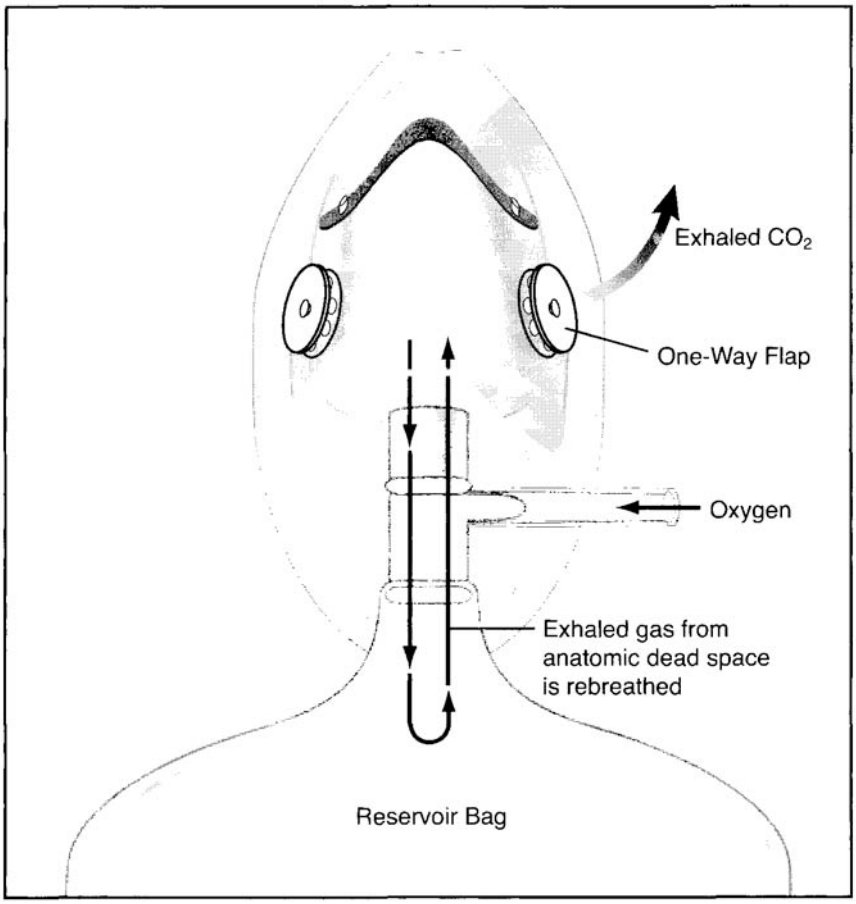


**FIGURE 21.2** Partial rebreathing system. The initial 100 to 150 mL of exhaled gas (anatomic dead space) is returned to the reservoir bag for rebreathing.

orifice, and this creates a high-velocity stream of gas (analogous to the effect created by a nozzle on a garden hose). This high-velocity jet stream generates a shearing force known as viscous drag that pulls room air into the mask. The volume of room air that moves into the mask (which determines the $FI0_2$) can be varied by varying the size of the openings (called entrainment ports) on the mask. These masks can increase the $FI0_2$ to a maximum of 0.50. At any given $FI0_2$, the proportion of inhaled gas provided by entrained room air remains constant; that is, FIO, remains fixed regardless of changes in oxygen flow rate or changes in inspiratory flow rate.

*Advantages and Disadvantages*

The major advantage of high-flow oxygen masks is the ability to deliver a constant $FI0_2$. This feature is desirable in patients with chronic

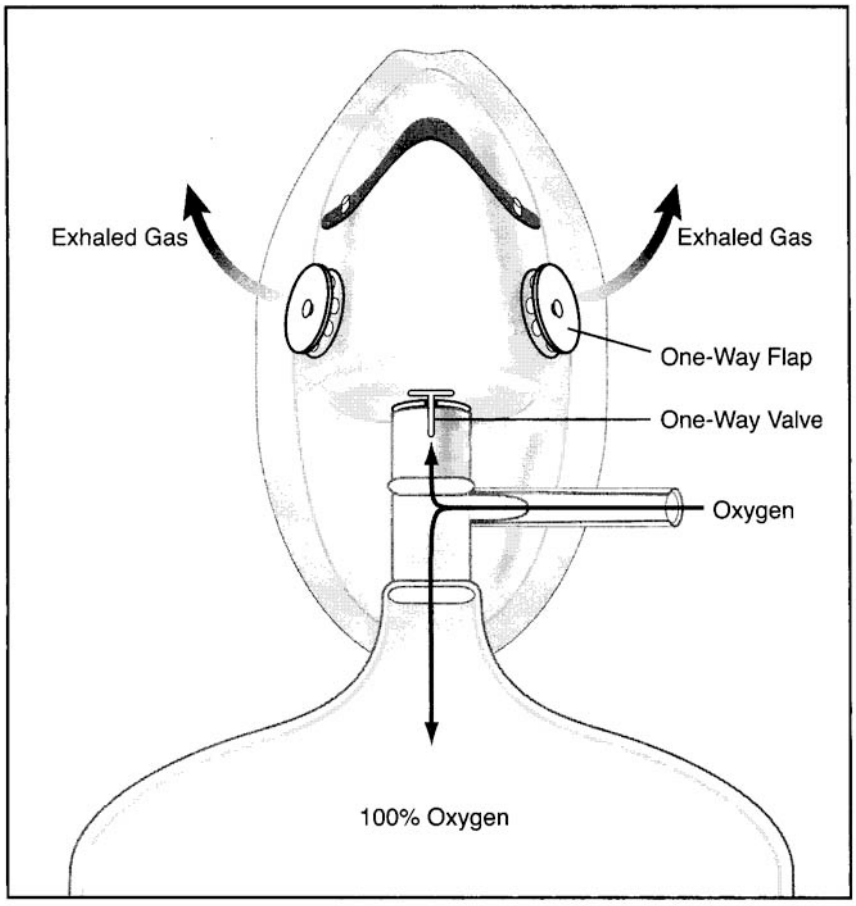


**FIGURE 21.3** Nonrebreathing system. A one-way valve prevents exhaled gas from returning to the reservoir bag.

hypercapnia because an inadvertent increase in $FIO_2$ in these patients can lead to further $CO_2$ retention. The major drawback with these masks is the inability to deliver high concentrations of inhaled $O_2$,

THE DARK SIDE OF OXYGEN

The overzealous and unregulated use of supplemental oxygen must be tempered by the potential for oxygen to act as a powerful and even lethal toxin (8). In fact, contrary to the nqtion that oxygen protects cells from injury, the accumulated evidence suggests that oxygen (via the production of toxic metabolites) is *responsible* for much of the cell injury in critically ill patients. The following is a brief description of the dark (toxic) side of oxygen.

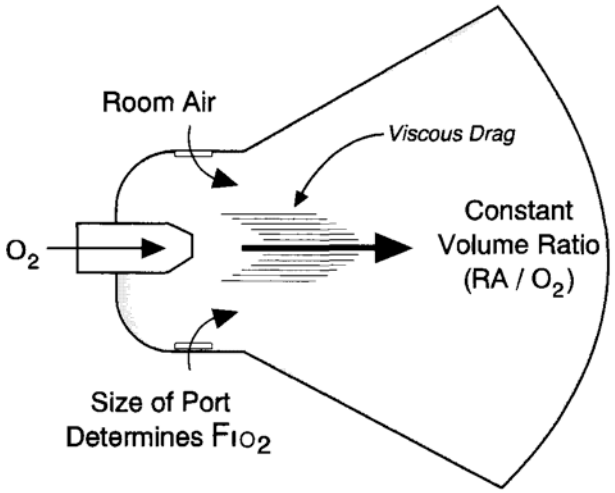


**FIGURE 21.4** High-flow oxygen inhalation device. *RA* = room air.

## Toxic Metabolites of Oxygen

The metabolism of oxygen takes place at the end of the electron transport chain in mitochondria, where electrons that accumulate as a result of ATP production are removed by using the electrons to reduce oxygen to water. The reaction sequence for this process is shown in Figure 21.5. Molecular oxygen has two unpaired electrons in its outer orbitals, which qualifies it as a *free radical.* (A free radical is an atom or molecule with one or more unpaired electrons in its outer orbitals.) Although most free radicals are highly-reactive, oxygen is only sluggishly reactive because the unpaired electrons in its outer orbitals have the same directional spin.

According to Pauli's Exclusion Principle (proposed by the Austrian physicist Wolfgang Pauli), no two electrons can occupy the same orbital if they have the same directional spin. This means it is not possible to add an electron pair to oxygen and reduce it to water in a one-step reaction because one orbital would have two electrons with the same directional spin, which is a quantum impossibility. This *spin restriction* limits oxygen metabolism to a series of single-electron reduction reactions, and this process produces a series of highly reactive intermediates.

The intermediates in oxygen metabolism, which are shown in Figure 21.5, include the superoxide radical, hydrogen peroxide, and the hydroxyl radical. All are powerful *oxidants* capable of damaging cell membranes, denaturing proteins, and breaking DNA into strands. The hydroxyl radical is the most reactive molecule known to biochemistry, and usually enters a reaction within three molecular diameters of its point of origin (8).

### *Granulocyte Activation*

The activation of granulocytes (as part of the inflammatory response) involves a marked (up to 20-fold) increase in oxygen consumption (9).

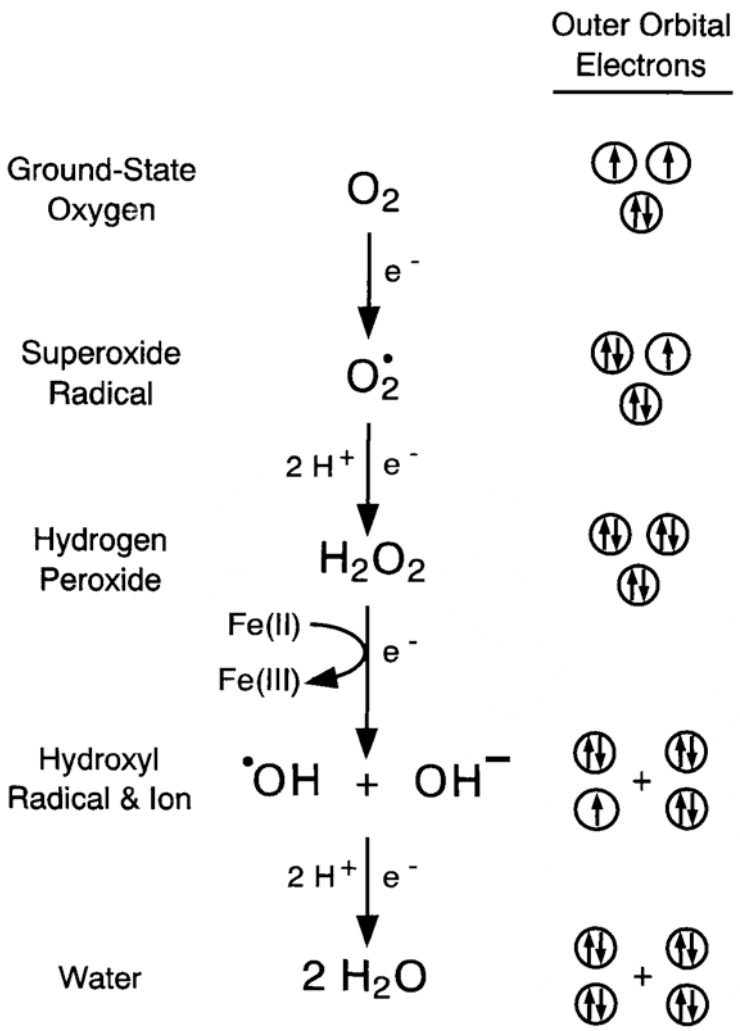


**FIGURE 21.5** The metabolism of molecular oxygen to water, which occurs as a series of four single-electron reduction reactions. Orbital diagrams on the right side of the figure show the electron configuration (*arrows*) in the outer orbitals of each reactant.

This is known as the *r espiratory burst,* and its purpose is to produce toxic oxygen metabolites, which are stored in cytoplasmic granules. These metabolites are released as part of the inflammatory response, and they can damage and destroy invading microorganisms. They can also damage and destroy the tissues of the host if adequate *antioxidant* protection is not available (see next). Toxic oxygen metabolites have been implicated in the inflammatory-mediated cell injury that occurs in the acute respiratory distress syndrome (ARDS) and the systemic inflammatory response syndrome (see Chapter 40) (20,21).

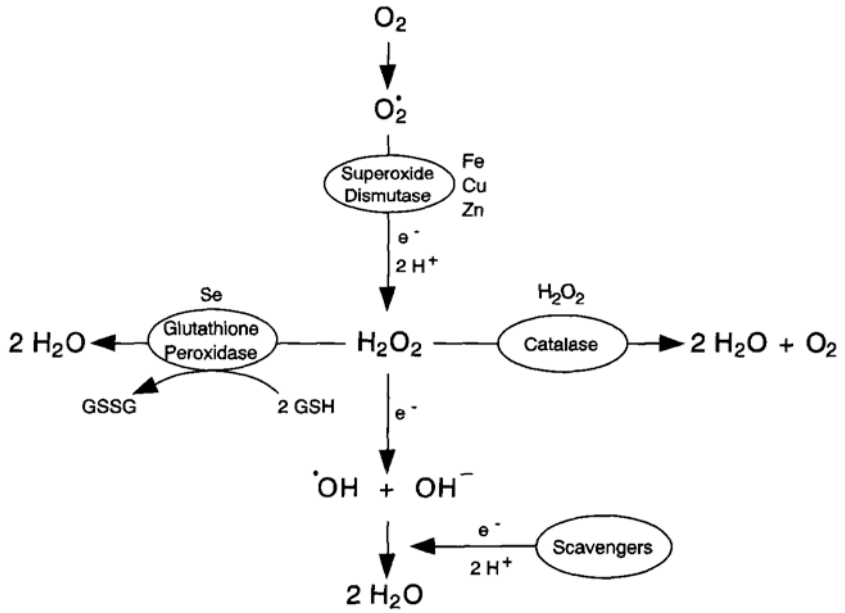


**FIGURE 21.6** Actions of antioxidant enzymes and free radical scavengers. Cofactors for superoxide dismutase can be iron (*Fe*), zinc (*Zn*) or copper (*Cu*). The cofactor for glutathione peroxidase is selenium (*Se*). *GSH* = reduced glutathione, *GSSG* = oxidized glutathione, which is a dipeptide connected by a disulfide bridge.

### *Antioxidant Protection*

Oxidative (oxygen-related) injury is kept in check by a vast array of endogenous antioxidants (22). (An antioxidant is a substance that delays or reduces the oxidation of a suitable substrate.) Some of the more important ones are described next.

### *Enzyme Antioxidants*

Normally, about 98% of the oxygen in mitochondria is reduced completely to water, and less than 2% of the toxic metabolites escape into the cytoplasm (23). This is a tribute to the actions of some en2ymes that are highlighted in Figure 21.6. Superoxide dismutase promotes the conversion of the superoxide radical to hydrogen peroxide. Although considered an antioxidant, superoxide dismutase promotes the production of another toxic oxygen metabolite (hydrogen peroxide) and, if clearance mechanisms for hydrogen peroxide are defective, superoxide dismutase can act as a prooxidant (24).

Catalase is an iron-containing heme protein that reduces hydrogen peroxide to water. It is present in most cells, and the lowest concentrations are in cardiac cells and neurons. Inhibition of the catalase enzyme does not enhance the toxicity of hydrogen peroxide for endothelial cells (25), so this enzyme may have a limited role in preventing oxidative cell injury.

Glutathione peroxidase enhances the reduction of hydrogen peroxide to water by first removing electrons from glutathione in its reduced form and then donating the electrons to hydrogen peroxide. The oxidized glutathione (GSSG) is then returned to its reduced state (GSH) by a reductase enzyme that transfers the reducing equivalents from NADPH. The total reaction can be written as follows:

Peroxidase reaction: $H_2O_2$ + 2 GSH --> 2 $H_2O$ + GSSG Reductase reaction: NADPH + $H^+$ + GSSG → 2 GSH + NADP

The activity of the glutathione peroxidase enzyme in humans is dependent on the trace element selenium. Selenium is an essential nutrient with a recommended daily allowance (RDA) of 70 micrograms for men and 55 micrograms for women (26). The absence of dietary selenium produces measurable differences in glutathione peroxidase activity after just one week (27). Selenium status can be monitored with whole blood selenium levels. The normal range is 0.5 to 2.5 mg/L. If needed, selenium can be given intravenously as sodium selenite (28). The highest daily dose that is considered safe is 200 micrograms, which can be given in divided doses of 50 $\mu$g IV every 6 hours.
Glutathione is a sulfur-containing tripeptide that is one of the major antioxidants in the human body, and is present in *molar* concentrations (0.5-10 mM/L) in most cells (29,30). It is found in all organs, but is particularly prevalent in the lung, liver, endothelium and intestinal mucosa. It is synthesized de novo within cells, and it remains sequestered in cells. Plasma levels of glutathione are three orders of magnitude lower than intracellular levels, and exogenous glutathione administration has little effect on intracellular levels (31). The popular mucolytic agent N-acetylcysteine is a glutathione analogue capable of crossing cell membranes and enhancing intracellular glutathione activity. This is the mechanism for the beneficial effects of N-acetylcysteine in acetaminophen toxicity (see Chapter 53).

*Other Antioxidants*
Vitamin E (alpha-tocopherol) is a lipid-soluble vitamin that is found within most cell membranes and helps to block oxidative injury to cell membranes. It is considered the major lipid-soluble antioxidant in the human body. The normal concentration of vitamin E in plasma is 1 mg/ dL, and a level below 0.5 mg/ dL is evidence of deficiency (32). Vitamin E deficiency may be common in critically ill patients (33), so it seems wise to check the vitamin E status in patients who are at risk for oxygenrelated injury (see later).
Vitamin C (ascorbic acid) is a water-soluble antioxidant that operates primarily in the extracellular space. Vitamin C is found in abundance in the lung, where it may playa protective role in inactivating pollutants that enter the airways.
Caeruloplasmin and transferrin account for most of the antioxidant activity in plasma (34). The antioxidant activity of both proteins is related to

their actions in limiting free iron in plasma. Caemloplasmin oxidizes iron from the Fe (II) to the Fe (III) state, and transferrin binds iron in the oxidized or *Fe III)* state. Free iron can promote oxidant cell injury by enhancing the formation of hydroxyl radicals (see Fig. 21.5) (35). The tendency for free iron to promote oxidant injury may be the reason that most of the iron in the body is sequestered and very little is allowed to roam free in plasma.

## Oxidant Stress

The risk of oxidant-induced (oxygen-induced) tissue injury is determined by the balance between oxidant and antioxidant activities. When oxidant activity exceeds the neutrali2ing capacity of the antioxidants, the excess or unopposed oxidant activity can promote tissue injury. This condition of unopposed biological oxidation is known as *oxidant stress*.

### *Pulmonary Oxygen Toxicity*

Inhaled $O_2$ can damage the lungs in any concentration, but the lungs are normally well-endowed with antioxidant activity (particularly glutathione and vitamin C) that protects the lungs from $O_2$ toxicity at the usual concentrations of inhaled $O_2$. When the inhaled $O_2$ exceeds the protective capacity of the endogenous antioxidants in the lungs, the result is a progressive and potentially lethal form of inflammatory lung injury that is clinically indistinguishable from the acute respiratory distress syndrome (ARDS), which is described in the next chapter.

#### *Species Differences*

The tendency to develop pulmonary oxygen toxicity varies in different species. For example, laboratory rats will die of respiratory failure after 5 to 7 days of breathing pure $O_2$, while sea turtles can breathe pure $O_2$ indefinitely without harm (36). This species-specific effect is important because experimental studies of pulmonary oxygen toxicity have been conducted almost solely in laboratory rats. As a result, little is known about the tendency of humans to develop pulmonary oxygen toxicity. In healthy volunteers, inhalation of 100% oxygen for brief periods of time (6 to 12 hours) results in a tracheobronchitis and a decrease in vital capacity believed to be a result of absorption atelectasis (37). The longest exposure to 100% oxygen in humans includes 5 patients with irreversible coma (3 to 4 days) and one healthy volunteer (4.5 days) (38,39). In all these cases, prolonged exposure to oxygen resulted in a pulmonary syndrome very much like ARDS.

#### *What FlO2* is *Toxic?*

Based on the observation that oxygen inhalation reduces the vital capacity when the $FIO_2$ is 0.60 or higher (37), the toxic level of $FI0_2$ was set at 0.60. The consensus seems to be that exposure to an $FI0_2$ above 0.60 for longer than 48 hours constitutes a toxic exposure to oxygen. The problem with adopting one $FI0_2$ that applies to all patients is that it neglects the

contribution of endogenous antioxidants to the risk of oxygen toxicity. If the antioxidant stores in the lungs are depleted, oxygen toxicity will develop at an $FIO_2$ that is much lower than 0.60. Antioxidant depletion may be common in ICU patients (40,41), which means that an $FI0_2$ below 0.60 may not be safe in ICU patients. Thus, it seems more reasonable to assume that any $FI0_2$ above 0.21 (room air) can represent a toxic exposure to oxygen in leu patients. Therefore, the best practice is to reduce the $FIO_2$ to the lowest tolerable level in all ICU patients. (Remember that, even though an $Ft0_2$ of 0.4 may seem safe, it is about twice the normal dose of a potentially toxic gas.)

*Promoting Antioxidant Protection*
Little attention has been given to supporting antioxidant protection to limit the risk of pulmonary oxygen toxicity. While it is not yet possible to evaluate the adequacy of antioxidant protection in individual patients, two measures may be helpful. The first is to maintain the recommended daily intake of selenium (70 μg/day for men and 55 μg/day in women), and the second is to monitor and correct deficiencies in vitamin E stores. A reliable measure of oxidant stress in exhaled breath is sorely needed to evaluate the risk of pulmonary oxygen toxicity in individual patients.

## A FINALWORD

There is little doubt that the use of oxygen in the ICU is excessive and dangerous. The routine use of oxygen should be abandoned, and the $Pa0_2$ and $Sa0_2$ should be replaced as markers of the need for inhaled oxygen because they bear no relationship to the integrity of tissue oxygenation. Possible replacements would be the $Sv0_2$ and the ($Sa0_2$ - $Sv0_2$). When cardiac output and serum hemoglobin are adequate, inhaled oxygen should be indicated for an $SvO_2$ < =50%, or an ($Sa0_2$ - $SvO_2$) > = 50% (see Chapter 11 for a description of these measurements). Finally, more attention must be given to the antioxidant status of individual patients to assess the risk of pulmonary oxygen toxicity.

## REFERENCES

## Chapter 22

## ACUTE RESPIRATORY DISTRESS SYNDROME

*Physicians think they do* a *lot for* a *patient when they- give his disease* a *name.*
*Immanuel Kant*

The condition described in this chapter has had several names over the years, including *shock lung, non-cardiogenic pulmonary edema, adult respiratory distress syndrome, acute lung injury,* and most recently, *acute respiratory distress syndrome,* or *ARDS.* None of these names provides any useful information about the condition, which is a type of inflammatory lung injury that is neither a primary disease or a single entity. Rather, it is an expression of myriad other diseases that produce diffuse inflammation in the lungs, often accompanied by inflammatory injury in other organs 0-3). It is also the leading cause of acute respiratory failure in the United States.

*PATHOGENESIS*
The first clinical report of ARDS included 12 patients with diffuse infiltrates on chest roentgenogram and hypoxemia that was resistant to supplemental oxygen (4). Seven patients died (mortality = 60%), and autopsy findings revealed dense infiltration of the lungs with leukocytes and proteinaceous material, similar to the photomicrograph in Figure 22.1. There was no evidence of infection, which indicated that ARDS is principally an inflammatory condition.

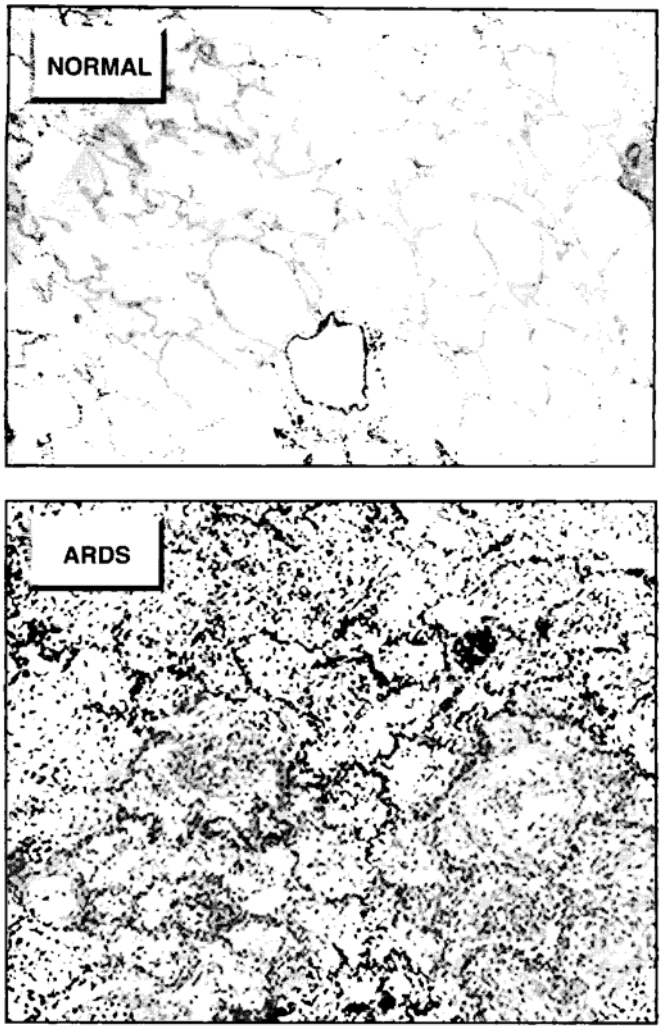


**FIGURE 22.1** Microscopic images of a normal lung and a lung in the advanced stages of ARDS. Note the dense infiltration of inflammatory cells in ARDS and the obliteration of the distal airspaces. (Photomicrograph of ARDS courtesy of Martha L Warnock, MD, University of California at San Francisco, San Francisco, CA. Image digitally retouched.)

### Inflammatory Injury

The basic pathology of ARDS is a diffuse inflammatory process that involves both lungs. The lung consolidation in ARDS is believed to originate from a systemic activation of circulating neutrophils (5). The activated neutrophils become sticky and adhere to the vascular endothelium in the pulmonary capillaries. The neutrophils then release the contents of their cytoplasmic granules (i.e., proteolytic enzymes and toxic oxygen metabolites), and this damages the endothelium and leads to a leaky-capillary type of exudation into the lung parenchyma. Neutrophils and proteinaceous material gain access to the lung parenchyma and fill the alveolar air spaces, as shown in Figure 22.1. The lung inflammation in ARDS is often destructive, and the resulting lung damage promotes further inflammation, creating a vicious cycle that leads to progressive respiratory insufficiency.

Fibrin deposition in the lungs is another characteristic feature of ARDS, and this fibrin can undergo remodeling and produce pulmonary fibrosis (similar to the process that occurs in wound healing) (6). The source of fibrin is a procoagulant state triggered by release of tissue factor from the lungs (6). The invelvement of the coagulation system in ARDS has important implications for the possible role of anticoagulation and fibrinolytic therapy in ARDS (see later).

Thus, ARDS is the resuit of inflammatory lung injury. Although it is often referred to as a type of pulmonary edema (e.g., leaky capillary or noncardiogenic pulmonary edema), this is misleading because the lungs are filled with an inflammatory exudate rather than watery edema fluid. This has important implications for the role of diuretic therapy in ARDS (see later).

### Predisposing Conditions

A variety of clinical disorders can predispose to ARDS, and the common ones are indicated on the body map in Figure 22.2. The one feature

TABLE 22.1 Predisposing Factors and Mortality in ARDS

| | Incidence of ARDS (%) | | |
|---|---|---|---|
| Predisposing Factor | ARDS | No ARDS | Mortality (%) |

| | | | |
|---|---|---|---|
| Sepsis syndrome | 41 | 69 | 50 |
| Multiple transfusions | 36 | 70 | 35 |
| Pulmonary contusion | 22 | 49 | 12 |
| Aspiration of gastric contents | 22 | 48 | 21 |
| Multiple fractures | 11 | 49 | 9 |
| Drug overdose | 9 | 35 | 4 |
| All high-risk conditions | 26 | 62 | 19 |

Data from Hudson LD el al. (7).

shared by all of these conditions is the ability to trigger a systemic inflammatory response. The incidence of ARDS in some high-risk conditions is shown in Table 22.1 (7). Overall, one of every four patients with a predisposing condition develops ARDS (see bottom of the table), and ARDS is most prevalent in patients with sepsis syndrome (defined as an infection associated with fever and leukocytosis). Note the negative impact of ARDS on survival.

**CLINICAL FEATURES**

The earliest clinical signs of ARDS include tachypnea and progressive hypoxemia, which is often refractory to supplemental oxygen. The chest roentgenogram can be unrevealing in the first few hours of the illness. However, within 24 hours, the chest roentgenogram begins to reveal bilateral pulmonary infiltrates (see Figure 22.3). Progressive hypoxemia requiring mechanical ventilation often occurs in the first 48 hours of the illness.

*Diagnostic Criteria*

In 1994, a consensus conference of experts from Europe and the United States published a set of diagnostic criteria for ARDS, which is shown in Table 22.2 (1). The hallmarks of ARDS are bilateral pulmonary infiltrates, severe hypoxemia ($PaO/FI0_2$ <200 mm Hg), the presence of a predisposing condition, and no evidence of left-heart failure (either clinically or by measuring a pulmonary artery occlusion

pressure that is < =18 mm Hg). Note that these criteria also include a condition known as *acute lung injury.* This is a less severe form of ARDS, and is distinguished from ARDS by the $PaO/FI0_2$ ratio.

*Lack of Specificity*
The diagnosis of ARDS based on clinical criteria in Table 22.2 can be problematic because many of the clinical features of ARDS are shared by other causes of acute respiratory failure (8). This is demonstrated in Table 22.3, which compares the diagnostic features of ARDS with the clinical features of severe pneumonia, acute pulmonary embolism, and

TABLE 22.2 Diagnostic Criteria for ALI and ARDS t

| |
|---|
| 1. Acute Onset |
| 2. Presence of a predisposing condition. |
| 3. Bilateral infiltrates on frontal chest x-ray. |
| 4. $Pa0_2 / FI0_2 < 200$ mm Hg for ARDS, < 300 mm Hg for ALI |
| 5. Pulmonary artery occlusion pressure , =18 mm Hg or no clinical evidence of left atrial hypertension. |

tFrom the consensus conference report in Reference 8.
*ALI* = acute lung injury, *ARDS* = acute respiratory distress syndrome.

TABLE 22.3 Features Shared by ARDS & Other Causes of Acute Respiratory Failure

| Feature | ARDS | Severe Pneumonia | Pulmonary Embolism | Cardiogenic Lung Edema |
|---|---|---|---|---|
| Acute Onset | ./ | ./ | ./ | ./ |
| Fever, Leukocytosis. | -./ | ./ | -./ | If Acute MI |
| Bilateral infiltrates | ./ | ./ | | ./ |
| $Pa0_2$ / $Fr0_2$ < 200 mm Hg | ./ | -./ | ./ | |
| PAOP < =18 mm Hg | -./ | ./ | ./ | |

cardiogenic pulmonary edema. Note the perfect match between ARDS and severe pneumonia, and the near-perfect match between ARDS and acute pulmonary embolism.

**ARDS Versus Cardiogenic Edema**

For patients who present with bilateral pulmonary infiltrates, the usual concern is to distinguish between ARDS and cardiogenic pulmonary edema (although a bilateral pneumonia is also a consideration). The appearance of the chest x-ray is usually of little or no value. A homogeneous infiltrate and the absence of pleural effusions is more characteristic of ARDS (see Figure 22.3), while patchy infiltrates emanating from the hilum and prominent pleural effusions is more characteristic of cardiogenic pulmonary edema. However, there is considerable overlap in these characteristics (e.g., pleural effusions can appear in ARDS), and the consensus view is that chest roentgenograms are not reliable for distinguishing ARDS from cardiogenic pulmonary edema 0,9,10).

*Severity of Hypoxemia*

The severity of the hypoxemia can sometimes help distinguish ARDS from cardiogenic pulmonary edema. In the early stages of ARDS, the hypoxemia is often more pronounced than the chest roentgenogram abnormalities, whereas in the early stages of cardiogenic pulmonary edema, the roentgenogram abnormalities are often more pronounced than the hypoxemia. However, there are exceptions, and severe hypoxemia can occur in cardiogenic pulmonary edema if the mixed venous oxygen pressure ($P0_2$) is reduced from a low cardiac output (see Figure 19.4).

*Pitfalls of the Wedge Pressure*

As indicated in Table 22.2, the pulmonary capillary wedge pressure (PCWP) is considered to be a valuable measurement for differentiating ARDS from cardiogenic pulmonary edema. The problem here is that the wedge pressure is not a measure of capillary hydrostatic pressure, as explained in Chapter 10. The PCWP is a measure of left-atrial pressure

(and is obtained in the absence of flow), and left-atrial pressure cannot be the same as the pulmonary capillary pressure in the presence of blood flow. That is, if the wedge (left-atrial) pressure were equivalent to the pressure in the pulmonary capillaries, there would be no pressure gradient for flow in the pulmonary veins. Thus, the capillary hydrostatic pressure must be higher than the wedge pressure.
The wedge pressure will therefore underestimate the actual capillary hydrostatic pressure. This difference is small in the normal lung, but in severe ARDS, the capillary hydrostatic pressure can be double the wedge pressure, as explained in Chapter 10. If this is the case, then a PCWP of 15 mm Hg could represent cardiogenic pulmonary edema because the capillary hydrostatic pressure may be twice this or 30 mm Hg. Because of this discrepancy, the wedge pressure should be abandoned as a diagnostic criterion for ARDS.

*Bronchoalveolar Lavage*
The most reliable method for confirming or excluding the diagnosis of ARDS is *brollchoalveolar lavage.* This procedure can be performed at the bedside using a flexible fiberoptic bronchoscope that is advanced into one of the involved lung segments. Once in place, the lung segment is lavaged with isotonic saline. The lavage fluid is then analyzed for neutrophil density and protein concentration, as described below (11).

*Neutrophils*
In normal subjects, neutrophils make up less than 5% of the cells recovered in lung lavage fluid, whereas in patients with ARDS, as many as 80% of the recovered cells are neutrophils (1). A low neutrophil count in lung lavage fluid can be used to exclude the diagnosis of ARDS, while a high neutrophil count is considered evidence of ARDS (even though pneumonia can produce similar results).

*Total Protein*
Because inflammatory exudates are rich in proteinaceous material, lung lavage fluid that is similarly rich in protein can be used as evidence of lung inflammation. When the protein concentration in lung lavage fluid is expressed as a fraction of the total protein concentration, the following criteria can be applied (2):

Protein (lavage/serum) <0.5 = Hydrostatic edema Protein (lavage/serum) >0.7 = Lung inflammation

Thus, lung inflammation is expected to produce a protein concentration that is greater than 70% of the protein concentration in serum. Although a positive test result is not specific for ARDS, it can be used as evidence of ARDS if other causes of lung inflammation (e.g., pneumonia) can be excluded on clinical grounds.
Bronchoalveolar lavage has not gained widespread acceptance as a diagnostic tool for ARDS, probably because most ICU physicians use the

diagnostic criteria in Table 22.2 to evaluate possible ARDS. Considering the nonspecific nature of these diagnostic criteria (as shown in Table 22.3), more reliable diagnostic methods like bronchoalveolar lavage are probably underutilized.

## MANAGEMENT OF ARDS

In the 40 years since ARDS was first described, only one therapeutic manipulation has proven effective in improving survival in ARDS: the use of low tidal volume mechanical ventilation. This is not really a specific therapy for ARDS, but is a lessening of the harmful effects of mechanical ventilation on the lungs. The realization that conventional mechanical ventilation is injurious to the lungs is one of the most important discoveries in critical care medicine in the last quarter-century.

### Lung-Protective Ventilation

Since the introduction of positive-pressure mechanical ventilation, large inflation volumes (tidal volumes) have been used to reduce the presumed tendency for atelectasis during mechanical ventilation. The standard tidal volumes are 10 to 15 mL/kg, which are twice the size of tidal volumes used during quiet breathing (6 to 7 mL/kg). In patients with ARDS, these large inflation volumes are delivered into lungs that have a marked reduction in functional volume. The decreased functional volume in ARDS is evident in the CT images in Figure 22.4. Note the dense lung consolidation in the posterior or dependent lung regions, and the small region of uninvolved lung in the anterior one third of the thorax.

Conventional chest radiographs in ARDS show what appears to be a homogeneous pattern of lung infiltration; however, CT images reveal that the lung infiltration in ARDS is not spread evenly throughout the lungs, but rather is confined to dependent lung regions (13). The remaining area of uninvolved lung is the functional portion of the lungs in ARDS. Because the functional lung volume in ARDS is markedly reduced, the large inflation volumes delivered by mechanical ventilation cause overdistention and rupture of the distal airspaces. This condition is called *ventilator-induced lunlg injury.*

*Ventilator-Induced Lung Injury*

Overdistention and rupture of the distal airspaces during mechanical ventilation is a volume-related rather than pressure-related injury (4), and is called *volutrauma.* (Pressure-related lung injury is called *barotrauma.)* Excessive inflation volumes produce stress fractures in the alveolar capillary interface, and this leads to infiltration of the distal airspaces with inflammatory cells and proteinaceous material. The resulting clinical condition, known as ventilator-induced lung injury (VILI), is strikingly similar to ARDS (4).

The organ injury from mechanical ventilation may not be confined to the lungs. Bronchoalveolar lavage studies have shown that volutrauma is accompanied by release of inflammatory cytokines from neutrophils that infiltrate the lungs (5). This effect is not explained by mechanical forces (volume and pressure), and is called *biotrauma.* Some have suggested that the cytokines released in the lungs could enter the systemic circulation and travel to distant organs to produce widespread inflammatory injury and multiorgan failure (6). This would mean that mechanical ventilation is as lethal as severe sepsis and other causes of multiorgan failure.

*Low- Volume Ventilation*

A total of 5 clinical trials have compared mechanical ventilation with low tidal volumes (usually 6 mL/kg) and conventional tidal volumes (usually 12 mL/kg) in patients with ARDS. In two trials, low tidal volumes were associated with fewer deaths, and in 3 trials, there was no survival benefit associated with low tidal volumes (7). The pooled results of all five trials suggests a benefit with low tidal volumes, particularly when the end-inspiratory plateau pressure (which correlates with the risk of volutrauma) is above 30 cm $H_2O$. (See Chapter 24 for an explanation of this pressure.)

The most successful trial of low tidal volume ventilation in ARDS was conducted by the ARDS Clinical Network (a network created by governmental health agencies to perform multicenter trials of ARDS treatments). This study enrolled over 800 patients with ARDS, and compared ventilation with tidal volumes of 6 mL/kg and 12 mL/kg using ***predicted body weight*** (which is the weight at which lung volumes are normal). Ventilation with low tidal volumes was associated with a 9% (absolute) reduction in mortality when the end-inspiratory plateau pressure was <30 cm H20 (8).

TABLE 22.4 Protocol for Low Volume Ventilation in ARDSt

GOALS: TV = 6 mL/kg, Ppl < 30 cm HP, pH = 7.30 - 7.45

I. FIRST STAGE:

1. Calculate patient's predicted body weight (PBW)*

Males: PBW = 50 + [2.3 x (height in inches - 60)]

Females: PBW = 45.5 + [2.3 x (height in inches - 60)]

2. Set initial tidal volume (TV) to 8 mL/kg PBW.

3. Add positive end-expiratory pressure (PEEP) at 5 - 7 cm HP,

4. Reduce TV by 1 mL/kg every 2 hours until TV = 6 mL/kg PBW.

II. SECOND STAGE

1. When TV down to 6 mL/kg, measure plateau pressure (Ppl).

A. Target Ppl < 30 cm Hp.

B. If Ppl > 30 cm HP, decrease TV in 1 mL/kg steps until Ppl drops below 30 cm $H_2O$ or TV down to 4 mL/kg.

III. THIRD STAGE

1. Monitor arterial blood gases for respiratory acidosis.

A. Target pH = 7.30 - 7.45

B. If pH 7.15 - 7.30, increase respiratory rate (RR) until pH > 7.30 or RR = 35 bpm.

C. If pH < 7.15, increase RR to 35 bpm. If pH still < 7.15, increase TV at 1 mL/kg increments until pH > 7.15.

~The predicted body weight is the weight at which lung volumes are normal.
tprotocol from the !\RDS Clinical Network web site (www.ardsnet.org).

A protocol for low volume ventilation recommended by the ARDS Clinical Network is shown in Table 22.4. This protocol is designed to achieve three goals: O) maintain a tidal volume of 6 mL/kg using predicted body weight, (2) keep the end-inspiratory plateau pressure below 30 cm $H_20$, and (3) avoid severe respiratory acidosis.

*Permissive Hypercapnia*

One of the consequences of low volume ventilation is a reduction in $CO_2$ elimination via the lungs leading to hypercapnia and respiratory acidosis. Allowing hypercapnia to persist in favor of maintaining lung-protective low-volume ventilation is known as *permissive hypercapnia* (9). The limits of tolerance to hypercapnia and respiratory acidosis are unclear, but individual reports show that $PaC0_2$levels as, high as 375 mm Hg and pH levels as low as 6.6 are remarkably free of serious side effects as long as tissue oxygenation is adequate (20). One of the more troublesome side effects of hypercapnia is brainstem respiratory stimulation with subsequent hyperventilation, which often requires neuromuscular blockade to prevent ventilator asynchrony.

There are few guidelines that identify a safe and appropriate level of hypercapnic acidosis. However, data from clinical trials of permissive

hypercapnia show that arterial $PC0_2$ levels of 60 to 70 mm Hg and arterial pH levels of 7.2 to 7.25 are safe for most patients (21). Often, the perceived risk of hypercapnic acidosis in individual patients is determined by the perceived benefit of maintaining low-volume ventilation to protect the lungs from volutrauma.

*Positive End-Expiratory Pressure*

(For a full description of this pressure, see Chapter 25.) Low-volume ventilation can be accompanied by collapse of terininal airways at the end of expiration and re-opening of the airways during lung inflation. This repetitive opening and closing of terminal airways can itself be a source of lung injury (possibly by creating shear forces that damage the airway epithelium) (22). Positive end-expiratory pressure (PEEP) can mitigate this problem by acting as a stcnt to keep small airways open at the end of expiration. For this reason, the addition of low-level PEEP (5-7 cm $H_20$) has become a standard practice during low-volume ventilation. There is no added benefit to the use of higher levels of PEEP in this condition (23).

PEEP is also used as an aid to arterial oxygenation in ARDS. The hypoxemia in ARDS can be refractory to increased (and potentially toxic) concentrations of inhaled oxygen, and the addition of PEEP often allows a reduction in the fractional concentration of inhaled oxygen (FJ02) to safer levels. The recommended combinations of PEEP and $Fi0_2$ for promoting arterial oxygenation in ARDS is shown in Table 22.5. These combinations represent the consensus views of members of the ARDS Clinical Network.

**It** is important to emphasize that the use of PEEP to promote arterial oxygenation is a flawed practice because PEEP can decrease cardiac output and this effect can counteract a PEEP-induced increase in arterial oxygenation. The effects of PEEP are described in more detail in Chapter 25.

*Fluid Management*

Fluid management in ARDS is usually aimed at reducing extravascular lung water with diuretics. While this approach has shown modest benefits in clinical measures like lung compliance, gas exchange, and length

TABLE 22.5 $FI0_2$: PEEP Combinations for Promoting Arterial Oxygenation in ARDSt

| GOAL: $Pa0_2$ = 55-80 mm Hg or Sp02 = 88-95% | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| FI02 | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 |
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 |
| $FI0_2$ | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0 | 1.0 | 1.0 |
| PEEP | 14 | 14 | 14 | 16 | 18 | 20 | 22 | 24 |

tFrom the ARDS Clinical Network web site

of time on the ventilator, there is little evidence of a consistent survival benefit (24,25). The following are some problems with diuretic therapy in ARDS that deserve mention.

*The Pitfalls of Diuretic Therapy* in *ARDS*

The first problem with the use of diuretic therapy in ARDS is the nature of the lung infiltration. While diuretics can remove the watery edema' fluid that forms as a consequence of heart failure, the lung infiltration in ARDS is an inflammatory process, and diuretics don't reduce inflammation. The photomicrograph of ARDS in Figure 22.1, which shows dense infiltration of the lungs with inflammatory cells, illustrates why diuretic therapy has had limited success in the treatment of ARDS (26).

The second problem with diuretic therapy in ARDS is the risk for hemodynamic compromise. Most patients with ARDS are receiving positive-pressure mechanical ventilation, and venous pressures must be high enough to exceed the positive intrathoracic pressure and maintain venous return to the heart. Aggressive diuretic therapy can reduce venous pressures and compromise venous return to the heart. This will ultimately compromise systemic oxygen transport (via a reduction in cardiac output), which is the single most important parameter to support in acute respiratory failure.

The hemodynamic risks of diuretic therapy in ARDS can be minimized by monitoring cardiac filling pressures and cardiac output using a pulmonary artery catheter. Diuretic therapy can then be tailored to achieve the lowest cardiac filling pressures that do not compromise cardiac output and systemic oxygen transport. Although the popularity of pulmonary artery catheters is rapidly declining, this is a situation where the information provided by the catheter would play an important role in patient management.

## Promoting Oxygen Transport

The ultimate goal of management in hypoxemic respiratory failure is to maintain oxygen delivery to the vital organs. The oxygen transport parameters are described in detail in Chapter 2, and the determinants of systemic oxygen delivery (DO) are shown in the equation below.

$$D0_2 = Q \times 13.6 \times Hb \times Sa0_2 \qquad (22.1)$$

Q is cardiac output, Hb is blood hemoglobin concentration, and $Sa0_2$ is the arterial oxyhemoglobin saturation. Systemic oxygen delivery should be maintained at a normal rate of 900 to 1100 mLlmin or 520 to 600 mL / *min/m*$^2$ when adjusted for body size (see Table 2.3 in Chapter 2 for the normal ranges of the oxygen transport parameters). Promoting systemic oxygen delivery is achieved by providing support for each of the variables identified in Equation 22.1. Support for the $Sa0_2$ has already been described in the section on ventilator management. Support for the other two components of $O_2$ delivery (cardiac output and hemoglobin) is described briefly in the sections that follow.

*Cardiac Output*
The cardiac output should be maintained at 5-6 L/min or 3-4 L/min/$m^2$ when adjusted for body size. If the cardiac output is below these normal ranges, check the central venous pressure or wedge pressure. If these pressures are not elevated, volume infusion is indicated. Despite the fear that infused fluids will move out into the lungs, the tendency for fluids to move into the lungs should be the same for ARDS and pneumonia (and there is no fear of volume infusion in pneumonia).
If volume infusion is not indicated, dobutamine is preferred over vasodilators for augmenting the cardiac output (26) because vasodilators will increase intrapulmonary shunt and will add to the gas exchange abnormality in ARDS. (See Table 16.2 for a dobutamine dose chart.) Dopamine should be avoided in ARDS because it constricts pulmonary veins, and this will cause an exaggerated rise in the pulmonary capillary hydrostatic pressure.

*Hemoglobin*
Transfusion is often recommended to keep the Hb above 10 g/dL, but this practice has no scientific basis or documented benefit, even in ventilator-dependent patients (27). Considering that blood transfusions can *calise* ARDS, and that this complication may be much more common than is currently recognized (28), it is wise to avoid transfusing blood products in patients with ARDS. If there is no evidence of tissue dysoxia or impending dysoxia (e.g., an oxygen extraction ratio 250%), there is no need to correct anemia with blood transfusions.

**Pharmacotherapy**
Despite nearly forty years of active research in search of a cure, ARDS remains an untreatable condition. The lack of effective therapy for ARDS may be reflection of the fact that ARDS is not an independent entity, but exists only as an expression of another disease entity.

*Steroids*
High-dose steroid therapy has no effect on ARDS when given within 24 hours of the onset of illness (29,30). However when steroids are given later in the course of illness, during the fibrinoproliferative phase that begins 7-14 days after the onset of illness, there is a definite survival benefit (31). One of the successful regimens involved methylprednisolone in a dose of 2 to 3 mg/kg/ day. The benefit of steroids in late ARDS may be explained by the ability of steroids to promote collagen breakdown and inhibit fibrosis (25).

*The Casualties*
The medical literature is littered with failed therapies in ARDS. Some of the more notable failures are surfactant (in adults), nitric oxide, pentoxyphylline, lisophylline, ibuprofen, prostaglandin E], ketoconazole (inhibits thromboxane) and N-acetylcysteine (an antioxidant) (24,25).

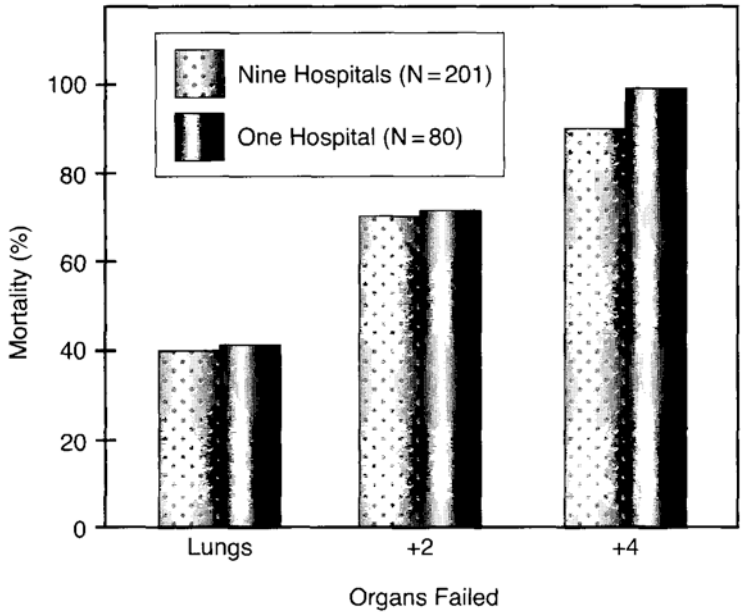


**FIGURE 22.5** Multiorgan failure and survival in ARDS. (Results of the multicenter study from Reference 33. Results of the single center study from Reference 34.)

### A Case of Misdirection?

Although the treatment of ARDS has been directed at the lungs, most of the deaths from ARDS are not due to respiratory failure. Fewer than 40% of deaths in ARDS are the result of respiratory failure (32-36). The majority of deaths are attributed to multiple organ failure. Age is also an important factor, with mortality being as much as five times higher in patients over 60 years of age (37).

The influence of multiorgan failure on survival in ARDS is shown in Figure 22.5. Included in this graph are the results of a multicenter study (33) and the results of a study conducted at a single hospital (34). Both show a steady rise in mortality as more organs fail in addition to the respiratory failure. This demonstrates that ARDS is often just one part of a multiorgan illness, and it emphasizes the limitations of management strategies that focus primarily on the lungs.

## A FINAL WORD

ARDS has been a major problem since it was first described in 1967. Some of the notable problems are listed below.

The name "acute respiratory distress syndrome" is a problem because it uses symptomatology to describe a disease entity.

(Imagine an upper respiratory tract infection being called the "acute cough syndrome".)
The diagnosis of ARDS is a problem because the diagnostic criteria are either nonspecific (e.g., acute onset) or flawed (using the wedge pressure as the hydrostatic pressure).
There is no treatment for ARDS. The one beneficial intervention (low-volume ventilation) is not really a treatment, but is a lessening of the harmful effects of mechanical ventilation.
There may never be a treatment for ARDS because it is not a single entity, but is an expression of several diverse conditions.

**REFERENCES**

**Chapter 23**

**SEVERE AIRFLOW OBSTRUCTION**

This chapter describes the acute management of patients with severe airflow obstruction as a result of asthma and chronic obstructive lung disease. The focus here is on the use of pharmacologic agents (bronchodilator drugs and corticosteroids) to relieve airways obstruction (1,2). The use of mechanical ventilation in these disorders is described in the next section of the book.

BEDSIDE MONITORING
The clinical examination is notoriously inaccurate in assessing the presence and severity of airflow obstruction (3). As a rpsult, objective measures of airflow obstruction are needed to aid in the evaluation and treatment of diseases that involve the airways. The standard index of airflow obstruction requires measurement of the forced expiratory volume in one second (FEV 1]) and the forced vital capacity (FVC): the ratio FEV 1/FVC is used as the measure of airflow obstruction (e.g., an FEV 1] /FVC ratio less than 0.7 indicates the presence of airflow obstruction). Unfortunately, these measurements are not easily obtained at the bedside. The following are some measurements that are easily performed at the bedside and can be used as alternative measures of airflow obstruction.

*Peak Expiratory Flow Rate*
The *peak expiratory flow rate* (PEFR) is the greatest flow velocity that can be obtained during a forced exhalation starting with the lungs fully inflated. The PEFR can be measured with a hand held device like the one in Figure 23.1. This device (the Mini-Wright™ peak flowmeter) is about 6 inches in length, and weighs only 3 ounces. The patient holds the device in a horizontal position close to the mouth and inhales as much air as possible (to total lung capacity). The patient then exhales as forcefully as possible into the mouthpiece of the device. The flow of exhaled gas follows a contour like the one illustrated in Figure 23.1, with the peak flow occurring very early in exhalation, when the elastic recoil of the lungs

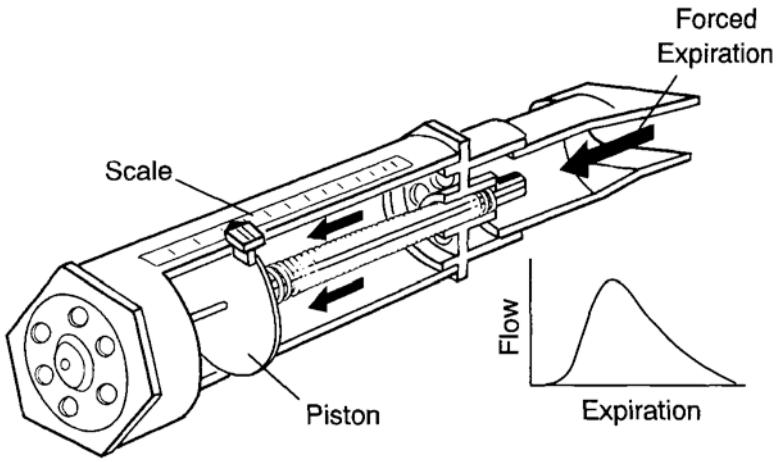


**FIGURE 23.1** A hand-held device for measuring peak expiratory flow rate (the highest point on the expiratory flow contour).

is the highest and the caliber of the airways is the greatest. The flow of exhaled gas displaces a spring-loaded piston in the peak flowmeter, and a pointer attached to the piston records the displacement on a calibrated scale etched on the outer surface of the device. The pointer remains at the point of maximal displacement, which is the PEFR in liters per minute (L/min). This maneuver is repeated twice, and the highest of the three measurements is recorded as the PEFR at that time (1).

The PEFR is an effort-dependent measurement, and is reliable only when the expiratory effort is maximal (4). Therefore, it is important to observe the patient during the peak flow maneuver to determine if a maximum effort is being expended. If not, the measurement is unreliable and should be discarded.

*The Normal PEFR*

The PEFR varies with age, gender, race, and height (5,6), and thus reference tables are needed to interpret the PEFR in individual patients (these tables are included in the Appendix at the end of the text). Predictive formulae are also available (6), but are tedious to use. The following are some general statements regarding the normal or expected PEFR.

The normal range of PEFR is 500 to 700 L/min for men and 380 to 500 L/min for women (5,6). At any given age, the PEFR in an average-sized male is at least 50% higher than the PEFR in an average-sized female.

In both sexes, the PEFR is 15 to 20% lower at age 70 than at age 20 (5).

The PEFR has a diurnal variation of 10 to 20%, with the nadir in the early morning (7,8). The relevance of this in hospitalized patients (where diurnal rhythms may be lost) is not known.

TABLE 23.1 Applications of the Peak Expiratory Flow Rate

| I. *Severity of Airways Obstruction* | |
|---|---|
| PEFR (% Predicted) | Interpretation |
| >70 | Mild obstruction |
| 50-70 | Moderate obstruction |
| <50 | *Severe* obstruction |
| <30 | Respiratory failure |
| II. *Bronchodilator Responsiveness* | |
| PEFR (% Increase) | Interpretation |
| >15 | Favorable response |
| 10-15 | Equivocal response |
| <10 | Poor response |

An alternative to the normal PEFR is the *personal best* PEFR, which is obtained when the patient is free of symptoms. This eliminates the multiple variables that must be considered when identifying the normal PEFR.

*Clinical Applications*

The PEFR can be used to evaluate the severity of airways obstruction and the response to bronchodilator therapy using the criteria shown in Table 23.1 (1). An example of how these criteria can be used is shown in the flow diagram in Figure 23.2.

*Bronchodilator Need*

Inhaled bronchodilators are often ordered routinely for hospitalized patients with a history of chronic obstructive lung disease (COPD) without determining if an individual patient responds favorably to bronchodilators. This practice does not seem justified because patients with COPD are poorly responsive to inhaled bronchodilators (which is one of the features that distinguishes COPD from asthma). The PEFR can help by providing a bedside test of bronchodilator responsiveness (see Table 23.1). The PEFR can be recorded just before, and again 20 minutes after, a bronchodilator aerosol treatment (the respiratory therapy department will perform the peak flow measurements on request). If the PEFR increases by 15% or more after the treatment (indicating a favorable response), then therapy with bronchodilator aerosols can be continued. If the post-bronchodilator PEFR does not change or increases by less than 10% (indicating a poor response), inhaled bronchodilators are not justified. This test can be performed more than once to add validity to the results.

*Peak Inspiratory Pressure*

Aerosol bronchodilator treatments are given routinely to ventilator dependent patients, often without documented need or benefit. One method

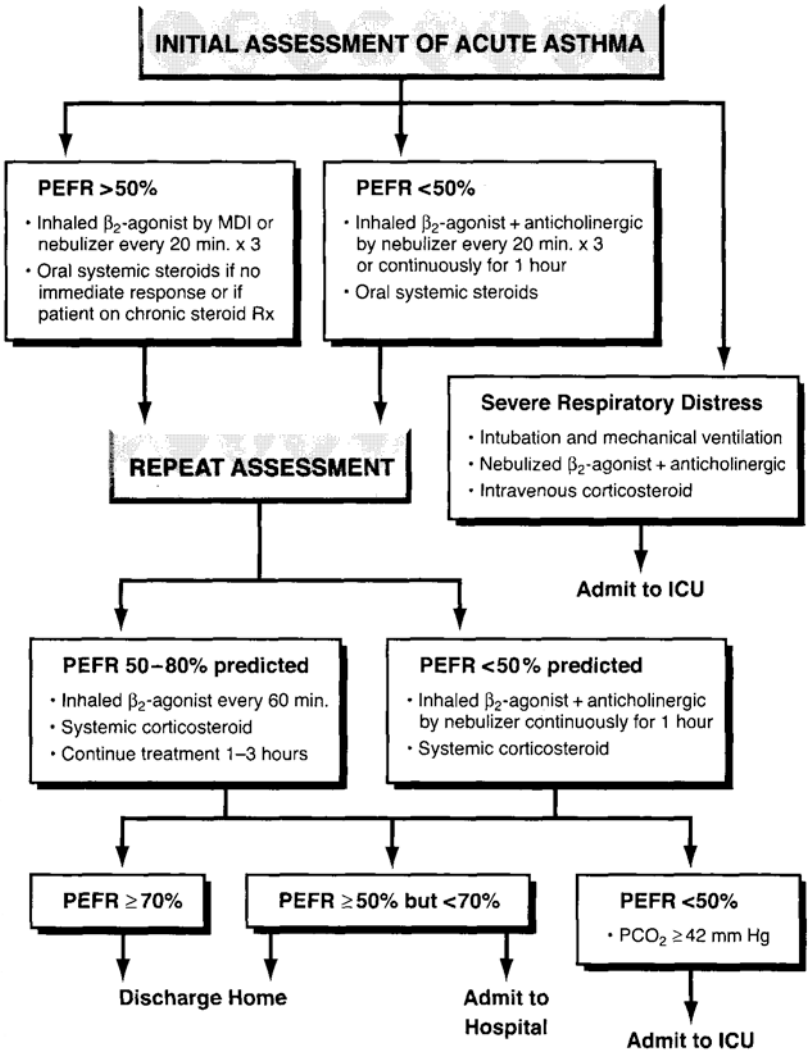


**FIGURE 23.2** Protocol for the early management of acute asthma in the emergency department. *PEFR* = peak expiratory flow rate. (Adapted from the National Asthma Education Program, Expert Panel Report 2 [1].)

of assessing bronchodilator responsiveness during positive-pressure mechanical ventilation is to monitor changes in the peak inspiratory pressure (PIP), which is the pressure in the proximal airways at the end of each lung inflation. This pressure varies in the same direction as changes in the tidal volume and changes in the resistance to flow in the endotracheal tube and airways, and it varies in the opposite direction with changes in the distensibility (compliance) of the lungs. If a bronchodilator treatment has effectively decreased airways resistance, the PIP will also decrease. Therefore, assuming all other variables are constant, a decrease

in PIP after an aerosol bronchodilator treatment can be used as evidence of bronchodilator responsiveness (9). A technique for calculating airways resistance using proximal airways pressures is described in Chapter 24.

*Auto-PEEP*
When resistance to flow in the airways is increased, exhaled gas does not escape completely from the lungs, and the gas that remains in the distal airspaces at the end of expiration creates a positive pressure relative to atmospheric pressure. (This is the same process that produces hyperinflation of the lungs in patients with severe asthma or obstructive lung disease.) The *positive end-expiratory pressure* (PEEP) in this situation is called intrinsic PEEP or *auto-PEEP,* and it is an indirect measure of the severity of airways obstruction. (The greater the airflow obstruction, the higher the auto-PEEP.) A favorable bronchodilator response should be accompanied by a decrease in the level of auto-PEEP. The measurement of auto-PEEP is described in Chapter 26.

**AEROSOL DRUG THERAPY**
The management of patients with severe airflow obstruction usually involves the administration of drugs directly into the airways. This is achieved by creating aerosols of drug solutions that can be inhaled directly into the airways. The following is a brief description of the different methods of aerosol therapy.

*Aerosol Generators*
The two devices used to generate bronchodilator aerosols are depicted in Figure 23.3 (see reference 10 for a detailed description of aerosol generators).

*Jet Nebulizer*
The jet nebulizer operates on the same principle as the high flow oxygen mask shown in Figure 21.4. One end of a narrow capillary tube is submerged in the drug solution, and a rapidly flowing stream of gas is passed over the other end of the tube. This gas jet creates a viscous drag that draws the drug solution up the capillary tube, and when the solution reaches the gas jet, it is pulverized to form the aerosol spray, which is then carried to the patient with the inspiratory gas flow. Small volume jet nebulizers use a reservoir volume of 3 to 6 mL (drug solution plus saline diluent) and can completely aerosolize the reservoir volume in less than 10 minutes.

*Metered-Dose Inhaler*
The metered dose inhaler (MOI) operates in much the same way as a canister of hair spray. The device has a pressurized canister that contains a drug solution with a boiling point below room temperature. When the canister is squeezed between the thumb and fingers, a valve opens that

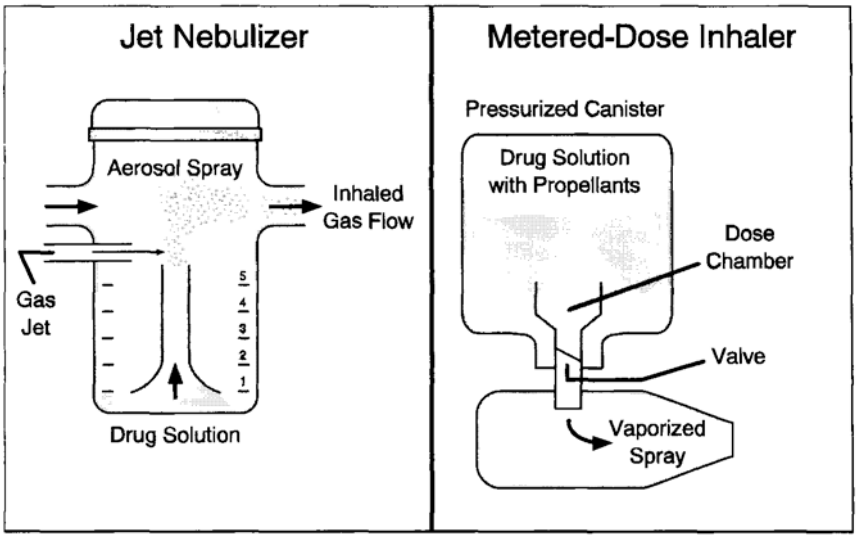


**FIGURE 23.3** Small-volume aerosol generators.

releases a fixed volume of the drug solution. The liquid immediately vaporizes when it emerges from the canister, and a liquid propellant in the solution creates a high-velocity spray. The spray emerging from the canister can have a velocity in excess of 30 meters per second (over 60 miles per hour) (11). Because of the high velocity of the emerging spray, when an MDI is placed in the mouth, most of the aerosol spray

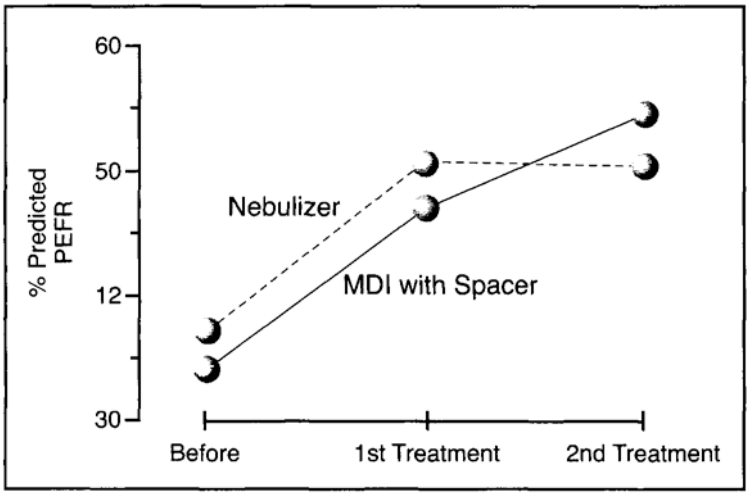


**FIGURE 23.4** Bronchodilator responses to albuterol delivered by a nebulizer (2.5 mg per treatment) and a metered-dose inhaler (*MDI*) (0.4 mg per treatment) in patients with acute exacerbation of asthma. *PEFR* = peak expiratory flow rate. (Data from Idris AH, et al. Emergency department treatment of severe asthma. Chest 1993;103:665–672.)

impacts on the posterior wall of the oropharynx and is not inhaled. This *inertial impaction* is reduced by using a spacer device to increase the distance between the MDI and mouth (this reduces the velocity of the spray reaching the mouth). Spacer devices (which are usually chambers that hold several sprays from an MOI) are now used routinely to improve lung deposition of aerosol sprays from MDIs.

*Dry Powder Inhalers*

Because of concern for the environmental hazards of liquid propellants (chlorofluorocarbons) used in MDIs, alternative inhalers were developed that produce micronized particles from powdered drug preparations. These *dry powder inhalers* require patients to generate high inspiratory flow rates (2:60 L/min) to ensure proper drug deposition in the airways (12). Because patients with severe airflow obstruction may not be able to achieve high inspiratory flow rates, dry powder inhalers are not recommended for patients with severe airflow obstruction.

*Nebulizer versus Metered-Dose Inhaler*

The dose of bronchodilators delivered by nebulizers is much greater than the dose delivered by MDIs (see Table 23.2), but the bronchodilator

TABLE 23.2 Drug Therapy for Acute Exacerbation of Asthma

| Drug Preparation | Dose | Comment |
|---|---|---|
| *Short-Acting Beta2-Receptor Agonist* | | |
| Albuterol nebulizer solution (5 mg/mL) | 2.5-5 mg *every* 20 min x 3 doses, or 10-15 mg/h r continuously, then 2.5-10 mg *every* 1-4 hrs as needed. | Dilute nebulizer solution to 5 mL and deliver at gas flows of 6-8 Umin. |
| Albuterol by MOI (90 μg/puff) | 4-8 puffs *every* 20 min up to 4 hrs, then *every* 1-4 hrs. as needed. | As *effective* as nebulizer Rx if patients able to cooperate. |
| *Anticholinergic Agent* | | |
| Ipatropium bromide nebulizer solution (0.25 mg/mL) | 0.5 mg *every* 20 min for 3 doses, then *every 2*-4 hours as needed. | Can mix in same nebulizer with albuterol. Should not be used as first-line therapy. |
| Ipatropium bromide by MOI (18 μg/puff) | 4-8 puffs as needed. | MOI delivery has not been studied in acute asthma. |
| *Corticosteroids* | | |
| Methylprednisolone (IV) prednisolone (oral) or prednisone (oral) | 120-180 mg/day in 3 or 4 divided doses for 48 hrs, then 60-80 mg/day until PEFR reaches 70% of predicted. | No difference in efficacy between IV and oral drug administration. Takes hours for drug effect to become evident. |

From Reference 1. Drug doses are for adults only.

response is often the same with both devices. This is demonstrated in Figure 23.4, which compares the response to a commonly used bronchodilator (albuterol) administered with a hand-held nebulizer (2.5 mg albuterol per treatment) or MOI with a spacer device (4 puffs or 0.36 mg albuterol per treatment) in a group of patients with severe asthma (13). After two treatments with each type of aerosol device, the increase in PEFR is equivalent. Thus, despite an almost tenfold difference in total drug dose (5 mg via nebulizer versus 0.7 mg via MDI), the bronchodilator response is the same. This discrepancy in drug doses is partly explained by the extensive drug loss (via condensation) in jet nebulizers.

*Mechanical Ventilation*

Both nebulizers and MDIs can be used to deliver effective bronchodilator treatments in ventilator-dependent patients (14,15). Aerosol deposition in the lungs with either device is reduced in intubated, mechanically ventilated patients compared with non-intubated, spontaneously breathing subjects (15), so the dose of aerosol bronchodilator may need to be increased in ventilator-dependent patients. The response to MDIs is best when a spacer is used (15): the spacer is connected to the inspiratory limb of the ventilator tubing (via a Y-connector), and five puffs from the MDI are actuated into the spacer and are inhaled during the ensuing lung inflations. Regardless of the aerosol device used, drug delivery into the airways can be enhanced by (16): *(a)* turning the humidifier off, *(b)* decreasing the inspiratory flow rate, and *(c)* increasing the inspiratory time.

*Summary*

Equivalent bronchodilator responses to nebulizer and metered-dose aerosols have been documented in both spontaneously breathing and ventilator-dependent patients (14-17). The lower doses used by MDIs provides a less costly method of aerosol bronchodilator therapy than nebulizer drug treatments. Because of the benefits in cost and labor, metered-dose inhalers should be the favored method of aerosol bronchodilator therapy in the hospital setting.

**ACUTE MANAGEMENT OF ASTHMA**

The management of adult patients with an acute exacerbation of asthma is summarized in Table 23.2 and Figure 23.2.

*Beta Receptor Agonists*

The favored bronchodilators in asthma are drugs that stimulate Beta adrenergic receptors in bronchial smooth muscle (13-2 subtype) to promote smooth muscle relaxation (12). Aerosol delivery of these Beta *2-agonists* is the preferred mode of treatment because it is more effective than oral (18) or intravenous (19) drug therapy, and has fewer side effects. Short-acting Beta agonists are preferred for the acute management of asthma because these drugs can be given in rapid succession with less risk of drug accumulation

in the body. The most extensively used short-acting 132-agonist is albuterol, which has a rapid onset of action (less than 5 minutes) when inhaled, and a bronchodilator effect that lasts 2-5 hours (12). Other short-acting Beta $_2$agonists available for use in acute asthma include metaproterenol, bitolterol, pibuterol, and levalbuterol, but none of these agents has been studied as extensively as albuterol in acute asthma. For this reason, the description of 132-agonist therapy in acute asthma will focus only on albuterol.

*Intermittent versus Continuous Aerosol Therapy*

For acute exacerbation of asthma, there are two recommended regimens for aerosol therapy with albuterol 0,2). The first regimen involves a series of repetitive 20-minute treatments using a nebulizer (with an albuterol dose of 2.5-5 mg per treatment) or an MOI (4-8 puffs per treatment with a dose of 90 $\mu$g albuterol per puff). The second regimen involves more continuous one-hour nebulizer treatments using 10-15 mg albuterol per treatment. Studies of these two regimens have revealed the following:

When using repetitive aerosol treatments every 20 minutes, there is no advantage to using an albuterol dose greater than 2.5 mg per treatment (20,21).

Most studies show no difference in efficacy between the continuous and repetitive aerosol regimens in acute asthma (20,22).

Continuous aerosol therapy is favored by many because it is easier to administer than the repetitive aerosol treatments.

*Parenteral Therapy*

For the rare asthmatic patient who does not tolerate bronchodilator aerosols (usually because of excessive coughing) parenteral therapy can be given using subcutaneous epinephrine (0.3 to 0.5 mg every 20 minutes for 3 doses) or subcutaneous terbutaline (0.25 mg every 20 minutes for 3 doses) 0). It is important to remember that parenteral Beta -agonist therapy (including intravenous therapy) offers no advantage over inhaled therapy, and is more likely to produce unwanted side effects 09,23)

*Side Effects*

High-dose aerosol therapy with Beta 2-agonists can produce a number of side effects, including tachycardia, tremors (from stimulation of skeletal muscle 132-receptors), hyperglycemia, and a decrease in serum potassium, magnesium, and phosphate levels 02,24,25). Cardiac ischemia has been reported, but is rare (24). The decrease in serum potassium is the result of a l3-receptor mediated shift of potassium into cells. This effect is particularly notable because large doses of inhaled Beta 2-agonists (e.g., 20 mg albuterol) can be used for the acute management of hyperkalemia (26).

*Anticholinergic Agents*

Despite conflicting results from clinical trials, aerosolized anticholinergic agents are recommended in combination with Beta 2-agonists for the

treatment of acute asthma (1,27). The only anticholinergic agent approved for clinical use in the United States is ipatropium bromide, a derivative of atropine that blocks muscarinic receptors in the airways. The recommended aerosol dose in acute asthma is 0.5 mg (which can be mixed with albuterol in the nebulizer) every 20 minutes for 3 doses, then every 2 to 4 hours as needed, or 4-8 puffs (18 $\mu$g per puff) by MOl (1). Systemic absorption is minimal, so anticholinergic side effects (tachycardia, dry mouth, blurred vision, urinary retention) are minimal. lpatropium is not a first-line bronchodilator drug in asthma, and is recommended in combination with Beta 2-agonist bronchodilator therapy.

*Corticosteroids*

Corticosteroids have enjoyed a 50-year reign of popularity in the management of asthma. The reason for this popularity is the anti-inflammatory effects of corticosteroids. In acute asthma, bronchospasm is an early manifestation, but lasts only 30 to 60 minutes. A second episode of airway obstruction occurs 3 to 8 hours later, and is caused by inflammation and edema in the walls of the small airways (28). Thus, bronchodilators should be effective in the early stages of acute asthma, whereas antiinflammatory agents like corticosteroids should be effective in the later stages. This may explain why steroid effects may not be apparent for 12 hours after therapy is started (29).

The relative potencies of the different therapeutic corticosteroids is shown in Table 23.3. Note that dexamethasone is the most potent antiinflammatory corticosteroid. If the efficacy of steroids in asthma is due to their anti-inflammatory actions, then why is dexamethasone almost never used to treat asthma? I will leave you to consider the answer to this question.

*Steroids in Acute Asthma*

According to the National Asthma Education Program (1,2), steroids are recommended for virtually *all* patients with acute asthma (see Fig. 23.2), even those who respond favorably to bronchodilators (where steroids are

TABLE 23.3 Comparison of Therapeutic Corticosteroids

| Corticosteroid | Equivalent Dose (mg) | RAIA* | RSRt |
|---|---|---|---|
| Hydrocortisone | 20 | 1 | 20 |
| Prednisone | 5 | 3.5 | 1 |
| Methylprednisolone | 4 | 5 | 0.5 |
| Dexamethasone | 0.75 | 30-40 | 0 |

'RAIA = relative anti-inflammatory activity.

tRSR = relative sodium retention.

From Zeiss CR. Intense pharmacotherapy. Chest 1992; 101

used to prevent relapse). The steroid preparations used most often in acute asthma are methylprednisolone (for intravenous therapy) and prednisone (for oral therapy), and the recommended dose of either is 30 to 40 mg every 6 hours (120 to 160 mg daily) for the first 48 hours, then 60 to 80 mg daily until the PEFR normalizes or reaches baseline levels. The following statements regarding steroid therapy in acute asthma deserve mention:

There is no difference in efficacy between oral and intravenous steroids (29).

The beneficial effects of steroids may not be apparent until 12 hours after therapy is started (29). Therefore, steroid therapy should not be expected to influence the clinical course of asthma in the emergency department.

There is no clearly defined dose-response curve for steroids, which means that higher doses of steroids are not superior to lower doses (29).

A IO-day course of steroids can be stopped abruptly without a tapering dose (30).

Some clinical studies show */10* benefit from steroid therapy in acute asthma (31-33).

Despite the overwhelming popularity of steroids in acute asthma, clinical studies often show meager (if any) responses to these agents in the acute care setting. This is consistent with the continued but unjustified popularity of steroids in other inflammatory conditions like septic shock and acute respiratory distress syndrome.

*Steroid Myopathy*

A myopathy has been reported in ventilator-dependent asthmatic patients treated with high dose steroids and neuromuscular blocking agents (34). Unlike the traditional steroid myopathy, which is characterized by proximal muscle weakness, the myopathy in ventilator dependent asthmatics involves both proximal and distal muscles, and is often associated with rhabdomyolysis. The etiology of this destructive myopathy is unknown, but the combination of steroids and paralyzing drugs is somehow involved. The muscle weakness can be prolonged and can hamper weaning from mechanical ventilation. Once the disorder is suspected, rapid taper of the paralyzing agents and steroids is advised. This disorder is usually reversible. (For more information on muscle weakness syndromes in ventilator-dependent patients, see Chapter 51.)

*Other Measures*

The following are some additional recommendations for the management of acute asthma:

The presence of wheezing does not always mean the presence of asthma. Other causes of wheezing include acute left heart failure (cardiac asthma), upper airway obstruction (wheezing may be

inspiratory), bronchopneumonia (wheezing may be localized), and anaphylaxis.
Supplemental oxygen is not justified if the arterial $O_2$ saturation measured by pulse oximetry is 92% or higher.
Chest x-rays are not necessary unless there is suspicion of pneumonia (e.g., fever and purulent sputum), acute pulmonary edema, or some other intrathoracic problem.
Arterial blood gases are not necessary unless the patient is in *extremis,* is cyanotic, or is refractory to initial bronchodilator therapy.
Antibiotics are not necessary unless there is specific evidence of a treatable infection.
Asthma is not a single disease entity, which means that the evaluation and management of acute asthma should be tailored to the individual patient, not the condition. The heterogeneity of asthma may explain why some patients respond promptly to therapy (with bronchodilators and steroids), while others do not.

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

*Chronic obstructive pulmonary disease* (COPD) is the term used to describe patients with constant airflow obstruction (FEV 1/FVC <70%) as a result of chronic bronchitis or emphysema. This condition is distinguished from asthma by limited responsiveness to bronchodilator therapy and the steady or chronic nature of the symptomatology (which usually involves dyspnea). Patients with COPD experience 1 or 2 episodes a year where there is a worsening of their dyspnea over a few days, often accompanied by an increase in the quantity or quality of sputum production. These *exacerbations* of COPD are responsible for about half a million hospital admissions yearly in the United States, and half of these admissions require care in an ICU (35).

*Bronchodilator Therapy*

Despite the limited responsiveness to bronchodilators that characterizes COPD, bronchodilators are used routinely in patients with COPD (often without objective evidence of benefit). For acute exacerbations of COPD, the same aerosol bronchodilators used in the acute management of asthma (albuterol and ipatropium) are recommended, but the aggressive use of bronchodilators in acute asthma (see Fig. 23.2) is not advocated for exacerbations of COPD. Also unlike asthma, the bronchodilating effects ofipatropium are equal to those of the Beta 2-agonists like albuterol, and ipatropium can be used alone as a bronchodilator in acute exacerbations of COPD (36,37). The common practice is to combine Beta 2-agonists and ipatropium, although at least three clinical studies do not support this practice (37).

*Corticosteroids*

A short course (2 weeks) of corticosteroid therapy is recommended for all patients with acute exacerbation of COPD (35-37). One example of an effective two-week steroid regimen is shown below (38).

Methylprednisolone: 125 mg IV every 6 hrs on days 1-3, then Prednisone: 60 mg once daily on days 4-7,
40 mg once daily on days 8-11,
20 mg once daily on days 12-15.

This regimen was used in the largest clinical trial of steroid therapy in acute exacerbations of COPD (38), and the results are shown in Figure 23.5 (the shaded area highlights the difference between patients who received steroids and patients who received placebo). The steroidtreated patients show a greater increase in FEV 1 in the first day of treatment (although the difference in FEV 1 is only about 120 mL, which may not be clinically significant), and this effect lasts for at least three days. It is lost by two weeks (the time when steroids are usually discontinued). The only significant side effect of this steroid treatment protocol is hyperglycemia, which occurs mostly in diabetic patients (38).

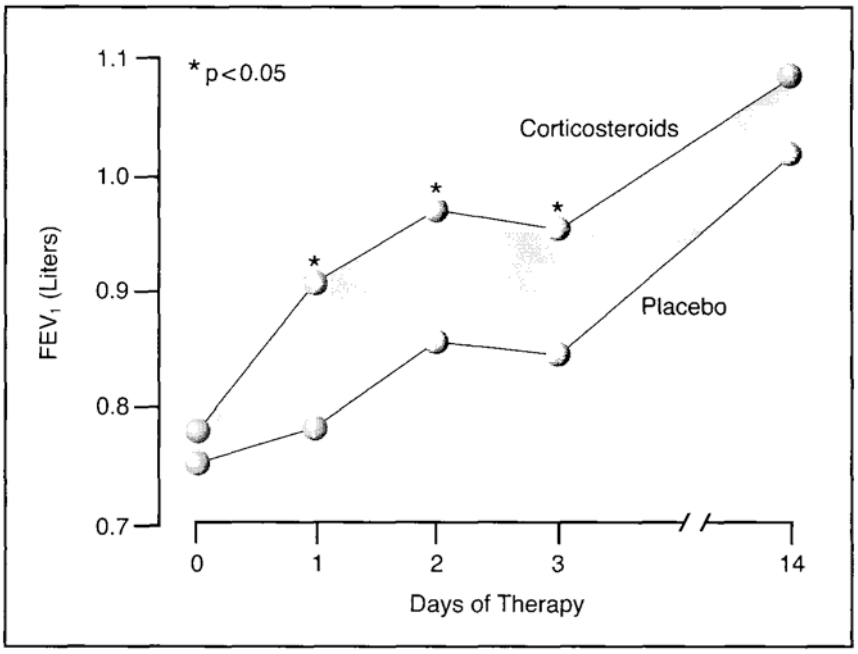


**FIGURE 23.5** Effects of a two-week course of steroid therapy on airway function in patients with acute exacerbation of COPD. $FEV_1$, is the forced expired volume in one second. Asterisks mark a significant difference between steroid-treated and placebo-treated patients (From Reference 38).

### *Antibiotic*s

Infection in the upper airways is believed to be the culprit in 80% of cases of acute exacerbation of COPD, and bacteria are isolated in about 50 to 60% of cases (39). The infections are usually polymicrobial, and the most frequent isolates that can be treated with antimicrobial agents are *Chlamydia pneumoniae, Haemophilus influenzae,* and *Streptococcus pneumoniae (39).*

Despite the prevalence of airway infection, the benefit of antimicrobial therapy in acute exacerbation of COPD has been debated for years. The major concern is that repeated use of antibiotics in this patient population had led to the emergence of antimicrobial resistance in many of the isolates (37,39). The most recent evidence using pooled data from 11 clinical trials indicates that antimicrobial therapy is justified (because of greater increments in airflow and more rapid resolution of symptoms) in patients with severe exacerbations who are at risk for a poor outcome (37). Sputum cultures are not necessary, and antibiotic selection is based on the likelihood of a poor outcome. A protocol for antibiotic selection based on risk assessment is shown in Table 23.4. The optimal duration of antimicrobial therapy is not known: the common practice is to continue therapy for at least 7 days.

### *Oxygen Inhalation*

In patients with severe COPD and chronic hypercapnia, the unregulated use of inhaled oxygen can result in further increases in arterial PC02. This phenomenon was first described in 1967 (40), and the rise in PC02 was attributed to relative hypoventilation from loss of hypoxic

TABLE 23.4 Antibiotic Selection for Acute Exacerbation of COPO Based on Risk Assessment

| | | |
|---|---|---|
| I. *Risk Assessment:* | | |
| Answer the following questions: | YES | NO |
| 1. Is the FEV, less than 50% of predicted? | | |
| 2. Does the patient *have* cardiac disease or other significant comorbid conditions? | | |
| 3. Has the patient had 3 or more exacerbations in the previous 12 months? | | |
| If the answer is YES to at least one of these questions, the patient is considered to be high-risk for an unfavorable outcome. | | |
| II. *Antibiotic Selection* | | |
| High Risk Patients: Amoxicillin-clavulanate or a newer f1uoroquinolone (gatifloxacin, levofloxacin, or moxifloxacin), | | |
| Low Risk Patients: Doxycycline, a second-generation cephalosporin (e.g., cefuroxime) or a newer macrolide (azithromycin or clarithromycin). | | |

From Sethi S. Acute exacerbation of COPD: A "multipronged" approach. J 2002; 23:217-225.

ventilatory drive. This is no longer considered to be the explanation for this phenomenon because the oxygen-induced rise in arterial $PC0_2$ is not accompanied by a decrease in ventilatory drive (41). (An increase in dead space ventilation may playa role in this phenomenon.) Regardless of the mechanism, it is important to avoid unregulated use of inhaled oxygen in patients with hypercapnic COPD to prevent unwanted increases in arterial $PC0_2$• The best practice in this regard is to monitor the arterial oxyhemoglobin saturation ($Sa0_2$) with pulse oximetry and maintain the $Sa0_2$ at about 90% and *no higher.* There is no evidence that raising the $Sa0_2$ above 90% will increase tissue oxygenation, so the common practice of maintaining the $Sa0_2$ at 95% or higher has no scientific basis.

## A FINAL WORD

The acute management of asthma and COPD can be reduced to the following simple scheme: *Give bronchodilators and steroids and wait to see what happens* (add antibiotics to the scheme for COPD). This is the same scheme that has been used for the past 30 to 40 years-only the drugs change with time.

## REFERENCES