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CHAPTER
TWENTY

RESPIRATORY ACIDOSIS

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The introduction to acid-base disorders presented in Chap. 17 should be read before proceeding with this discussion. Respiratory acidosis is a clinical disorder characterized by a reduced arterial pH (or increased H^+ concentration), an elevation in the P_{CO_2} (hypercapnia), and a variable increase in the plasma HCO_3^- concentration. Hypercapnia also constitutes the respiratory compensation to metabolic alkalosis. However, the increase in the P_{CO_2} is appropriate in this setting, since it lowers the arterial pH toward normal.

PATHOPHYSIOLOGY AND ETIOLOGY

Endogenous metabolism results in the production of approximately 15,000 mmol of CO_2 per day. Although CO_2 is not an acid, it combines with H_2O as it is added to the bloodstream, resulting in the formation of H_2CO_3:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (20\text{-}1)$$

The ensuing elevation in the H^+ concentration is then minimized because most of the excess H^+ ions combine with intracellular buffers, including hemoglobin (Hb) in red cells:

$$H_2CO_3 + Hb^- \leftrightarrow HHb + HCO_3^- \quad (20\text{-}2)$$

The HCO_3^- generated by this reaction leaves the erythrocyte and enters the extracellular fluid in exchange for extracellular Cl^-.

The net effect is that metabolically generated *CO_2 is primarily carried in the bloodstream as HCO_3^-, with little change in the extracellular pH.* These processes are reversed in the alveoli. As HHb is oxygenated, H^+ is released. These H^+ ions combine with HCO_3^- to form H_2CO_3 and then CO_2, which is excreted.

Control of Ventilation

Before we discuss how hypercapnia can occur, it is helpful to review briefly the basic aspects of ventilatory regulation. Alveolar ventilation provides the oxygen necessary for oxidative metabolism and eliminates the CO_2 produced by these metabolic processes. It is therefore appropriate that the *main physiologic stimuli to respiration are a reduction in the arterial P_{O_2} (hypoxemia) and an elevation in the arterial P_{CO_2}* (Fig. 20-1).[1,2]

The CO_2 stimulus to ventilation occurs primarily in chemosensitive areas in the respiratory center in the medulla, which respond to CO_2-induced changes in the cerebral interstitial pH.[1-3] In contrast, the initial hypoxemic enhancement of ventilation is mostly mediated by chemoreceptors in the carotid bodies, which are located near the bifurcation of the carotid arteries.[1,4] In normal subjects, these regulatory processes permit adequate oxygenation to be maintained and the arterial P_{CO_2} to be held within narrow limits (40 ± 4 mmHg), despite the large daily CO_2 load and variability in the respiratory quotient and metabolic rate.

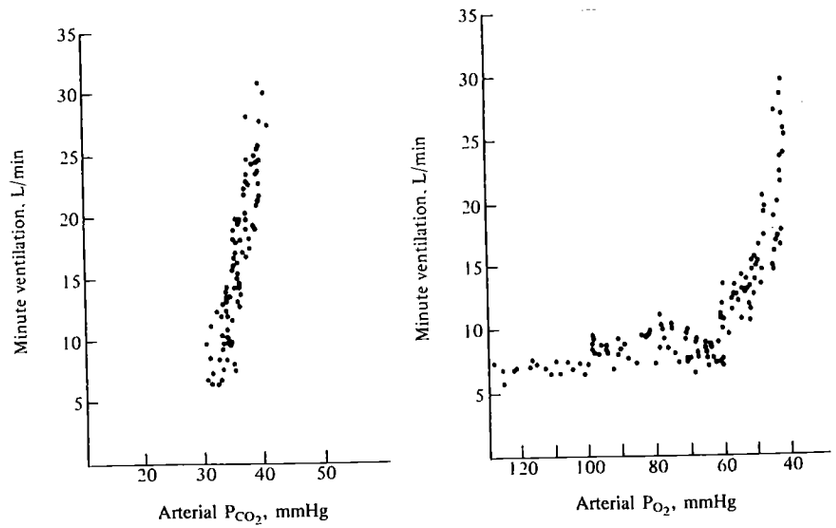

Figure 20-1 Relationship between arterial P_{CO_2} (left panel) and P_{O_2} (right panel) and the respiratory minute volume in normal subjects. (*Adapted from Hudgel DW, Control of breathing in asthma, in Weiss EB, Segal MS, Stein M (eds):* Bronchial Asthma: Mechanisms and Therapeutics, *2d ed. Boston, Little, Brown, 1984, with permission.*)

Carbon dioxide is the major stimulus to respiration, and minute ventilation is enhanced by even minor elevations in the arterial P_{CO_2} (Fig. 20-1). For example, among most normal subjects in whom hypercapnia is induced by breathing a hypercapnic gas mixture, minute ventilation rises by 1 to 4 L for every 1 mmHg in the P_{CO_2}.[2,5]

In contrast, hypoxemia does not begin to substantially promote ventilation until the arterial P_{O_2} is less than 50 to 60 mmHg (Figs. 20-1 and 20-2). Lesser degrees of hypoxemia initially increase ventilation; however, the ensuing fall in P_{CO_2} raises the extracellular pH, which depresses respiration and blunts the hypoxemic stimulus.

The importance of pH in influencing the ventilatory response to hypoxemia is illustrated by the upper curve in Fig. 20-2. If the arterial P_{CO_2} is held at normal values (or is elevated because of intrinsic lung disease), then the limiting respiratory alkalosis does not occur and ventilation begins to be enhanced at a much higher arterial P_{O_2} of 70 to 80 mmHg (Fig. 20-2).[2] This relationship has important implications for the control of ventilation in patients with chronic respiratory acidosis (see below).

Development of Hypercapnia

Since the CO_2 stimulus to ventilation is so strong, hypercapnia and respiratory acidosis are almost always due to a reduction in effective alveolar ventilation, not

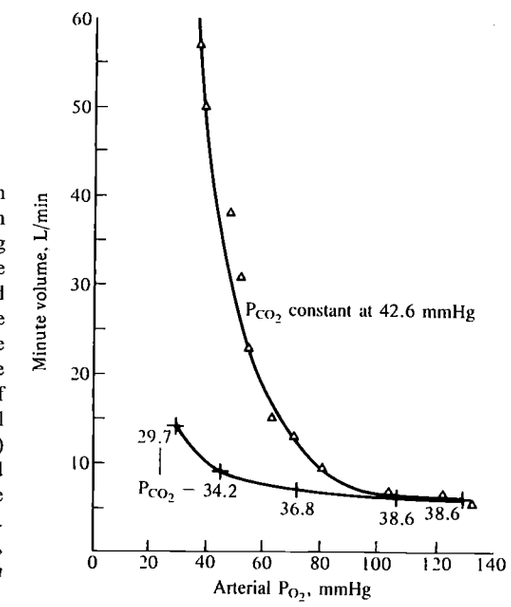

Figure 20-2 Influence of arterial P_{CO_2} on the ventilatory response to hypoxemia. In normal subjects (lower curve), lowering the partial pressure of oxygen in the inspired air increases ventilation and lowers the arterial P_{CO_2}. However, these changes are relatively minor until the arterial P_{O_2} falls below 50 mmHg. The earlier and greater degree of hyperventilation seen when the arterial P_{CO_2} is held constant (upper curve) indicates that the development of mild hypocapnic alkalosis normally limits the ventilatory response to hypoxemia. (*Adapted from Loeschcke HH, Gertz KH,* Arch Ges Physiol *267:460, 1958, with permission.*)

an increase in CO_2 production. Hypoventilation can occur when there is interference with any step in the ventilatory process (Table 20-1).[5] In patients with reduced respiratory drive or neuromuscular dysfunction, for example, there tends to be a generalized fall in alveolar ventilation. In contrast, CO_2 retention in intrinsic pulmonary disease is thought to be due primarily to an *imbalance between ventilation and perfusion* (which is functionally equivalent to increasing the amount of dead space to tidal volume ratio).[6] The hypercapnia in this setting is

Table 20-1 Causes of acute and chronic respiratory acidosis

Inhibition of the medullary respiratory center
- A. Acute
  1. Drugs: opiates, anesthetics, sedatives
  2. Oxygen in chronic hypercapnia
  3. Cardiac arrest
  4. Central sleep apnea
- B. Chronic
  1. Extreme obesity (Pickwickian syndrome)
  2. Central nervous system lesions (rare)
  3. Metabolic alkalosis (although hypercapnia is an appropriate response to the rise in pH in this setting)

Disorders of the respiratory muscles and chest wall
- A. Acute
  1. Muscle weakness: crisis in myasthenia gravis, periodic paralysis, aminoglycosides, Guillain-Barré syndrome, severe hypokalemia or hypophosphatemia
- B. Chronic
  1. Muscle weakness: spinal cord injury, poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, myxedema
  2. Kyphoscoliosis
  3. Extreme obesity

Upper airway obstruction
- A. Acute
  1. Aspiration of foreign body or vomitus
  2. Obstructive sleep apnea
  3. Laryngospasm

Disorders affecting gas exchange across the pulmonary capillary
- A. Acute
  1. Exacerbation of underlying lung disease (including increased CO_2 production with high-carbohydrate diet)
  2. Adult respiratory distress syndrome
  3. Acute cardiogenic pulmonary edema
  4. Severe asthma or pneumonia
  5. Pneumothorax or hemothorax
- B. Chronic
  1. Chronic obstructive pulmonary disease: bronchitis, emphysema
  2. Extreme obesity

Mechanical ventilation

in part beneficial in that it allows the metabolically produced CO_2 to be excreted at a lower minute ventilation, thereby diminishing the work of breathing and often reducing the feeling of breathlessness.[5]

If ventilatory function is not restored, the decrease in pH produced by CO_2 retention is minimized by the cell buffers and by increased renal H^+ secretion, both of which result in an elevation in the plasma HCO_3^- concentration. Since the renal response occurs over several days,[7] protection of the extracellular pH in acute respiratory acidosis is much less efficient than that in chronic respiratory acidosis (see Figs. 20-3 and 20-4).

Relationship between Hypercapnia and Hypoxemia

All patients with hypercapnia who are breathing room air experience a fall in alveolar and arterial P_{O_2} because the sum of partial pressures of all gases in the alveoli must equal atmospheric pressure. In most cases, *hypoxemia occurs earlier and is more prominent than hypercapnia.* Two factors contribute to this difference:

- CO_2 can diffuse across the alveolar capillary wall 20 times as quickly as O_2.
- As patients attempt to increase ventilation in relatively normal segments of the lung, more CO_2 can be excreted but *more O_2 cannot be taken up*, since the saturation of hemoglobin already approaches 100 percent in these areas.

The clinical importance of this relationship between the arterial P_{O_2} and P_{CO_2} can be illustrated by the sequence seen in patients with acute asthma.[8] The combination of mucous plugs and bronchoconstriction initially induces hypoxemia; both the fall in P_{O_2} and activation of intrapulmonary mechanoreceptors then lead to enhanced ventilation.[8,9] Thus, a mild to moderate asthmatic attack is associated with hypocapnia and respiratory *alkalosis*. With increasing severity of the attack,

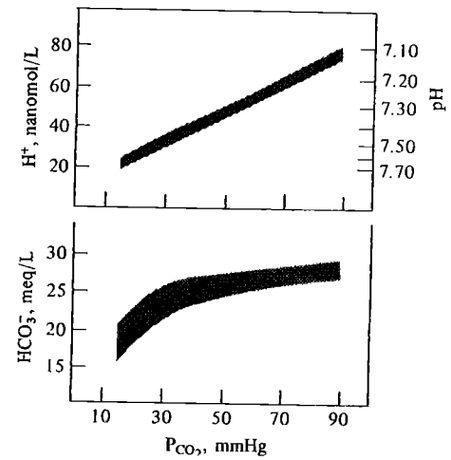

Figure 20-3 Combined significance bands for plasma pH and H^+ and HCO_3^- concentration in acute hypocapnia and hypercapnia in humans. In uncomplicated acute respiratory acid-base disorders, values for the H^+ and HCO_3^- concentrations will, with an estimated 95 percent probability, fall within the band. Observations lying outside the band indicate the presence of a complicating metabolic acid-base disturbance. (*From Arbus GS, Herbert LA, Levesque PR, et al,* N Engl J Med *280:117, 1969. By permission from the* New England Journal of Medicine.)

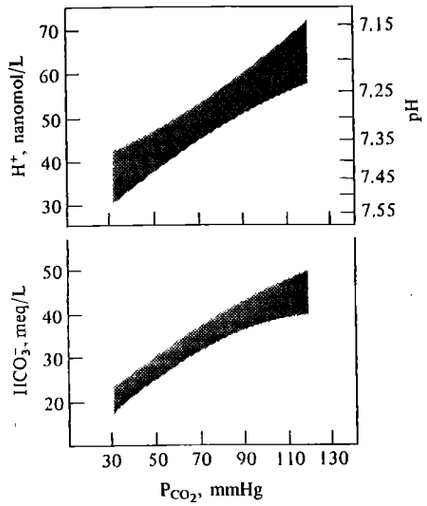

Figure 20-4 Ninety-five percent significance bands for plasma pH and H^+ and HCO_3^- concentrations in chronic hypercapnia. Note that, per change in P_{CO_2}, there is much less change in H^+ concentration and pH than in acute hypercapnia (Fig. 20-3). This reflects the effect of increased renal HCO_3^- generation. (*From Schwartz WB, Brackett NC Jr, Cohen JJ,* J Clin Invest *44:291, 1965, by copyright permission of the American Society for Clinical Investigation.*)

airway resistance rises, the maximal minute ventilation falls, and consequently the P_{CO_2} rises, eventually to normal and even hypercapnic levels. Thus, the combination of hypoxemia and a "normal" P_{CO_2} of 40 mmHg represents severe disease in the acute asthmatic.[8] This principle can be applied generally to patients with intrinsic lung disease: Hypercapnia is a *late finding*, and even a small elevation in the P_{CO_2} of a few millimeters of mercury indicates *advanced pulmonary dysfunction* or a concomitant insult to ventilatory drive (e.g., narcotic use), since CO_2 is normally such a powerful stimulus to ventilation (Fig. 20-1).

Although hypoxemia-induced hyperventilation helps to delay the onset or minimize the degree of hypercapnia, there is a 16-fold variability (probably inherited) in the sensitivity to hypoxemic stimuli.[5,10,11] Those subjects who are less sensitive to hypoxemia will be more likely to develop respiratory acidosis in the presence of an appropriate cause, such as chronic bronchitis or marked obesity (see below).

Regulation of Ventilation in Chronic Respiratory Acidosis

Two general statements are often made concerning ventilatory control in the patient with chronic hypercapnia:

- The respiratory centers become less sensitive to the CO_2 and therefore the acidemic drive to ventilation.
- As a result, hypoxemia becomes the primary stimulus to respiration.

However, these conclusions are based upon observations that are subject to somewhat different interpretation.

Insensitivity to CO_2 Evidence for insensitivity to CO_2 is primarily based upon experiments that showed that patients with chronic respiratory acidosis have a *lesser increase in ventilation* than normals when the P_{CO_2} is raised by increasing the CO_2 content of inspired air (Fig. 20-5). This apparent insensitivity, however, may, at least in part, reflect the high plasma HCO_3^- concentration induced by the renal compensation in this setting.[5,12] From the law of mass action,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \tag{20-3}$$

it can be seen that a given rise in the P_{CO_2} will induce a smaller increase in the arterial H^+ concentration when the plasma HCO_3^- concentration is elevated. Thus, the lesser increment in ventilation in chronic respiratory acidosis and therefore the apparent insensitivity to CO_2 may simply reflect the *lesser rise in H^+ concentration.*[12,13]

Consider, for example, the response to ammonium chloride, which is metabolized to hydrochloric acid and reverses the compensatory rise in the plasma HCO_3^- concentration. In this setting, the slope of the curve between alveolar ventilation and the P_{CO_2} increases toward normal (Fig. 20-5), being limited by the mechanical properties of the diseased lung, not by the responsiveness to pH.[12] This enhanced sensitivity to CO_2 is directly related to the fall in the plasma HCO_3^- concentration, since the increase in ventilation *per increase in H^+ concentration* is the same in the control state and after the administration of ammonium chloride.[12,13]

In addition to normalizing the slope, reducing the plasma HCO_3^- concentration also leads to an increase in the baseline rate of ventilation, resulting in a fall in

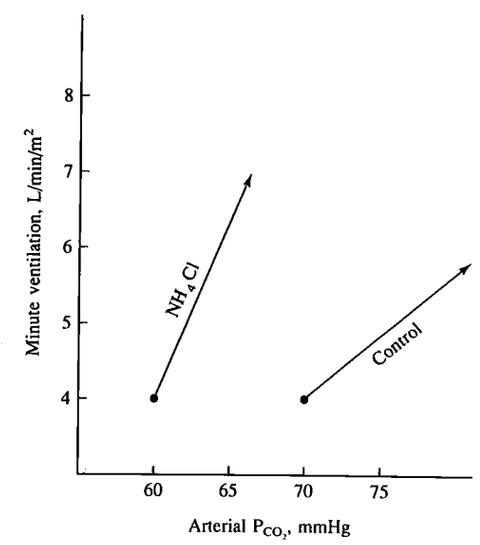

Figure 20-5 Ventilatory responses to inhalation of CO_2 in a patient with chronic hypercapnia in the control state and after the HCO_3^- concentration has been lowered by the administration of ammonium chloride. The latter therapy increases baseline ventilation (as evidenced by a lower initial P_{CO_2}) and increases the respiratory responsiveness to CO_2 toward normal. (*From Goldring RM, Turino GM, Heinemann HO,* Am J Med *51:772, 1971, with permission.*)

P_{CO_2} and a rise in P_{O_2} (Fig. 20-5).[12-14] These findings indicate that the renal compensation to chronic hypercapnia has two effects: *It protects the extracellular pH, but, in so doing, it limits the stimulus to respiration, aggravating the hypoxemia and hypercapnia.* Similarly, the induction of metabolic alkalosis with diuretic therapy also suppresses ventilation, further evidence that the pH stimulus is intact.[15]

Dependence upon hypoxemia Patients with chronic respiratory acidosis do rely upon hypoxemia to stimulate ventilation.[16] This relationship, however, is based not upon insensitivity to pH, but upon two other factors. First, the renal compensation, plus the frequent concomitant use of diuretics for edema in cor pulmonale, results in a rise in the plasma HCO_3^- concentration that returns the extracellular pH toward or, in some cases, above normal. Thus, there is little or no acidemic stimulus to ventilation in many patients with chronic hypercapnia.

Second, the relationship between the P_{O_2} and ventilation is altered in the presence of a high P_{CO_2}. As shown in Fig. 20-2, hypoxemia does not importantly stimulate respiration in normals until the P_{O_2} is below 50 to 60 mmHg, because of the potent suppressive effect of concurrent hypocapnia and respiratory alkalosis. In comparison, this fall in P_{CO_2} does not occur in chronic respiratory acidosis; as a result, ventilation is enhanced as soon as the P_{O_2} falls below 80 mmHg.

Correction of hypoxemia is important clinically, since maintaining the P_{O_2} above 55 mmHg improves both survival and the quality of life in patients with chronic lung disease (see "Treatment," below).[17-19] However, oxygen must be given carefully, because rapid and excessive correction can produce a further elevation in the P_{CO_2} that, if marked, can lead to neurologic symptoms.[11,16,17]

Interestingly, a reduction in minute ventilation is not the primary factor responsible for the development of worsening hypercapnia.[11,20,21] In one study, for example, the administration of oxygen to patients with chronic lung disease and acute respiratory failure produced a 7 percent reduction in minute ventilation, which accounted for only 5 mmHg of the 23 mmHg elevation in P_{CO_2}.[11] Of greater importance were worsening of ventilation/perfusion mismatching due to attenuation of hypoxemia-induced vasoconstriction (which will increase the dead space to tidal volume ratio by increasing blood flow to poorly ventilated areas) and decreased affinity of hemoglobin for CO_2 (the Haldane effect).

Acute Respiratory Acidosis

The ability to acutely protect the extracellular pH is different in metabolic and respiratory acidosis. In the former, extracellular and intracellular buffering and compensatory hyperventilation all minimize the fall in pH (see Chap. 19). In contrast, the body is not so well adapted to handle an acute elevation in the P_{CO_2}. There is *virtually no extracellular buffering*, because HCO_3^- cannot buffer H_2CO_3:[22]

$$H_2CO_3 + HCO_3^- \rightarrow H_2CO_3 + HCO_3^- \qquad (20\text{-}4)$$

Since the renal response takes time to develop, the cell buffers, particularly hemoglobin [Eq. (20-2)] and proteins, constitute the only protection against acute hypercapnia:

$$H_2CO_3 + Buf^- \rightarrow HBuf + HCO_3^- \qquad (20\text{-}5)$$

As a result of these buffering reactions, there is an increase in the plasma HCO_3^- concentration, averaging *1 meq/L for every 10 mmHg rise in the* P_{CO_2} (Fig. 20-4).[23,24] Thus, if the P_{CO_2} is acutely increased to 80 mmHg, there will be approximately a 4-meq/L elevation in the plasma HCO_3^- concentration to 28 meq/L and a potentially serious reduction in the extracellular pH to 7.17:

$$pH = 6.10 + \log \frac{28}{0.03(80)}$$
$$= 7.17$$

This is not very efficient, since the pH would have been only slightly lower at 7.10 if there were no buffering and the plasma HCO_3^- concentration had remained at 24 meq/L. A more severe reduction in the pH to below 7.00 can occur when there is a combined respiratory and metabolic acidosis, as with acute pulmonary edema and lactic acidosis due to severe heart failure.[25]

Etiology Common causes of acute respiratory acidosis include acute exacerbations of underlying lung disease, severe asthma or pneumonia, pulmonary edema, and suppression of the respiratory center following a cardiac arrest, a drug overdose, or the administration of oxygen to a patient with chronic hypercapnia.[11,26]

In addition, an increasingly recognized cause of hypercapnia is the *sleep apnea syndrome*.[27-29] This disorder is characterized by multiple (up to several hundred) apneic episodes per night associated with short periods of arousal (which are not apparent to the patient) due to hypoxemia and hypercapnia. Three different types of sleep apnea have been recognized: *central*, in which rare cerebral disorders interfere with the medullary control of ventilation; *obstructive*, in which there is abnormal passive collapse of the pharyngeal muscles during inspiration, such that the airway becomes occluded from the apposition of the tongue and soft palate against the posterior oropharynx; and a *mixed* central and obstructive picture.[28-30] Most patients have at least some obstructive component, which is typically manifested by loud snoring. Obesity, hypothyroidism, tonsillar enlargement, and nasal obstruction also may contribute to the development of inspiratory obstruction.[31]

The sleep apnea syndrome is associated with a variety of occasionally subtle clinical manifestations, which are due both to the repeated episodes of hypoxemia and hypercapnia and/or to the lack of uninterrupted sleep. These include headaches, daytime somnolence and fatigue, morning confusion with difficulty in concentration, personality changes, depression, persistent pulmonary and systemic hypertension, and potentially life-threatening cardiac arrhythmias.[28,29,32] Serious job-related and familial problems frequently ensue.

The diagnosis of sleep apnea should be suspected from the clinical history (particularly loud snoring and daytime somnolence) and can be confirmed by appropriate evaluation while the patient is asleep.[33] Cardiac monitoring is performed as part of the polysomnographic evaluation to check for the presence of serious arrhythmias. Effective treatment can rapidly reverse almost all of the clinical findings.[34]

Chronic hypercapnia is unusual in the sleep apnea syndrome, since the CO_2 retained during apneic episodes can be excreted when the patient is awake and ventilation is relatively normal.[5] In a minority of cases, the combination of underlying lung disease, obesity, and repetitive apneic episodes (including those due to daytime somnolence) can lead to a low total daily alveolar ventilation and persistent CO_2 retention.[35,36] This disorder is called the obesity hypoventilation syndrome.[37]

Finally, mechanical ventilation may be associated with hypercapnia if the rate of effective alveolar ventilation is inadequate. These patients, in whom ventilation is *fixed*, may also retain CO_2 if the rate of CO_2 production is increased. This sequence can occur either with the administration of $NaHCO_3$ to treat lactic acidosis during cardiopulmonary resuscitation[27,38-40] or with enteral or parenteral overfeeding.[41] In the former setting, the presence of marked hypercapnia may be missed if arterial blood is measured, since the lungs are capable of removing CO_2 from the diminished amount of blood flow that is delivered. Use of mixed venous blood is required to more closely measure acid-base status at the tissue level (see page 598).[42]

Chronic Respiratory Acidosis

The acid-base picture is different with chronic hypercapnia because of the compensatory renal response. The persistent elevation in the P_{CO_2} stimulates renal H^+ secretion, resulting in the addition of HCO_3^- to the extracellular fluid (see page 348).[7] The net effect is that, after 3 to 5 days, a new steady state is attained in which there is roughly a *3.5-meq/L increase in the plasma HCO_3^- concentration for every 10 mmHg increment in the P_{CO_2}* (Fig. 20-4).[43,44]

If, for example, the P_{CO_2} were chronically increased to 80 mmHg, the plasma HCO_3^- concentration should rise by approximately 14 meq/L, up to a level of 38 meq/L. This response is extremely effective, since the arterial pH falls only to 7.30, in contrast to 7.17, as seen above, with a similar degree of acute hypercapnia. The efficiency of the renal compensation has allowed some patients to tolerate a P_{CO_2} as high as 90 to 110 mmHg without a fall in the arterial pH to less than 7.25 and without symptoms as long as adequate oxygenation is maintained.[45]

The extent of the rise in the plasma HCO_3^- concentration in chronic respiratory acidosis is determined *solely by the increase in renal H^+ secretion*, which is presumably mediated by a fall in renal tubular cell pH induced by the extracellular acidemia. The net result is that maximal HCO_3^- reabsorptive capacity is enhanced and the plasma HCO_3^- concentration rises to a new steady state level as in

Fig. 20-4. Exogenous alkali therapy is both unnecessary (since the pH is so well protected) and ineffective, as the excess HCO_3^- is rapidly excreted in the urine without raising the final plasma HCO_3^- concentration.[46]

Etiology Chronic respiratory acidosis is a relatively common clinical disturbance that is most often due to chronic obstructive lung disease (bronchitis and emphysema) in smokers. Despite the presence of severe intrinsic pulmonary dysfunction, it is not completely understood why some patients become hypercapnic and hypoxemic relatively early ("blue bloaters"), whereas others do not ("pink puffers"). Some *unaffected* family members of patients with chronic hypercapnia have a reduced ventilatory response to hypoxemia and, to a lesser degree, hypercapnia, presumably because of genetic variation in the sensitivity of the respiratory center.[47]

Such genetic factors can lead to the following sequence: Lung disease initially impairs net alveolar gas exchange, resulting in hypoxemia and eventually hypercapnia, both of which can stimulate ventilation and return the arterial P_{O_2} and P_{CO_2} toward normal. Persistent hypercapnia will occur relatively early (as in blue bloaters) when the ventilatory response to these stimuli is impaired. If, on the other hand, the central control of respiration is normal, persistent hypercapnia will not occur until pulmonary dysfunction is more severe (as in pink puffers).[5]

A similar problem may be present when chronic respiratory acidosis occurs in extremely obese patients (called the obesity hyperventilation or Pickwickian syndrome).[36-38] It had been assumed that the primary problem in this disorder was increased weight of the chest wall, leading to enhanced work of breathing and inspiratory muscle weakness.[48] Reversal of the hypercapnia with weight loss in some patients is consistent with this hypothesis. However, the following observations suggest that factors other than obesity also play a contributory role. First, most morbidly obese patients do not become hypercapnic, and, in those who do, there is no correlation between the degree of obesity and the ventilatory abnormalities.[49] Second, a more normal ventilatory pattern can be produced in some patients with progesterone (a direct respiratory stimulant);[29,50,51] this finding indicates that these patients can increase alveolar ventilation and raises the possibility of an associated central defect.

An abnormality in respiratory control is also suggested by the demonstration that obese hypoventilators have decreased respiratory responsiveness to both hypoxemia and hypercapnia.[49,52,53] In contrast, obese patients with normal ventilation respond normally to these stimuli.[53,54] Once again, an inherited defect in ventilatory regulation may select out those obese patients who will develop chronic hypercapnia.

Obese hypoventilators may also have a component of obstructive sleep apnea.[31] The symptoms are somewhat similar to these two conditions, as many Pickwickian patients complain of excessive daytime somnolence. However, there are also important differences, since obstructive sleep apnea alone is uncommonly associated with chronic CO_2 retention.[35]

SYMPTOMS

Severe *acute* respiratory acidosis can produce a variety of neurologic abnormalities.[55] The initial symptoms include headache, blurred vision, restlessness, and anxiety, which can progress to tremors, asterixis, delirium, and somnolence (called CO_2 narcosis). The cerebrospinal fluid (CSF) pressure is often elevated, and papilledema may be seen. These latter effects may be mediated in part by an acidemia-induced elevation in cerebral blood flow.[56] This hemodynamic change can be viewed as an appropriate response, since the increase in cerebral perfusion will tend to wash away the excess CO_2, thereby returning the cerebral pH toward normal.[56]

Both the neurologic symptoms and the increase in cerebral blood flow appear to be related to changes in the CSF (or cerebral interstitial) pH, not to the arterial pH or P_{CO_2}.[57,58] CO_2 is lipid-soluble and rapidly equilibrates across the blood-brain barrier; HCO_3^-, in comparison, is a polar compound that crosses this barrier very slowly. Thus, acute hypercapnia produces a greater fall in CSF pH than does acute metabolic acidosis;[57] this probably explains why neurologic abnormalities are less prominent in the latter disorder. Symptoms are also less common with *chronic* hypercapnia, since the renal compensation returns the arterial pH and ultimately the CSF pH toward normal.

In addition to neurologic abnormalities, arrhythmias and peripheral vasodilation may combine to produce severe hypotension if the systemic pH is reduced to below 7.10. In the patient with underlying lung disease, this problem is most often seen when respiratory acidosis is complicated by a superimposed metabolic acidosis.

Chronic respiratory acidosis is also commonly associated with cor pulmonale and peripheral edema. The cardiac output and glomerular filtration rate (GFR) are usually normal to near normal in this disorder, which generally occurs only in those patients with severe lung disease who are hypercapnic.[58] These findings suggest a direct role for CO_2 in the renal Na^+ retention in this setting, although marked hypoxemia also may contribute (see page 509).[58,59]

DIAGNOSIS

The presence of an acid pH and hypercapnia is diagnostic of respiratory acidosis. However, identifying the underlying acid-base disorder is more complicated than in metabolic acidosis or alkalosis, since the responses to acute and chronic respiratory acidosis are different. The following examples will illustrate how the confidence bands in Figs. 20-3 and 20-4 can be used in the evaluation of patients with respiratory acidosis. As will be demonstrated, there is *no substitute for an accurate and complete history*, since a given set of arterial blood values can be associated with several different disorders.

In acute hypercapnia, the plasma HCO_3^- concentration should be between 24 and 29 meq/L (Fig. 20-3). Values above or below this range indicate superimposed metabolic disorders. For example:

Case history 20-1 A previously well patient is brought into the emergency room in a moribund state. Physical examination and chest x-ray suggest acute pulmonary edema. The laboratory tests include the following:

$$\text{Arterial pH} = 7.02$$
$$P_{CO_2} = 60 \text{ mmHg}$$
$$[HCO_3^-] = 15 \text{ meq/L}$$
$$P_{O_2} = 40 \text{ mmHg}$$

Comment Since the plasma HCO_3^- concentration should rise 1 meq/L for each 10 mmHg increment in P_{CO_2} in acute respiratory acidosis, an acute elevation of the P_{CO_2} to 60 mmHg should increase the plasma HCO_3^- concentration to 26 meq/L (pH of 7.24). Therefore, the findings in this patient represent a combined respiratory and metabolic acidosis, a life-threatening combination not infrequently seen in severe acute pulmonary edema in which lactic acidosis is superimposed upon the pulmonary dysfunction.[25]

The difficulties in interpretation in chronic respiratory acidosis are illustrated in Figs. 20-6 to 20-8. Consider the following set of arterial blood tests:

$$\text{Arterial pH} = 7.27$$
$$P_{CO_2} = 70 \text{ mmHg}$$
$$[HCO_3^-] = 31 \text{ meq/L}$$
$$P_{O_2} = 35 \text{ mmHg}$$

The 30 mmHg increase in the P_{CO_2} should be associated with a 3-meq/L elevation in the plasma HCO_3^- concentration to 27 meq/L in acute hypercapnia or an 11-meq/L increment (3.5 meq/L per 10 mmHg rise in the P_{CO_2}) to 35 meq/L in chronic hypercapnia. The observed value of 31 meq/L falls *between* the confidence bands for acute and chronic respiratory acidosis (Fig. 20-6*a*, point A). This can represent (1) metabolic acidosis complicating chronic hypercapnia (Fig. 20-6*b*); (2) acute, superimposed on chronic, respiratory acidosis (Fig. 20-6*c*); or (3) metabolic alkalosis and acute hypercapnia (Fig. 20-6*d*). *These possibilities cannot be distinguished without the respective histories*:

- A patient with chronic bronchitis develops persistent diarrhea.
- A patient with chronic hypercapnia complains of fever and increased sputum production. The chest x-ray is consistent with pneumonia.

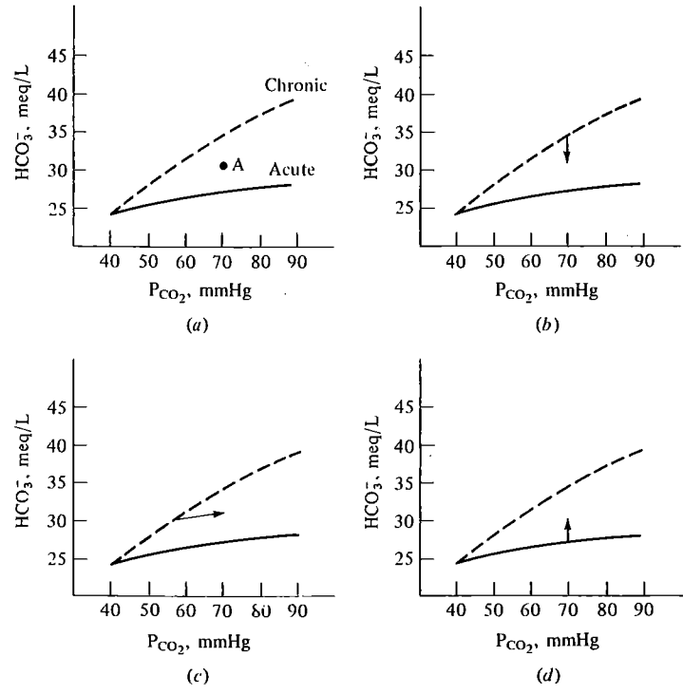

Figure 20-6 Confidence bands for acute and chronic hypercapnia have been transposed from Figs. 20-3 and 20-4. (*a*) Point A lies between the curves and can represent three different disorders. (*b*) Metabolic acidosis complicating chronic respiratory acidosis. (*c*) Acute, superimposed on chronic, hypercapnia. (*d*) Acute respiratory acidosis and metabolic alkalosis. (*Adapted from Cohen JJ, Schwartz WB,* Am J Med *41:163, 1966, with permission.*)

- A patient with a history of extrinsic asthma has 5 days of vomiting as a result of theophylline toxicity and then develops an acute asthmatic attack after the theophylline is discontinued.

A different problem in interpretation is present in the following example. The initial laboratory data were as follows:

$$\text{Arterial pH} = 7.53$$
$$P_{CO_2} = 50 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$
$$P_{O_2} = 45 \text{ mmHg}$$

Oxygen was started and repeat tests were obtained:

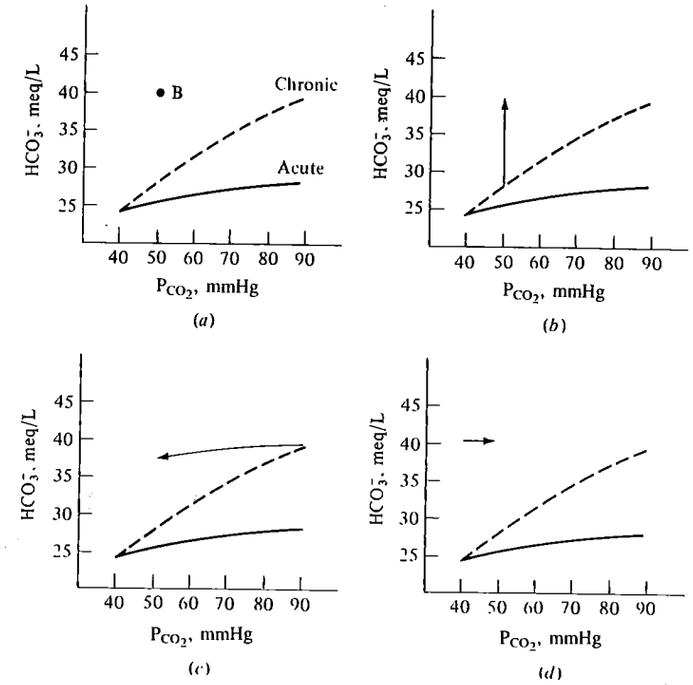

Figure 20-7 Confidence bands for acute and chronic respiratory acidosis. (*a*) Point B lies outside the confidence bands and can be due to one of three disorders. (*b*) Metabolic alkalosis complicating chronic (or acute) hypercapnia. (*c*) An acute reduction in the P_{CO_2} in a patient with chronic respiratory acidosis. (*d*) Primary metabolic alkalosis with compensatory CO_2 retention.

$$\text{Arterial pH} = 7.47$$
$$P_{CO_2} = 57 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$
$$P_{O_2} = 80 \text{ mmHg}$$

Because of the increase in P_{CO_2} oxygen was discontinued for fear of further hypercapnia and CO_2 narcosis. After appropriate therapy with NaCl, the following values were noted:

$$\text{Arterial pH} = 7.41$$
$$P_{CO_2} = 39 \text{ mmHg}$$
$$[HCO_3^-] = 24 \text{ meq/L}$$
$$P_{O_2} = 68 \text{ mmHg}$$

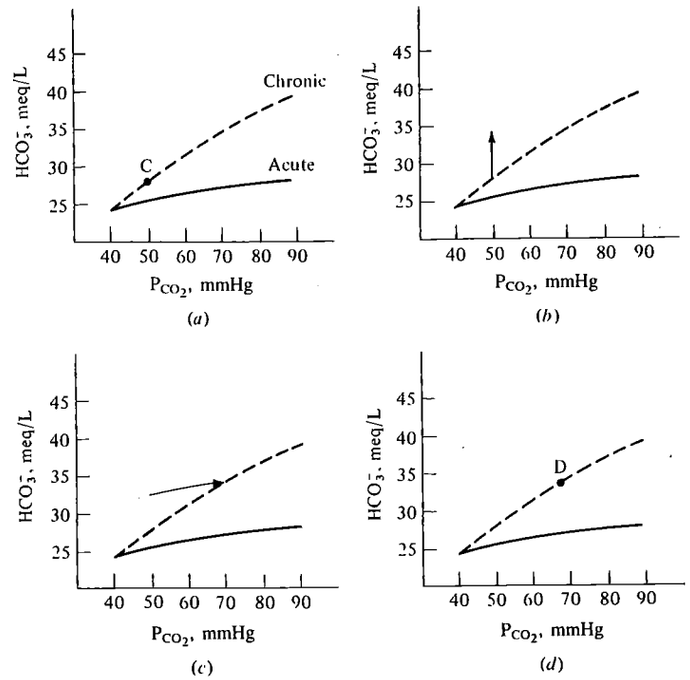

Figure 20-8 A patient with stable chronic hypercapnia (*a*, point C) develops metabolic alkalosis due to vomiting (*b*). During one episode, he aspirates some vomitus and has an acute increase in P_{CO_2} (*c*). At this point, his blood values lie within the confidence band and are indistinguishable from those seen in uncomplicated chronic respiratory acidosis (*d*, point D).

Despite the high P_{CO_2} on admission, the pH was alkaline. Most commonly, this degree of hypercapnia in an alkalemic patient is due to metabolic alkalosis complicating chronic hypercapnia (Fig. 20-7*b*). However, this can also represent acute hypocapnia superimposed on chronic respiratory acidosis (Fig. 20-7*c*) or hypercapnia as part of the normal respiratory compensation to metabolic alkalosis (Fig. 20-7*d*). This specific diagnosis cannot be made directly from the laboratory data, and the respective clinical histories are required:

- A patient with chronic obstructive pulmonary disease develops pedal edema due to cor pulmonale and is started on diuretics.
- Tracheal intubation and mechanical ventilation are begun in a patient with severe CO_2 retention. This entity is referred to as *posthypercapnic alkalosis.*
- A patient has 5 days of persistent vomiting.

The correction of the alkalemia and hypercapnia with NaCl indicates that this patient's primary problem was metabolic alkalosis due to vomiting. Although a

high P_{CO_2} that increases after the administration of oxygen is most often seen with chronic respiratory acidosis, it may also occur with metabolic alkalosis, since the development of severe hypoxemia can limit the degree of compensatory hypoventilation. This is most likely to occur in patients with underlying lung disease; the postcorrection P_{O_2} of only 68 mmHg in this patient is compatible with this possibility.

It should also be noted that the further increment in P_{CO_2} after oxygen therapy is *beneficial* in this setting, as the arterial pH decreased toward normal (from 7.53 to 7.47). There was no danger of CO_2 narcosis, and oxygen could safely have been continued.

Finally, one *cannot assume that values within the confidence bands connote an uncomplicated disorder.* Suppose a patient with stable chronic hypercapnia (Fig. 20-8*a*, point C) develops recurrent vomiting (Fig. 20-8*b*) and then aspiration pneumonia (Fig. 20-8*c*). Although this represents a triad of chronic respiratory acidosis, metabolic alkalosis, and acute respiratory acidosis, the final blood values lie within the confidence band and cannot be distinguished from pure, severe chronic hypercapnia (Fig. 20-8*d*).

In summary, the confidence bands are useful guides in the interpretation of acid-base measurements. However, this interpretation cannot proceed in a vacuum and must be correlated with a complete history and physical examination.

Use of the Alveolar-Arterial Oxygen Gradient

Calculation of the alveolar-arterial (A-a) oxygen gradient may be helpful in differentiating intrinsic pulmonary disease from extrapulmonary disorders as the cause of hypercapnia. The derivation of a formula that can be used to estimate this gradient requires a brief review of the physiology of alveolar gas exchange.[60] At a barometric pressure of 1 atm (P_B equals 760 mmHg) in the inspired air at sea level, water vapor accounts for approximately 47 mmHg, nitrogen for 563 mmHg, and oxygen for the remaining 150 mmHg (Fig. 20-9). Since the pressure in the alveolus remains at 1 atm and there is no net movement of nitrogen or water vapor across the alveolar capillary, the P_{N_2} and P_{H_2O} in the alveolus are the same as those in the inspired air and equal 610 mmHg. Thus, the *sum of the partial pressures of the other gases in the alveolus must be equal to 150 mmHg*, i.e., to the partial pressure of oxygen in the inspired air ($P_{I_{O_2}}$) (Fig. 20-9).

In the alveolus, inspired O_2 enters the blood, and CO_2 leaves the blood and enters the alveolus. If the amount of CO_2 added were equal to the amount of O_2 taken up, then the alveolar P_{O_2}($P_{A_{O_2}}$) would be less than the inspired P_{O_2} ($P_{I_{O_2}}$) by an amount equal to the alveolar P_{CO_2} ($P_{A_{CO_2}}$):

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \tag{20-6}$$

However, more O_2 is usually taken up than CO_2 produced, since, on a normal diet, each molecule of CO_2 generated represents the utilization of 1.25 molecules of O_2, i.e., the respiratory quotient is 0.8. To account for this, Eq. (20-6) can be rewritten:

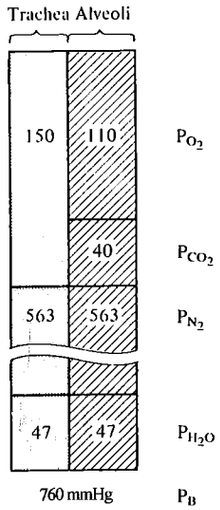

Figure 20-9 Composition of gas in the trachea at end inspiration (the same as that in the inspired air) and composition of alveolar gas. The total pressure and the partial pressures of nitrogen and water vapor are the same in both compartments; alveolar P_{O_2} goes down in proportion to the increase in alveolar P_{CO_2}. It should be noted that these values are for a patient breathing room air. If a patient is given supplemental oxygen, the alveolar P_{O_2} will be proportionately increased. (*Adapted from Snider GL,* Chest *63:801, 1973, with permission.*)

$$PA_{O_2} = PI_{O_2} - 1.25PA_{CO_2} \tag{20-7}$$

Since CO_2 diffuses across the alveolar capillary rapidly (20 times as fast as O_2), the PA_{CO_2} is essentially equal to the arterial P_{CO_2} (Pa_{CO_2}). Therefore,

$$PA_{O_2} = PI_{O_2} - 1.25Pa_{CO_2} \tag{20-8}$$

In a subject inspiring room air (PI_{O_2} equals 150 mmHg) with a Pa_{CO_2} of 40 mmHg,

$$PA_{O_2} = 150 - (1.25 \times 40)$$
$$= 100\,\text{mmHg}$$

Not all of this oxygen enters the blood, however, since there is an alveolar-arterial (A-a) oxygen gradient averaging, on room air, 5 to 10 mmHg in subjects under the age of 30 and gradually increasing to 15 to 20 mmHg in the elderly. This gradient probably is due both to pulmonary arteriovenous shunts and to perfusion of underventilated areas of the lung. Since

$$\text{(A-a) } O_2 \text{ gradient} = PA_{O_2} - Pa_{O_2} \tag{20-9}$$

by substituting Eq. (20-8) for PA_{O_2}, we have

$$\text{(A-a) } O_2 \text{ gradient} = PI_{O_2} - 1.25Pa_{CO_2} - Pa_{O_2} \tag{20-10}$$

The (A-a) oxygen gradient is always increased in hypercapnic patients with intrinsic pulmonary disease and may be increased in some patients with extrapulmonary disorders.[60] However, a normal gradient essentially excludes pulmonary disease and suggests some form of central alveolar hypoventilation (including primary metabolic alkalosis) or an abnormality of the chest wall or inspiratory muscles.

TREATMENT

A complete discussion of the treatment of all of the causes of acute and chronic respiratory acidosis is beyond the scope of this chapter. Nevertheless, it is useful to review some of the general principles that are involved, particularly those related to acid-base balance.

Acute Respiratory Acidosis

Patients with acute respiratory acidosis are at risk from both hypercapnia and hypoxemia. Although the P_{O_2} can usually be raised by the administration of supplemental oxygen, reversal of the hypercapnia requires an increase in effective alveolar ventilation. This can be achieved by control of the underlying disease (as with bronchodilators and corticosteroids in asthma) or by mechanical ventilation, delivered via either a tight-fitting mask or an endotracheal tube. Indications for mechanical ventilation include refractory severe hypoxemia, symptomatic or progressive hypercapnia, and depression of the respiratory center due, for example, to a drug overdose.

Sodium bicarbonate The role of $NaHCO_3$ in the treatment of acute respiratory acidosis (without concomitant metabolic acidosis) is not well defined. Although the primary aim of therapy is to restore normal ventilation, small doses of $NaHCO_3$ (44 to 88 meq) can be infused over 5 to 10 min if the P_{CO_2} cannot be promptly controlled in a severely acidemic patient (pH less than 7.15). This regimen may be particularly beneficial in patients with severe status asthmaticus requiring mechanical ventilation.[61] In this setting, elevating the plasma HCO_3^- concentration allows the pH to be controlled at a high P_{CO_2} and, therefore, at a lower minute ventilation with lower transpulmonary pressures. The latter change may minimize the incidence of potentially serious complications such as pneumothorax or pneumomediastinum.[61]

There are, however, several potential hazards with the use of $NaHCO_3$ in acute respiratory acidosis:

- The administration of $NaHCO_3$ should be avoided, if possible, in patients with pulmonary edema, because it can increase the degree of pulmonary congestion. In general, most of these patients can be managed without $NaHCO_3$, since correction of the pulmonary edema and hypoxemia is usually sufficient to restore acid-base balance.[25,62]
- Bicarbonate therapy does not protect against the central nervous system effects of hypercapnia, since bicarbonate does not readily cross the blood-brain barrier.
- The infusion of $NaHCO_3$ can result in an increase in CO_2 generation and therefore in the P_{CO_2} by the following reaction:

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

Normally, the CO_2 that is generated is rapidly eliminated by the lungs. However, in patients with inadequate pulmonary blood flow (especially during a cardiac arrest), the CO_2 may be retained, and the resultant elevation in the P_{CO_2} can exacerbate the tissue acidemia.[38-40,42] Thus, careful monitoring is required; furthermore, during cardiopulmonary resuscitation, measurement of the mixed venous pH may be the best indicator of the acid-base status at the tissue level (see page 452).[42]

- Metabolic alkalosis (due to the excess HCO_3^-) may ensue after the P_{CO_2} has returned to normal. This is usually not a major problem.

Tromethamine The limitations and potential deleterious effects of bicarbonate therapy have promoted investigation into the use of alternative buffering agents, such as tromethamine (THAM; trometamol). THAM is an inert amino alcohol that buffers acids and CO_2 by virtue of its amine moiety via the following reactions:[63]

$$\text{THAM}-NH_2 + H^+ \rightarrow \text{THAM}-NH_3^+$$

$$\text{THAM}-NH_2 + H_2O + CO_2 \rightarrow \text{THAM}-NH_3^+ + HCO_3^-$$

Protonated THAM is excreted in the urine at a rate slightly higher than creatinine clearance in conjunction with either chloride or bicarbonate. Thus, THAM supplements the buffering capacity of blood without generating carbon dioxide but is less effective in patients with renal failure. Reported toxicities include hyperkalemia, hypoglycemia, and respiratory depression; the last complication probably results from the ability of THAM to rapidly increase the pH and decrease the P_{CO_2} in the central nervous system.

Published clinical experience with THAM is limited, but the drug has been used to treat severe acidemia due to sepsis, hypercapnia, diabetic ketoacidosis, and other disorders.[63] Its clinical efficacy compared to that of sodium bicarbonate in the treatment of respiratory acidosis remains unproven, and THAM is of uncertain safety.

Chronic Respiratory Acidosis

The primary goals of therapy in patients with chronic respiratory acidosis are to maintain adequate oxygenation and, if possible, to improve effective alveolar ventilation. Because of the effectiveness of the renal compensation, it is usually not necessary to treat the pH, even in patients with severe hypercapnia.[45] In addition, the frequent concurrent use of diuretics in patients with cor pulmonale can further raise the pH, occasionally to normal or even alkalemic levels.

The appropriate treatment varies with the underlying disease.[26] As a general rule, excessive oxygen and sedatives should be avoided, since they can act as respiratory depressants, producing further hypoventilation. For patients with chronic obstructive lung disease, bronchodilators and, when infection is present, antimicrobials may ameliorate the airflow characteristics of the disease.[6,64]

Dietary modification to reduce the respiratory quotient also may be helpful in selected patients by reducing CO_2 production.[65] In obese patients, weight reduction can improve alveolar ventilation, leading to an elevation in the arterial P_{O_2} and reduction in the P_{CO_2} (of as much as 10 mmHg each).[48,66] Although the loss of weight may directly improve ventilatory mechanics, carbohydrate restriction itself (to about 200 g/day) can produce a similar improvement in the absence of any change in weight.[67] The beneficial effect seen in this setting appears to involve increased central stimulation of ventilation; how this occurs, however, is not clear. (The appropriate management of the obesity hypoventilation syndrome is beyond the scope of this discussion.[34])

If severe hypoxemia persists (arterial P_{O_2} below 50 to 55 mmHg), continuous low-flow oxygen therapy is indicated to prolong survival, diminish the severity of cor pulmonale, and improve the quality of life.[17-19,26,68] The pulmonary benefits derived from correction of hypoxemia may result from improved perfusion due to reversal of pulmonary vasoconstriction and of secondary polycythemia, which increases blood viscosity. The aim of therapy is to raise the P_{O_2} to 60 to 65 mmHg (hemoglobin saturation above 90 percent), while carefully monitoring the P_{CO_2} to ascertain that ventilation has not been suppressed to a clinically important degree by partial correction of the hypoxemia.

Mechanical ventilation may be required when there is an acute exacerbation of chronic hypercapnia (as with the development of pneumonia). In this setting, care must be taken to *lower the P_{CO_2} gradually*. Rapid correction of hypercapnia to near normal levels can lead to an overshoot alkalemia and a marked rise in the pH in the central nervous system (CNS), since CO_2 can easily diffuse out of the brain. The acute increase in CNS pH can, in selected cases, lead to severe neurologic abnormalities, such as seizures and coma.[69,70] These findings typically improve if the P_{CO_2} is allowed to rise toward its previous level.

Effect of superimposed metabolic alkalosis As described above, the influence of pH on ventilation is maintained in chronic respiratory acidosis.[12-15] Thus, the induction of metabolic alkalosis (usually due to diuretic therapy for cor pulmonale) will further depress ventilation, aggravating both the hypoxemia and the hypercapnia.[15,71] In this setting, lowering the plasma HCO_3^- concentration can reverse these abnormalities and may improve the patient's sense of well-being.[15]

Correction of a superimposed metabolic alkalosis can be achieved by discontinuing diuretic therapy and administering NaCl. This is not practical, however, in the patient who is still significantly edematous. In this circumstance, acetazolamide (250 to 375 mg once or twice a day) can both lower the plasma HCO_3^- concentration and increase the urine output by inhibiting proximal $NaHCO_3$ reabsorption (see Chap. 15). Monitoring the urine pH is a simple method of assessing the efficacy of this regimen, since a HCO_3^- diuresis leads to an elevation in the urine pH to above 7.0.

Despite its effectiveness in many patients, there are two potential problems with the use of acetazolamide. First, the plasma HCO_3^- concentration should be lowered to the level *appropriate for the degree of hypercapnia* (see Fig. 20-4). Returning the plasma HCO_3^- concentration to the normal value of 24 meq/L can lead to severe acidemia due to persistent marked hypercapnia.[14] Second, acetazolamide can produce a *transient elevation* in the P_{CO_2} (usually 3 to 7 mmHg) prior to its diuretic effect.[72] This complication, which is generally not clinically important, may be due to partial inhibition of carbonic anhydrase in the red blood cell.[14,72] This enzyme catalyzes the hydration of CO_2 to H_2CO_3, a reaction that is essential for CO_2 transport by the red cell [see Eqs. (20-1) and (20-2)] and, therefore, for the elimination of CO_2 by the lungs.

PROBLEMS

20-1 Match the clinical histories with the appropriate arterial blood values:

	pH	P_{CO_2}, mmHg	$[HCO_3^-]$, meq/L
(*a*)	7.37	65	37
(*b*)	7.22	60	26
(*c*)	7.35	60	32

1. A 60-year-old man with chronic bronchitis develops persistent diarrhea.
2. A 24-year-old man is markedly obese.
3. A 14-year-old girl has a severe acute asthmatic attack.
4. A 56-year-old woman with chronic bronchitis is started on diuretic therapy for peripheral edema, resulting in a 3-kg weight loss.

20-2 A 54-year-old man with a history of chronic obstructive lung disease has a 2-day episode of increasing shortness of breath and sputum production. The chest radiograph reveals a left lower-lobe pneumonia. The following laboratory data are obtained with the patient breathing room air:

$$\text{Artertial pH} = 7.25$$
$$P_{CO_2} = 70 \text{ mmHg}$$
$$[HCO_3^-] = 30 \text{ meq/L}$$
$$P_{O_2} = 30 \text{ mmHg}$$
$$\text{Urine } [Na^+] = 4 \text{ meq/L}$$

The patient is started on intravenous aminophylline and nasal oxygen and becomes less responsive. Repeat blood tests are obtained and show the following:

$$\text{Arterial pH} = 7.18$$
$$P_{CO_2} = 86 \text{ mmHg}$$
$$[HCO_3^-] = 31 \text{ meq/L}$$
$$P_{O_2} = 62 \text{ mmHg}$$

(a) What is the probable acid-base disturbance on admission?
(b) What is responsible for the increase in the P_{CO_2} in the hospital?
(c) What further therapy would you recommend?

(d) If the P_{CO_2} is rapidly lowered to 40 mmHg, what will happen to the arterial pH?
(e) If the patient is then maintained on a low-sodium diet, how long will it take for the plasma HCO_3^- concentration to return to normal?

20-3 A 65-year-old man has a history of smoking and hypertension, which is treated with a diuretic. The following arterial blood values are obtained on room air:

$$\text{Arterial pH} = 7.48$$
$$P_{CO_2} = 51 \text{ mmHg}$$
$$[HCO_3^-] = 36 \text{ meq/L}$$
$$P_{O_2} = 73 \text{ mmHg}$$

(a) What is the most likely acid-base disturbance?
(b) Does the patient have significant underlying lung disease?

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CHAPTER

TWENTY-ONE

RESPIRATORY ALKALOSIS

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The introduction to acid-base disorders presented in Chap. 17 should be read before proceeding with this discussion. Respiratory alkalosis is a clinical disturbance characterized by an elevated arterial pH (or a decreased H^+ concentration), a low P_{CO_2} (hypocapnia), and a variable reduction in the plasma HCO_3^- concentration. It must be differentiated from metabolic acidosis, in which the plasma HCO_3^- concentration and P_{CO_2} also are diminished, but the pH is reduced rather than increased.

PATHOPHYSIOLOGY

A primary decrease in the P_{CO_2} occurs when effective alveolar ventilation is increased to a level beyond that needed to eliminate the daily load of metabolically produced CO_2. Before discussing the different disorders that can cause a respiratory alkalosis, it is helpful to first review how the body responds to hypocapnia. From the law of mass action,

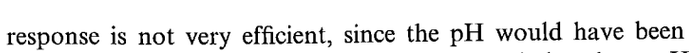
$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

it can be seen that the reduction in the extracellular H^+ concentration induced by hypocapnia can be minimized by lowering the HCO_3^- concentration. This protective response involves two steps: rapid cell buffering and a later decrease in net

renal acid excretion. As a result of the time differential between the cellular and renal effects, the changes in acute and chronic respiratory alkalosis are different.

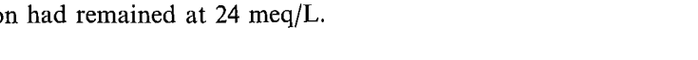
Acute Respiratory Alkalosis

Within 10 min after the onset of respiratory alkalosis, H^+ ions move from the cells into the extracellular fluid; they then combine with HCO_3^-, resulting in an appropriate fall in the plasma HCO_3^- concentration:



$$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

These H^+ ions are primarily derived from the protein, phosphate, and hemoglobin buffers in the cells,



$$HBuf \rightarrow H^+ + Buf^-$$

and from an alkalemia-induced increase in cellular lactic acid production.[1]

In general, enough H^+ ions enter the extracellular fluid to lower the plasma HCO_3^- concentration 2 meq/L for each 10 mmHg decrease in the P_{CO_2} (see Fig. 20-3).[2] If, for example, the P_{CO_2} were reduced to 20 mmHg (20 mmHg less than normal), the plasma HCO_3^- concentration should fall by 4 meq/L to 20 meq/L (pH equals 7.63):

$$pH = 6.10 + \log \frac{20}{0.03(20)}$$

$$= 7.63$$

This cellular response is not very efficient, since the pH would have been only slightly greater, at 7.70, if there were no cell buffering and the plasma HCO_3^- concentration had remained at 24 meq/L.

Chronic Respiratory Alkalosis

In the presence of persistent hypocapnia, there is a compensatory decrease in renal H^+ secretion that begins within 2 h but is not complete for 2 to 3 days.[3-5] This response, which is presumably mediated at least in part by a parallel rise in renal tubular cell pH, is manifested by HCO_3^- loss in the urine and by decreased urinary ammonium excretion.[4,5] Both of these effects lower the plasma HCO_3^- concentration, the latter by preventing the excretion of the daily H^+ load, thereby resulting in H^+ retention.

On average, the combined effects of the cell buffers and the renal compensation result in a new steady state in which the plasma HCO_3^- concentration falls in humans approximately 4 meq/L for each 10 mmHg reduction in the P_{CO_2} (Fig. 21-1).[6] Thus, if the P_{CO_2} were chronically reduced to 20 mmHg, the plasma HCO_3^- concentration should fall by 8 meq/L, to 16 meq/L. This response effectively protects the extracellular pH, which is increased only to 7.53, as compared to 7.63 with a similar degree of acute hypocapnia.

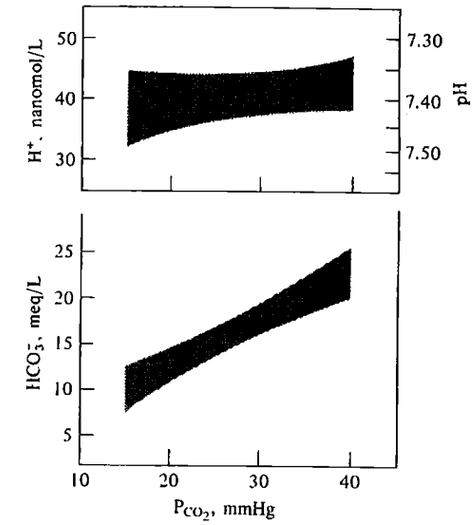


Figure 21-1 Significance bands of 95 percent probability for plasma pH and H^+ and HCO_3^- concentrations in chronic hypocapnia. Note that there is only a minimal change in the H^+ concentration and pH as the P_{CO_2} is reduced. (*From Gennari JF, Goldstein MB, Schwartz WB,* J Clin Invest *51:1722, 1972, by copyright permission of the American Society for Clinical Investigations.*)

ETIOLOGY

Respiration is physiologically governed by two sets of chemoreceptors: those in the respiratory center in the brainstem and those in the carotid and aortic bodies, located at the bifurcation of the carotid arteries and in the aortic arch, respectively.[7,8]

- The central chemoreceptors are stimulated by an increase in the P_{CO_2} or by metabolic acidosis, both of which appear to be sensed as a fall in the pH of the surrounding cerebral interstitial fluid.[9]
- The peripheral chemoreceptors are primarily stimulated by hypoxemia, although they also contribute to the acidemic response.[7,8,10]

Thus, *primary* hyperventilation resulting in respiratory alkalosis can be produced by hypoxemia or anemia, a reduction in the cerebral pH (an apparently rare event, since the cerebrospinal fluid pH is usually elevated in respiratory alkalosis) or other stimuli for hyperventilation, such as pain, anxiety, stimulation of mechanoreceptors within the respiratory system, or direct stimulation of the central respiratory center (Table 21-1).[11-13]

Hypoxemia

The respiratory response to hypoxemia (which includes reduced oxygen delivery due to severe hypotension or anemia) occurs in two stages, which illustrate the interaction between the peripheral and central chemoreceptors (Fig. 21-2).[8,14,15]

Table 21-1 Causes of respiratory alkalosis

Hypoxemia
A. Pulmonary disease: pneumonia, interstitial fibrosis, emboli, edema
B. Congestive heart failure
C. Hypotension or severe anemia
D. High-altitude residence
Pulmonary disease
Direct stimulation of the medullary respiratory center
A. Psychogenic or voluntary hyperventilation
B. Hepatic failure
C. Gram-negative septicemia
D. Salicylate intoxication
E. Postcorrection of metabolic acidosis
F. Pregnancy and the luteal phase of the menstrual cycle (due to progesterone)
G. Neurologic disorders: cerebrovascular accidents, pontine tumors
Mechanical ventilation

Hypoxemia initially activates the peripheral chemoreceptors, resulting in hyperventilation, hypocapnia, and mild increases in the arterial and cerebral pH. However, the cerebral alkalosis inhibits the central respiratory center, thereby limiting the degree of hyperventilation. Thus, hypoxemia does not significantly stimulate respiration acutely unless the arterial P_{O_2} falls below 50 to 60 mmHg or hypocapnia does not occur because of underlying lung disease (Fig. 21-2). In the

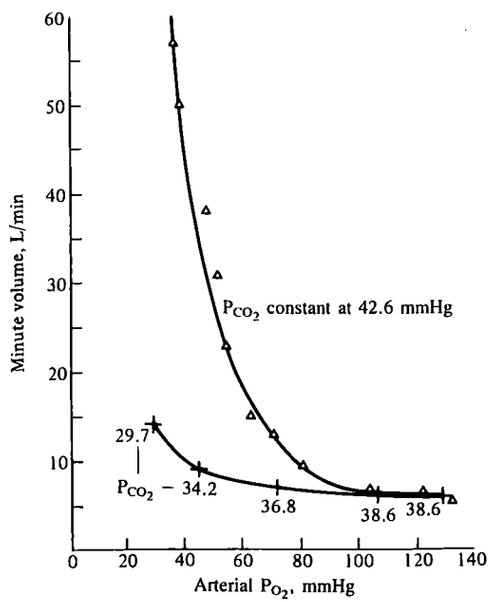


Figure 21-2 Influence of arterial P_{CO_2} on the ventilatory response to hypoxemia. In normal subjects (lower curve), lowering the partial pressure of oxygen in the inspired air increases ventilation and lowers the arterial P_{CO_2}. However, these changes are relatively minor until the arterial P_{O_2} falls below 50 mmHg. The earlier and greater degree of hyperventilation seen when the arterial P_{CO_2} is held constant (upper curve) indicates that the development of mild hypocapnic alkalosis normally limits the ventilatory response to hypoxemia. (*Adapted from Loeschcke HH, Gertz KH,* Arch Ges Physiol *267:460, 1958, with permission.*)

latter setting, ventilation begins to rise rapidly when the P_{O_2} is less than 70 to 80 mmHg.

Persistent hypoxemia, on the other hand, can lead to a greater degree of hyperventilation. The initial fall in P_{CO_2} induces a compensatory reduction in the plasma HCO_3^- concentration that lowers the extracellular pH toward normal (Fig. 21-1). This response partially removes the alkalemic inhibition of ventilation, thereby allowing a greater respiratory response to hypoxemia.

Pulmonary Disease

Respiratory alkalosis is a common finding in a variety of pulmonary diseases, including pneumonia, pulmonary embolism, and interstitial fibrosis.[16-18] It may also occur in pulmonary edema, but metabolic and respiratory acidosis are much more common in this disorder.[19]

Although hyperventilation in pulmonary disease may be due in part to hypoxemia, it is frequently not corrected by the administration of oxygen.[16,17] This observation indicates that other factors contribute to the increase in ventilation. The most important appear to be mechanoreceptors located throughout the airways, lungs, and chest wall, which stimulate the respiratory center via afferent signals sent through the vagus nerves.[16,17,20]

Several different receptors may participate in this response, including *juxtacapillary* receptors in the interstitium of the alveolar wall—which can be activated by interstitial edema, fibrosis, or pulmonary vascular congestion—and *irritant* receptors in the epithelial lining of the airways, which can be activated by the inhalation of irritants and perhaps by local inflammatory processes such as pneumonia and asthma.[16,20] Although direct confirmation of the importance of these receptors in humans is limited, vagal blockade can reverse the hyperventilation associated with pulmonary disease in experimental animals.[16,20,21]

These receptors play little role in the control of ventilation in normal subjects, and their effect in pulmonary disease can be somewhat maladaptive. For example, dyspnea and breathlessness are common complaints in diffuse pulmonary interstitial fibrosis, even in patients without severe hypoxemia. These symptoms are probably due at least in part to increased ventilatory drive.[13,16]

Direct Stimulation of the Medullary Respiratory Center

Primary hyperventilation due to stimulation of the respiratory center may be found in a variety of disorders (Table 21-1). The possible mechanisms by which this occurs are variable and include the primary effect of cortical centers in psychogenic hyperventilation,[22] retained amines in hepatic failure,[23,24] bacterial toxins in gram-negative septicemia,[25] salicylates in salicylate intoxication,[26,27] progesterone in pregnancy and, to a lesser degree, the luteal phase of the menstrual cycle,[28,29] and a persistently acid cerebrospinal fluid (CSF) pH following the rapid correction of metabolic acidosis.[30,31]

In the last situation, the administration of $NaHCO_3$ raises the extracellular HCO_3^- concentration and pH. As the increase in pH is sensed by the peripheral chemoreceptors, there is a decrease in the degree of compensatory hyperventilation and a moderate elevation in the P_{CO_2}. Since CO_2 but not HCO_3^- rapidly crosses the blood-brain barrier, the brain initially senses only the higher P_{CO_2}. This produces a paradoxical fall in the CSF pH,[31] which tends to prolong the hyperventilatory state.[30]

Respiratory alkalosis is also an occasional finding in neurologic disorders. With pontine tumors, a reduction in the cerebral pH due to local lactic acid production may be responsible for increased ventilation.[32] Hypocapnia also may be seen with acute cerebrovascular accidents.

Mechanical Ventilation

The use of mechanical ventilation not uncommonly leads to respiratory alkalosis. The imposition of forced hyperventilation often results from an attempt to correct hypoxemia. If necessary, the respiratory alkalosis can be reversed by increasing the dead space or reducing either the tidal volume or the respiratory rate.

SYMPTOMS

The symptoms produced by respiratory alkalosis are related to increased irritability of the central and peripheral nervous systems and include light-headedness, altered consciousness, paresthesias of the extremities and circumoral area, cramps, carpopedal spasm that is indistinguishable from that seen with hypocalcemia, and syncope.[22,33] A variety of supraventricular and ventricular arrhythmias also may occur, particularly in critically ill patients.[34]

These abnormalities are thought to be related to the ability of alkalosis to impair cerebral function and to increase membrane excitability. Respiratory alkalosis also reduces cerebral blood flow (by as much as 35 to 40 percent if the P_{CO_2} falls by 20 mmHg),[35] which may contribute to the neurologic symptoms. In addition, some complaints may be unrelated to the change in pH. Patients with psychogenic hyperventilation, for example, frequently complain of headache, shortness of breath, chest pain or tightness, and other somatic symptoms that may be emotional in origin and not caused by the alkalemia.

The above problems primarily occur in *acute* respiratory alkalosis when the P_{CO_2} falls below 25 to 30 mmHg, a setting in which there is a substantial rise in cerebral pH. They are much less likely to be seen in chronic respiratory alkalosis (since the pH is so well protected) or in metabolic alkalosis, where there is a lesser elevation in CSF pH because of the relative inability of HCO_3^- to cross the blood-brain barrier.[11,36]

An additional finding in many patients with severe respiratory alkalosis is a reduction in the plasma phosphate concentration (measured in the laboratory as the plasma concentration of inorganic phosphorus) to as low as 0.5 to 1.5 mg/dL (normal equals 2.5 to 4.5 mg/dL).[37] This finding reflects a rapid shift of phosphate from the extracellular fluid into the cells. It may be mediated by the stimulation of glycolysis by intracellular alkalosis, resulting in increased formation of phosphorylated compounds such as glucose 6-phosphate and fructose 1,6-diphosphate.

DIAGNOSIS

The physical finding of tachypnea may be an important clue to the presence of hypocapnia, due either to primary respiratory alkalosis or to the respiratory compensation to metabolic acidosis. Once the presence of respiratory alkalosis has been confirmed by measurement of the extracellular pH, P_{CO_2}, and HCO_3^- concentration, the cause of this condition should be identified (Table 21-1). For example, respiratory alkalosis is a relatively early finding in septicemia,[25] and this diagnosis should be considered in the appropriate clinical setting when there is no other apparent cause for the hyperventilation.

Since the responses to acute and chronic hypocapnia are different, the determination of the correct acid-base disorder is more difficult than in metabolic acidosis or alkalosis. Suppose, for example, that a patient has the following arterial blood values:

$$\text{Arterial pH} = 7.48$$
$$P_{CO_2} = 20 \text{ mmHg}$$
$$[HCO_3^-] = 16 \text{ meq/L}$$

The alkaline pH and hypocapnia are diagnostic of respiratory alkalosis. With a P_{CO_2} of 20 mmHg, the plasma HCO_3^- concentration should be roughly 20 meq/L in acute respiratory alkalosis (a reduction of 2 meq/L per 10 mmHg fall in the P_{CO_2}) and 16 meq/L in chronic respiratory alkalosis (a reduction of 4 meq/L per 10 mmHg fall in the P_{CO_2}).

Thus, 16 to 20 meq/L describes the approximate normal range for the plasma HCO_3^- concentration in a patient with respiratory alkalosis and P_{CO_2} of 20 mmHg. Values significantly above or below this range represent superimposed metabolic alkalosis or acidosis. In this patient, the plasma HCO_3^- concentration of 16 meq/L is consistent with uncomplicated chronic respiratory alkalosis. However, it is also compatible with acute respiratory alkalosis combined with metabolic acidosis to produce the greater than expected reduction in the plasma HCO_3^- concentration. Thus, evaluation of the laboratory data must proceed in conjunction with the history and physical examination, as illustrated by the following example:

Case History 21-1 A 5-year-old child is brought into the emergency room in a stuporous condition. The only pertinent history is that he had been playing with a bottle of aspirin tablets earlier that day.

Comment The most likely explanation for the above laboratory findings is a salicylate overdose. The acute respiratory alkalosis in this disorder is often complicated by a salicylate-induced metabolic acidosis, leading to a reduction in the plasma HCO_3^- concentration (from the expected value of 20 meq/L down to 16 meq/L).[27]

TREATMENT

In general, treatment of the alkalemia is not necessary, and therapy should be aimed at the diagnosis and correction of the underlying disorder. There is no rationale for the use of respiratory depressants or for the administration of acid, such as HCl, in an effort to normalize the pH. In severely symptomatic patients with acute respiratory alkalosis, rebreathing into a paper bag—i.e., increasing the P_{CO_2} in the inspired air—may partially correct the hypocapnia and relieve the symptoms. The extracellular pH should be monitored in this setting, since the compensatory decrease in the plasma HCO_3^- concentration will persist and may result in metabolic acidosis as the P_{CO_2} is increased toward normal. This is usually mild but rarely may require small amounts of $NaHCO_3$.

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