Review Articles

Medical Progress

MANAGEMENT OF LIFE-THREATENING ACID–BASE DISORDERS

First of Two Parts

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ACID–BASE homeostasis exerts a major influence on protein function, thereby critically affecting tissue and organ performance. Deviations of systemic acidity in either direction can have adverse consequences and, when severe, can be life-threatening. Yet it is the nature of the condition responsible for severe acidemia or alkalemia that largely determines the patient's status and prognosis. Whereas a blood pH of 7.10 can be of little consequence when caused by a transient or easily reversible condition, such as an isolated seizure, it forecasts an ominous outcome if it is the result of methanol intoxication. Similarly, a blood pH of 7.60 seldom has serious consequences when caused by the anxiety–hyperventilation syndrome, but it imparts a major risk to a patient with cardiomyopathy treated with digitalis and diuretics. Consequently, the management of serious acid–base disorders always demands precise diagnosis and treatment of the underlying disease, and in certain circumstances, it requires steps to combat the deviation in systemic acidity itself. In this article, we address general concepts and some specific aspects of the management of life-threatening acid–base disorders.

ADVERSE CONSEQUENCES OF SEVERE ACIDEMIA

The major adverse consequences of severe acidemia (blood pH, <7.20) are listed in Table 1; they can occur independently of whether the acidemia is of metabolic, respiratory, or mixed origin. The effects on the cardiovascular system are particularly pernicious and can include decreased cardiac output, decreased arterial blood pressure, decreased hepatic and renal blood flow, and centralization of blood volume.[1,2] Reentrant arrhythmias and a reduction in the threshold for ventricular fibrillation can occur, while the defibrillation threshold remains unaltered.[3,4] Acidemia triggers a sympathetic discharge but also progressively attenuates the effects of catecholamines on the heart and the vasculature; thus, at pH values below 7.20, the direct effects of acidemia become dominant.

Although metabolic demands may be augmented by the associated sympathetic surge, acidemia decreases the uptake of glucose in the tissues by inducing insulin resistance and inhibits anaerobic glycolysis by depressing 6-phosphofructokinase activity.[5,6] This effect can have grave consequences during hypoxia, since glycolysis becomes the main source of energy for the organism. The uptake of lactate by the liver is curtailed, and the liver can be converted from the premier consumer of lactate to a net producer.[1] Acidemia causes potassium to leave the cells, resulting in hyperkalemia, an effect that is more prominent in nonorganic acidoses than in organic and respiratory acidoses.[7,8] Increased net protein breakdown and development of a catabolic state also occur in patients with acidosis.[9-11] Brain metabolism and the regulation of its volume are impaired by severe acidemia, resulting in progressive obtundation and coma.

MANAGEMENT OF LIFE-THREATENING ACIDOSES

Metabolic Acidosis

In the presence of an appropriate ventilatory response, severe metabolic acidemia implies a plasma bicarbonate concentration of 8 mmol per liter or lower.[12] What options are available for replenishing the depleted bicarbonate stores? In certain organic acidoses (e.g., ketoacidosis and lactic acidosis), effective treatment of the underlying disease can foster conversion of the accumulated organic anions to bicarbonate within hours. By contrast, in hyperchloremic acidosis (e.g., that produced by diarrhea), such an endogenous regeneration of bicarbonate cannot occur. Although the kidneys can, of course, contribute to bicarbonate neogenesis in both types of acidoses, several days are required to obtain a meaningful effect. Therefore, even if the cause of the acidosis can be reversed, exogenous alkali is often re-

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quired for the prompt attenuation of severe acidemia.

Alkali Therapy

The goal of alkali therapy is to prevent or reverse the detrimental consequences of severe acidemia, especially those affecting the cardiovascular system (Table 1). In moderating acidemia, the physician buys time, thus allowing general and cause-specific measures as well as endogenous reparatory processes to take effect. Alkali therapy also provides a measure of safety against additional acidifying stresses caused by a further decrease in plasma bicarbonate or an increase in the partial pressure of arterial carbon dioxide.[1,13,14]

Currently, intravenous sodium bicarbonate is the mainstay of alkali therapy. Other alkalinizing salts, such as sodium lactate, citrate, or acetate, are not reliable substitutes, since their alkalinizing effect depends on oxidation to bicarbonate, a process that can be seriously impaired in several clinical conditions (e.g., liver disease and circulatory failure).

How much bicarbonate need be dispensed? Because the administration of sodium bicarbonate entails certain risks, it should be given judiciously in amounts that will return blood pH to a safer level of about 7.20. To accomplish this goal, plasma bicarbonate must be increased to 8 to 10 mmol per liter. There is no simple prescription for reaching this target, since several ongoing, and at times competing, processes can affect the acid–base status (e.g., increased net lactic acid production, vomiting, or renal failure), and the apparent space of distribution of infused bicarbonate is variable. (The apparent space of distribution is calculated by dividing the administered alkali load, in millimoles per kilogram of body weight, by the observed change in the plasma bicarbonate concentration, in millimoles per liter, and multiplying the ratio by 100.) Whereas patients with very low plasma bicarbonate concentrations can have a bicarbonate space of 100 percent of body weight or greater, others with less severe metabolic acidosis have a space closer to 50 percent of body weight, the normal value.[15]

Being mindful of overtreatment, we recommend that, as the starting point, bicarbonate space be taken to be 50 percent of body weight. Thus, to raise the plasma bicarbonate concentration from 4 to 8 mmol per liter in a 70-kg patient, one should administer $4 \times 70 \times 0.5$, or 140, mmol of sodium bicarbonate. Except in cases of extreme acidemia, sodium bicarbonate should be dispensed as an infusion (over a period of several minutes to a few hours) rather than a bolus. Follow-up monitoring of the patient's acid–base status will determine additional alkali requirements. About 30 minutes must elapse after the infusion of bicarbonate is completed before its clinical effect can be judged.[15]

TABLE 1. MAJOR ADVERSE CONSEQUENCES OF SEVERE ACIDEMIA.

Cardiovascular
Impairment of cardiac contractility
Arteriolar dilatation, venoconstriction, and centralization of blood volume
Increased pulmonary vascular resistance
Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow
Sensitization to reentrant arrhythmias and reduction in threshold of ventricular fibrillation
Attenuation of cardiovascular responsiveness to catecholamines
Respiratory
Hyperventilation
Decreased strength of respiratory muscles and promotion of muscle fatigue
Dyspnea
Metabolic
Increased metabolic demands
Insulin resistance
Inhibition of anaerobic glycolysis
Reduction in ATP synthesis
Hyperkalemia
Increased protein degradation
Cerebral
Inhibition of metabolism and cell-volume regulation
Obtundation and coma

Risks of Sodium Bicarbonate Therapy

The administration of sizable amounts of sodium bicarbonate is associated with certain risks.[1,13,14,16] Infusion of the usual undiluted 1 *N* preparation (containing 1000 mmol of sodium bicarbonate per liter) can give rise to hypernatremia and hyperosmolality. This complication can be avoided by adding two 50-ml ampules of sodium bicarbonate (each containing 50 mmol of sodium bicarbonate) to 1 liter of 0.25 *N* sodium chloride or three ampules to 1 liter of 5 percent dextrose in water, thereby rendering these solutions nearly isotonic. Alkali therapy can lead to extracellular-fluid volume overload, especially in patients with congestive heart failure or renal failure. Administration of loop diuretics may prevent or treat this complication. If adequate diuresis cannot be established, hemofiltration or dialysis may be required. "Overshoot" alkalosis, in which an abrupt and poorly tolerated transition from severe acidemia to alkalemia develops, can result from overly aggressive alkali loading (especially when compounded by endogenous regeneration of bicarbonate from accumulated organic anions) and persistent hyperventilation (Fig. 1).

Alkali stimulates 6-phosphofructokinase activity and organic acid production, effects that must be considered in the management of lactic acidosis and ketoacidosis.[6,17] Such effects are usually viewed as nonsalutary, since they limit the alkalinizing action of bicarbonate. However, alkali-induced stimulation of 6-phosphofructokinase activity may allow the par-

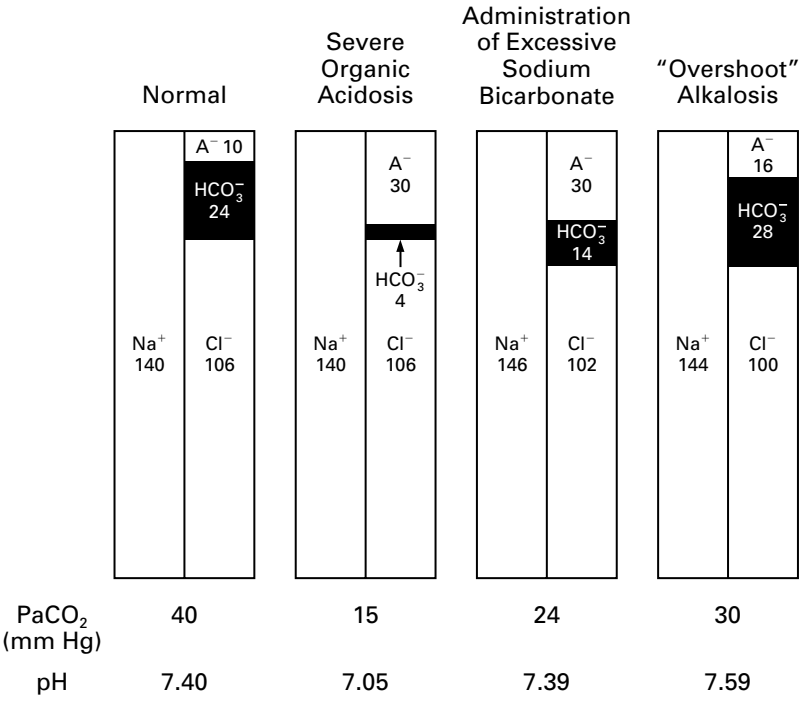

Figure 1. Schematic Illustration of "Overshoot" Alkalosis.

From left to right, the panels depict normal acid–base status; severe, high-anion-gap, organic acidosis (e.g., lactic acidosis); a rise in plasma bicarbonate to a higher than appropriate concentration after the administration of excessive amounts of sodium bicarbonate; and "overshoot" alkalosis resulting from a further rise in plasma bicarbonate (caused by partial conversion of the accumulated organic anion to bicarbonate) and persistent hyperventilation. A^- denotes unmeasured plasma anions, and $PaCO_2$ partial pressure of arterial carbon dioxide. The numbers within the bars give ion concentrations in millimoles per liter.

tial regeneration of depleted ATP stores in vital organs (e.g., in cases of tissue hypoperfusion and hypoxemia), thereby fostering survival.

Buffering of protons by bicarbonate releases carbon dioxide ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$) and can raise the prevailing partial pressure of carbon dioxide in body fluids. This effect can be consequential in patients with limited ventilatory reserve, those in advanced circulatory failure, or those undergoing cardiopulmonary resuscitation. Under these circumstances, paradoxical worsening of intracellular (and even extracellular) acidosis can occur if the fractional increase in partial pressure of carbon dioxide exceeds the fractional increase in the bicarbonate concentration. This counterproductive effect may be evident only in mixed venous blood, which better reflects the acid–base status of the tissues.[18,19]

Alternative Alkalinizing Agents

Concern about the carbon dioxide–producing effect of bicarbonate led to the development of Carbicarb, which consists of equimolar concentrations of sodium bicarbonate and sodium carbonate.[20-22] Because carbonate is a stronger base, it is used in preference to bicarbonate for buffering hydrogen ions, generating bicarbonate rather than carbon dioxide in the process ($CO_3^{2-} + H^+ \rightarrow HCO_3^-$). In addition, the carbonate ion can react with carbonic acid, thereby consuming carbon dioxide ($CO_3^{2-} + H_2CO_3 \rightarrow 2HCO_3^-$). Thus, Carbicarb limits but does not eliminate the generation of carbon dioxide. In experimental lactic acidosis, Carbicarb increased blood and intracellular pH with little or no rise in the arterial or venous partial pressure of carbon dioxide.[23,24] However, the risks of hypervolemia and hypertonicity are similar with the two alkalinizing agents, and neither agent prevented the progressive reduction in myocardial-cell pH in animals with ventricular fibrillation.[25,26] Clinical experience with Carbicarb is limited, and this product is not yet commercially available for clinical use.

Another carbon dioxide–consuming alkalinizing agent is THAM, a commercially available solution of 0.3 *N* tromethamine.[27,28] This sodium-free solu-

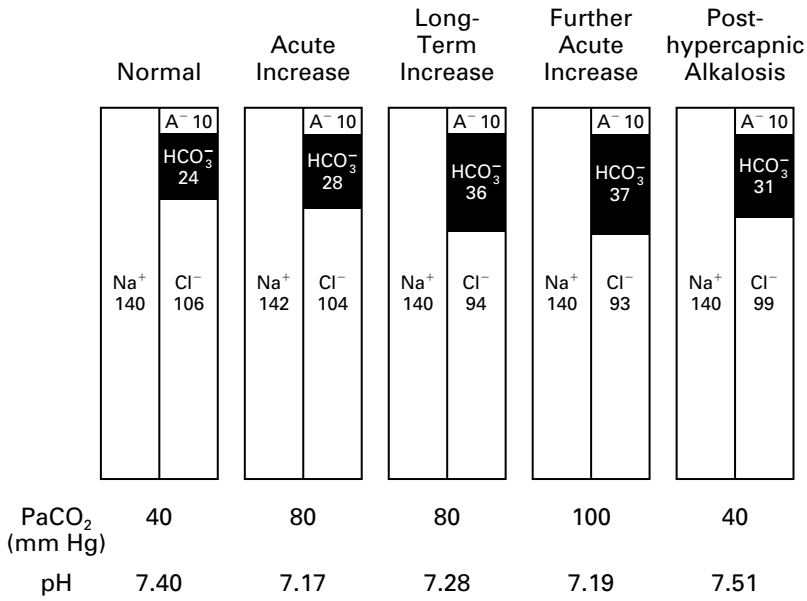

Figure 2. Changes in Acid–Base and Electrolyte Composition in Patients with Respiratory Acidosis.
From left to right, the panels depict normal acid–base status; adaptation to an acute rise in the partial pressure of arterial carbon dioxide ($PaCO_2$) to 80 mm Hg; adaptation to a long-term rise in $PaCO_2$ to 80 mm Hg; superimposition of an acute further increment in $PaCO_2$ (to a level of 100 mm Hg) in the same patient; and posthypercapnic alkalosis resulting from an abrupt reduction in $PaCO_2$ to the level of 40 mm Hg in the same patient. A^- denotes unmeasured plasma anions. The numbers within the bars give ion concentrations in millimoles per liter.

tion buffers both metabolic acids ($THAM + H^+ \rightarrow THAM^+$) and respiratory acids ($THAM + H_2CO_3 \rightarrow THAM^+ + HCO_3^-$). Like Carbicarb, THAM limits carbon dioxide generation and increases both extracellular and intracellular pH. Nevertheless, THAM has not been documented to be clinically more efficacious than bicarbonate. In fact, serious side effects, including hyperkalemia, hypoglycemia, ventilatory depression, local injury in cases of extravasation, and hepatic necrosis in neonates, markedly limit its usefulness.[27]

Specific Disorders

Lactic Acidosis

Conventionally, two broad types of lactic acidosis are recognized: type A, in which there is evidence of impaired tissue oxygenation, and type B, in which no such evidence is apparent.[29-31] However, inadequate tissue oxygenation may at times defy clinical detection, and tissue hypoxia can be a part of the pathogenesis of certain conditions that cause type B lactic acidosis. Thus, the distinction between the two types is occasionally blurred. Most cases of lactic acidosis are caused by tissue hypoxia arising from circulatory failure. Both overproduction and underuse of lactic acid contribute to its accumulation. In turn, the resultant acidemia, when severe, compounds the hemodynamic disarray and further suppresses lactate consumption by the liver and the kidneys, thereby establishing an ominous vicious circle.[1,29-32] Experimental data have implicated the lactate ion itself, in addition to the acidemia associated with lactic acid, as a contributor to circulatory malfunction.[33-35] Therapy should focus primarily on securing adequate tissue oxygenation and on identifying and treating the underlying cause.[1,29-32,36] Improvement of tissue oxygenation may require a number of measures, including maintenance of a high inspired oxygen fraction, ventilator support, repletion of the volume of extracellular fluid, afterload-reducing agents, and inotropic compounds such as dopamine and dobutamine. Drugs causing vasoconstriction (such as norepinephrine) should be avoided, since they can worsen tissue hypoxia.[1,29,30]

Cause-specific measures should be instituted promptly, including antibiotics for sepsis; operative intervention for trauma or tissue ischemia; dialytic removal of certain toxins, such as methanol and ethylene glycol; discontinuation of metformin and nitroprusside; administration of insulin in patients with diabetes mellitus; glucose infusion in those with alco-

holism and certain forms of congenital lactic acidosis; correction of thiamine deficiency in cases of ethanol intoxication, short-bowel syndrome, fulminant beriberi, and pyruvate dehydrogenase deficiency; a low-carbohydrate diet and antibiotics in cases of D-lactic acidosis (for example, with short-bowel syndrome); and treatment of an underlying cancer or pheochromocytoma.[1,29,30,37]

In the presence of severe metabolic acidemia, these measures should be supplemented by the cautious administration of sodium bicarbonate, initially at a dose of no more than 1 to 2 mmol per kilogram of body weight, given as an infusion rather than as a bolus.[1,13,32] Infusion of additional sodium bicarbonate should be guided by careful monitoring of the patient's acid–base status. Amelioration of extreme acidemia with alkali should be regarded as a temporizing measure adjunctive to cause-specific measures. Particular restraint should be exercised in using alkali during cardiopulmonary resuscitation; the markedly reduced pulmonary blood flow can lead to retention of some of the carbon dioxide generated in the process of buffering, potentially exacerbating the prevailing acidosis.[26]

There is considerable excitement about the therapeutic potential of dichloroacetate in lactic acidosis. This investigational agent stimulates pyruvate kinase, thereby accelerating the oxidation of pyruvate to acetyl–coenzyme A.[1,32] Although the effects of dichloroacetate in experimental lactic acidosis were impressive, and the initial clinical observations were promising, a controlled clinical study failed to demonstrate a substantial advantage of dichloroacetate over conventional management of lactic acidosis.[38]

The prognosis of patients with lactic acidosis remains ominous, because the underlying disease frequently cannot be managed effectively. Its development should therefore be prevented by maintaining adequate fluid balance, optimizing cardiorespiratory function, managing infection, and being cautious when prescribing drugs that promote lactic acidosis. Particular attention should be paid to patients at special risk for lactic acidosis, such as those with diabetes mellitus or advanced cardiac, respiratory, renal, or hepatic disease.

Diabetic Ketoacidosis

Insulin administration is the cornerstone of the treatment of diabetic ketoacidosis.[39] Water, sodium, and potassium deficits should also be replaced. Alkali should not be administered routinely, since the metabolism of the retained ketoacid anions in response to insulin therapy results in swift regeneration of bicarbonate with partial or complete resolution of the acidemia.[40] Indeed, the administration of alkali may even delay recovery by augmenting hepatic ketogenesis.[17] Nonetheless, small amounts of bicarbonate may benefit patients with marked acidemia (blood pH, <7.10), in whom decreased myocardial performance can worsen tissue perfusion. Patients with a substantial component of hyperchloremic acidosis (i.e., those with a relatively normal anion gap) due to urinary loss of ketoacid anions with sodium or potassium can benefit from alkali therapy, even when acidemia is moderately severe. In these patients, endogenous correction of the hypobicarbonatemia depends largely on increased renal acid excretion, a process requiring several days for completion.[41-43]

Alcoholic Ketoacidosis

Alcoholic ketoacidosis can induce severe hypobicarbonatemia that largely corrects itself spontaneously with the provision of nutrients and interruption of ethanol intake.[44] The infusion of dextrose stimulates insulin secretion but inhibits glucagon secretion, thereby promoting the regeneration of bicarbonate stores from the metabolism of retained ketoacid anions. The administration of saline will repair the existing extracellular-fluid volume deficit and thus suppress counterregulatory hormones that enhance ketoacidosis; the often coexisting element of lactic acidosis will also be reversed.

Methanol and Ethylene Glycol Intoxications

Methanol and ethylene glycol intoxications can produce severe, high-anion-gap metabolic acidoses caused by the accumulation of toxic metabolites. Large amounts of alkali are often required to combat the severe acidemia. Additional therapeutic measures include gastric lavage, oral charcoal, intravenous or oral ethanol (which inhibits the generation of toxic metabolites from ingested alcohols because of its higher affinity for alcohol dehydrogenase), and in severe cases, single-pass hemodialysis.[45] Forced diuresis can prevent acute renal failure in patients with ethylene glycol intoxication. Although it is not available in the United States, 4-methylpyrazole is a potent inhibitor of alcohol dehydrogenase that effectively reduces the generation of toxic metabolites.[46]

Aspirin Intoxication

Aspirin intoxication can result in respiratory alkalosis, mixed respiratory alkalosis and metabolic acidosis, or (less commonly) simple metabolic acidosis. Respiratory alkalosis is caused by direct stimulation of the respiratory center by salicylate, whereas the accumulation of lactic acid and ketoacids largely accounts for metabolic acidosis. Because the risk of death and the severity of neurologic manifestations depend on the concentration of salicylate in the central nervous system, therapy is directed at limiting further drug absorption by administering activated charcoal and promoting the exit of the toxin from the cerebral tissues by increasing the alkalinity of the

blood.[47] Thus, unless the blood is already alkalinized by respiratory alkalosis, sodium bicarbonate must be administered to raise the blood pH to about 7.45 to 7.50. In turn, the resultant alkalinization of the urine promotes the excretion of salicylate by minimizing the back-diffusion of salicylic acid from the lumen of the kidney tubules.[48] Establishing a high urinary flow rate by means of the infusion of fluid also enhances salicylate excretion. Hemodialysis is reserved for severe cases, especially those involving renal dysfunction.[45]

Toluene Exposure

Exposure to toluene by sniffing glue can cause severe metabolic acidosis resulting from the stepwise metabolism of toluene to benzoic acid and hippuric acid. If renal function is reasonably well maintained, swift excretion of the hippurate anion with sodium and potassium can convert a high-anion-gap acidosis to hyperchloremic acidosis simulating distal renal tubular acidosis.[49]

Bicarbonate Loss

Loss of bicarbonate from the digestive tract can lead to marked metabolic acidosis that requires exogenous replenishment of body alkali stores, in addition to replenishment of water, sodium, and potassium. Patients with severe diarrhea (for example, from acute salmonella enteritis or cholera) and those with pancreatic allografts, in whom the exocrine pancreas drains into the urinary bladder,[50] have this type of acidosis. Although hyperchloremic metabolic acidosis is usually seen, a high anion gap can develop when fluid losses are profuse; hyperproteinemia, hyperphosphatemia, renal failure, and lactic acidosis all contribute to raising the plasma anion gap.[41,51]

Renal Failure

Renal failure, especially acute renal failure in a patient in a catabolic state, can cause severe metabolic acidosis reflecting retention of the endogenous acid load. Patients with classic (type 1) renal tubular acidosis can present with profound hypobicarbonatemia and hypokalemia that require prompt administration of potassium and alkali.[52] The resulting acidemia can be compounded by an inadequate ventilatory response caused by paresis of the respiratory muscles induced by potassium depletion.

Dilutional Acidosis

Sizable expansion of the extracellular-fluid volume with solutions that do not contain bicarbonate can give rise to dilutional acidosis. Severe examples of this entity have recently been identified as a complication of aggressive volume resuscitation in patients with right ventricular myocardial infarction.[53] Provision of the requisite amounts of sodium bicarbonate in the infusate should prevent this complication.

Respiratory Acidosis

Respiratory acidosis is observed whenever carbon dioxide excretion by the lungs lags behind carbon dioxide production, resulting in positive carbon dioxide balance. The rise in the partial pressure of arterial carbon dioxide elicits an acute increase in plasma bicarbonate that originates from buffering mechanisms, but the overall magnitude of this adaptation is quite small (Fig. 2).[54-56] When hypercapnia is sustained, the plasma bicarbonate concentration is amplified markedly as a result of up-regulation of renal acidification.[54,57-59] Three to five days are required for this adaptation, with increased acid excretion and chloruresis generating the hypochloremic hyperbicarbonatemia characteristic of chronic hypercapnia (Fig. 2). Consequently, life-threatening acidemia of respiratory origin occurs during severe, acute respiratory acidosis or during respiratory decompensation in patients with chronic hypercapnia.

Acute respiratory acidosis develops as a consequence of upper- or lower-airway obstruction, status asthmaticus, severe alveolar defects such as those occurring in pneumonia or pulmonary edema, central nervous system depression, neuromuscular impairment, and ventilatory restriction (as in patients with rib fractures with flail chest).[54,60] The alveolar-gas equation predicts that the rise in the partial pressure of arterial carbon dioxide will cause obligatory hypoxemia in patients breathing room air. The resultant fall in the partial pressure of arterial oxygen limits hypercapnia to approximately 80 to 90 mm Hg; a higher partial pressure of arterial carbon dioxide imposes a partial pressure of arterial oxygen that is incompatible with life.[60,61] Under these circumstances, it is hypoxemia, not hypercapnia or acidemia, that poses the principal threat to life. Consequently, oxygen administration represents a critical element in the management of respiratory acidosis. Whenever possible, treatment must be directed at removing or ameliorating the underlying cause. Immediate therapeutic efforts should focus on securing a patent airway and restoring adequate oxygenation by delivering an oxygen-rich inspired mixture. Mechanical ventilation must be initiated in the presence of apnea, severe hypoxemia unresponsive to conservative measures, or progressive respiratory acidosis (partial pressure of arterial carbon dioxide, >80 mm Hg).[54,60,61]

Chronic hypercapnia results from many conditions, including chronic obstructive or restrictive pulmonary diseases, upper-airway obstruction, central nervous system depression, neuromuscular impairment, and abnormal chest-wall mechanics.[60,61] Respiratory decompensation in patients with these conditions, commonly resulting from infection, use of narcotics, or uncontrolled oxygen therapy, superimposes an acute element of carbon dioxide retention and acidemia on the chronic base-line disorder (Fig. 2). Progressive narcosis and coma, known as

hypercapnic encephalopathy, can ensue. Management of respiratory decompensation depends on the cause, severity, and rate of progression of carbon dioxide retention.[61] Vigorous treatment of pulmonary infections, bronchodilator therapy, and removal of secretions can offer considerable benefit. Naloxone will reverse the suppressive effect of narcotic agents on ventilation. Avoidance of tranquilizers and sedatives, gradual reduction of supplemental oxygen (aiming at a partial pressure of arterial oxygen of about 60 mm Hg), and treatment of a superimposed element of metabolic alkalosis will optimize the ventilatory drive.

Whereas an aggressive approach that favors the early use of ventilator assistance is most appropriate for patients with acute respiratory acidosis, a more conservative approach is advisable in those with chronic diseases that limit pulmonary reserve, because of the great difficulty often encountered in weaning such patients from ventilators. However, if the patient is obtunded or unable to cough, and if hypercapnia and acidemia are worsening, mechanical ventilation should be instituted. Minute ventilation should be raised so that the partial pressure of arterial carbon dioxide gradually returns to near its long-term base line and excretion of excess bicarbonate by the kidneys is accomplished (assuming that chloride is provided).[60,61] By contrast, overly rapid reduction in the partial pressure of arterial carbon dioxide risks the development of posthypercapnic alkalosis (Fig. 2), with potentially serious consequences. Should posthypercapnic alkalosis develop, it can be ameliorated by providing chloride, usually as the potassium salt, and administering the bicarbonate-wasting diuretic acetazolamide at doses of 250 to 375 mg once or twice daily. Noninvasive mechanical ventilation with a nasal or facial mask is being used with increasing frequency to avert the possible complications of endotracheal intubation.[61]

Permissive Hypercapnia

It has long been standard practice to prescribe tidal volumes two to three times normal (i.e., 10 to 15 ml per kilogram) when instituting mechanical ventilation for patients with acute respiratory distress syndrome, severe airway obstruction, or other types of respiratory failure. This approach is being challenged by data indicating that alveolar overdistention can cause tissue injury, culminating in increased microvascular permeability and lung rupture.[62,63] Although the evidence is incomplete, there is a growing tendency to prescribe tidal volumes of 5 to 7 ml per kilogram (or less) to achieve a plateau airway pressure no higher than 35 cm of water. Because an increase in the partial pressure of arterial carbon dioxide might ensue, the strategy is referred to as permissive hypercapnia or controlled hypoventilation. The severity of carbon dioxide retention varies widely in different reports, but the partial pressure of arterial carbon dioxide rarely exceeds 80 mm Hg.

Uncontrolled clinical trials and a preliminary report of a randomized study suggest that permissive hypercapnia results in lower morbidity and mortality than conventional mechanical ventilation.[64,65] However, the available results remain inconclusive. The increased respiratory drive associated with permissive hypercapnia causes extreme discomfort, making sedation necessary. Because the patients commonly require neuromuscular blockade as well, accidental disconnection from the ventilator can cause sudden death. Furthermore, after the neuromuscular-blocking agent is discontinued, there may be weakness or paralysis for several days or weeks. There are several contraindications to the use of permissive hypercapnia, including cerebrovascular disease, brain edema, increased intracranial pressure, and convulsions; depressed cardiac function and arrhythmias; and severe pulmonary hypertension. It is important to note that most of these entities can develop as adverse effects of permissive hypercapnia itself,[62,63] especially when hypercapnia is associated with substantial acidemia. In fact, some experimental evidence indicates that correction of acidemia attenuates the adverse hemodynamic effects of permissive hypercapnia.[66] It appears prudent, although still controversial, to keep the blood pH at approximately 7.30 by administering intravenous alkali when controlled hypoventilation is prescribed.[67]

Alkali Therapy

The presence of an element of metabolic acidosis is the primary indication for alkali therapy in patients with respiratory acidosis. However, this practice entails some risks, including pH-mediated depression of ventilation, enhanced carbon dioxide production from bicarbonate decomposition, and volume expansion. Yet alkali therapy may have a special role in patients who have acidemia and severe bronchospasm from any cause by restoring the responsiveness of the bronchial musculature to beta-adrenergic agonists,[60,61] as well as in patients treated with controlled hypoventilation. The use of THAM has been suggested in patients with chronic hypercapnia, because of its theoretical potential to decrease the partial pressure of arterial carbon dioxide. However, this expectation has not been borne out.[54] The resultant decrease in alveolar ventilation worsens hypoxemia and offsets the disposal of carbonic acid that is due to the buffering effect of THAM.

Mixed Acidoses

Coexistent respiratory acidosis and metabolic acidosis can be observed in several clinical conditions, including cardiorespiratory arrest, chronic obstructive pulmonary disease complicated by circulatory failure or sepsis, severe pulmonary edema, combined

respiratory and renal failure, diarrhea or renal tubular acidosis complicated by hypokalemic paresis of the respiratory muscles, and poisoning with various toxic agents and drugs.[68] The additive effects on blood acidity of primary hypercapnia, on the one hand, and the bicarbonate deficit, on the other, can produce profound acidemia requiring prompt therapy. Whenever possible, treatment must be targeted at both components of the mixed acidosis.

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