

*Medical Progress***MANAGEMENT OF LIFE-THREATENING
ACID-BASE DISORDERS****Second of Two Parts**

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**ADVERSE CONSEQUENCES OF SEVERE
ALKALEMIA**

Severe alkalemia (blood pH greater than 7.60) can compromise cerebral and myocardial perfusion by causing arteriolar constriction, an effect that is more pronounced in respiratory than in metabolic alkalosis (Table 2).⁶⁹⁻⁷¹ Neurologic abnormalities may ensue, including headache, tetany, seizures, lethargy, delirium, and stupor. The associated reduction in the plasma concentration of ionized calcium probably contributes to these manifestations. Although it exerts a moderate positive inotropic effect on the isolated heart, alkalemia reduces the anginal threshold and predisposes the patient to refractory supraventricular and ventricular arrhythmias. This arrhythmogenic action is more pronounced in patients with underlying heart disease. Alkalemia depresses respiration, causing hypercapnia and hypoxemia. Such effects are of little consequence in patients with adequate ventilatory reserve, but they can be consequential in patients with compromised ventilation. Even mild alkalemia can frustrate efforts to wean patients from mechanical ventilation.

Hypokalemia is an almost constant feature of alkalemic disorders, but it is more prominent in those of metabolic origin. Translocation of potassium into cells and renal and extrarenal losses contribute in

varying degrees to its generation.^{7,69-71} In turn, hypokalemia can have several adverse effects, including neuromuscular weakness; sensitization to digitalis-induced arrhythmias; polyuria; and increased ammonia production, which can heighten the risk of hepatic encephalopathy. Alkalemia stimulates anaerobic glycolysis and increases the production of lactic acid and ketoacids.^{6,17} Along with the alkalemic titration of plasma proteins and the hyperproteinemia accompanying chloride-responsive metabolic alkalosis, this effect contributes to the characteristic moderate elevation in the plasma anion gap.^{41,72} Although acute alkalemia can reduce the release of oxygen to the tissues by tightening the binding of oxygen to hemoglobin, chronic alkalemia negates this effect by increasing the concentration of 2,3-diphosphoglyceric acid in red cells.⁶⁹⁻⁷¹

**MANAGEMENT OF LIFE-THREATENING
ALKALOSIS****Metabolic Alkalosis**

In the presence of an appropriate ventilatory response, severe alkalemia of metabolic origin requires that the plasma bicarbonate concentration exceed 45 mmol per liter.¹² Just as in severe metabolic acidemia, the immediate goal of therapy is moderation but not full correction of the alkalemia. Reducing plasma bicarbonate to less than 40 mmol per liter is an appropriate short-term goal, since the corresponding pH is on the order of 7.55 or lower. Most severe metabolic alkalosis is of the chloride-responsive form, the most common causes being loss of gastric acid and the administration of loop or thiazide diuretics.^{69,71} The characteristic hypochloremic hyperbicarbonatemia results from the loss of hydrochloric acid in gastric secretions or from urinary excretion of excess ammonium chloride caused by these chloruretic diuretics.

Substantial contraction of the volume of extracellular fluid as a result of diuretic-induced losses of sodium chloride can further amplify the resulting hyperbicarbonatemia by limiting the space of distribution of bicarbonate. Such a "contraction alkalosis" is particularly likely in patients with massive edema treated with combination regimens of diuretics (such as furosemide and metolazone). Maintenance of chloride-responsive metabolic alkalosis is then effected by heightened renal bicarbonate reabsorption, frequently coupled with a reduced glomerular filtration rate, changes that are mediated by chloride depletion itself, contraction of extracellular-fluid volume, and the associated potassium deficit.

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TABLE 2. MAJOR ADVERSE CONSEQUENCES OF SEVERE ALKALEMIA.

Cardiovascular
Arteriolar constriction
Reduction in coronary blood flow
Reduction in anginal threshold
Predisposition to refractory supraventricular and ventricular arrhythmias
Respiratory
Hypoventilation with attendant hypercapnia and hypoxemia
Metabolic
Stimulation of anaerobic glycolysis and organic acid production
Hypokalemia
Decreased plasma ionized calcium concentration
Hypomagnesemia and hypophosphatemia
Cerebral
Reduction in cerebral blood flow
Tetany, seizures, lethargy, delirium, and stupor

If the processes that generate metabolic alkalosis are still ongoing, every effort should be made to moderate or stop them, even if only temporarily. Vomiting should be countered with antiemetics. If continuation of gastric drainage is required, the loss of gastric acid can be reduced by administering H_2 -receptor blockers or inhibitors of the gastric $H^+/K^+-ATPase$. Notably, these treatments substitute loss of sodium chloride for loss of hydrochloric acid. Decreasing the dose of loop and thiazide diuretics can be coupled with the addition of potassium-sparing diuretics (spironolactone, amiloride, or triamterene), drugs that decrease distal acidification and curtail potassium excretion.

Prompt attention should be given to additional factors that might compound the alkalosis. Administration of bicarbonate or its precursors, such as lactate, citrate, and acetate (the latter being a common ingredient of parenteral-nutrition solutions), should be discontinued. At times, absorbable alkali is not a complicating factor but the very cause of the metabolic alkalosis, as in patients ingesting inordinate amounts of calcium carbonate or large quantities of absorbable alkali and milk; severe metabolic alkalosis coupled with variable degrees of hypercalcemia and renal impairment can occur. Coadministration of cation-exchange resins with aluminum hydroxide in effect renders the nonabsorbable alkali absorbable.⁷³ If drugs with mineralocorticoid activity, such as fludrocortisone and various glucocorticoid compounds, are being administered, their indication and dose should be reassessed.

Having addressed the factors that cause or aggravate the alkalosis, the clinician must then focus on ameliorating the existing hyperbicarbonatemia. Patients with volume depletion require provision of both sodium chloride and potassium chloride. Re-

pair of the prevailing sodium, potassium, and chloride deficits and of the often-present functional azotemia will promote bicarbonaturia heralded by alkalinization of the urine. Administration of acetazolamide (250 to 375 mg once or twice daily) fosters bicarbonaturia but requires consideration of the associated kaliuresis and phosphaturia.

If the pace of correction of the alkalemia must be accelerated, alkali stores can be titrated by infusing hydrochloric acid. Hydrochloric acid administered intravenously as a 0.1 to 0.2 N solution (that is, one containing 100 to 200 mmol of hydrogen per liter) is safe and effective for the management of severe metabolic alkalosis. The acid can be infused as such or can be added to amino acid and dextrose solutions containing electrolytes and vitamins without causing adverse chemical reactions.^{74,75} Because of its sclerosing properties, hydrochloric acid must be administered through a central venous line at an infusion rate of no more than 0.2 mmol per kilogram of body weight per hour. However, it can also be administered through a peripheral vein if it is added to an amino acid solution and mixed with a fat emulsion.⁷⁴

Calculation of the amount of hydrochloric acid solution to be infused is based on a bicarbonate space of 50 percent of body weight.¹⁵ Thus, to reduce plasma bicarbonate from 50 to 40 mmol per liter in a 70-kg patient, the estimated amount of hydrochloric acid required is $10 \times 70 \times 0.5$, or 350 mmol. Precursors of hydrochloric acid, such as ammonium chloride (20 g per liter, with 374 mmol of hydrogen per liter) and arginine monohydrochloride (100 g per liter, with 475 mmol of hydrogen per liter), can substitute for hydrochloric acid, but they entail substantial risks and are used less commonly. Both of these preparations are hyperosmotic solutions; to avoid local tissue injury, they must be infused through a central catheter. In addition, ammonium chloride can raise serum ammonia concentrations in patients with liver failure, and arginine monohydrochloride can induce serious hyperkalemia in patients with renal failure, especially when there is coexisting liver disease.^{69,71,76}

Treatment of severe chloride-responsive metabolic alkalosis is considerably more challenging in patients with cardiac or renal dysfunction.^{69,71} Expansion of the extracellular-fluid volume may either accompany alkalemia or develop as a result of treatment. Potassium chloride can induce hyperkalemia in patients with renal failure. In certain cases, downgrading the diuretic regimen, adding acetazolamide, and cautiously administering sodium chloride and potassium chloride may suffice. In many other cases, however, cardiac and renal failure pose such limitations that the physician must resort to more aggressive measures. Infusion of hydrochloric acid can be efficacious, but the associated fluid load is often prob-

lematic. Under these circumstances, use of an extracorporeal device is advisable. Hemodialysis and ultrafiltration can rapidly correct severe alkalemia and volume overload, especially if the bicarbonate concentration of the standard dialysate is reduced. In patients with unstable hemodynamics, the same goals can be achieved by continuous arteriovenous or venovenous hemofiltration with sodium chloride as the replacement solution.

Life-threatening alkalemia is a very rare occurrence in chloride-resistant metabolic alkalosis. Disorders of mineralocorticoid excess, severe potassium depletion, and Bartter's or Gitelman's syndrome are the causes of this form of alkalosis. Aggressive potassium repletion will correct or ameliorate chloride-resistant alkalosis, but the thrust of the therapy should be directed at reversing the underlying disorder, if possible. When the cause of the mineralocorticoid excess cannot be reversed, potassium-sparing diuretics coupled with moderate restriction of sodium chloride can provide symptomatic relief.⁷⁷ Identifying laxative abuse as the culprit may prevent recurrence of the problem. Potassium-sparing diuretics, nonsteroidal antiinflammatory drugs, or angiotensin-converting-enzyme inhibitors can ameliorate Bartter's or Gitelman's syndrome.^{69,71,78-80}

Respiratory Alkalosis

Respiratory alkalosis is the most frequently encountered acid-base disorder, since it occurs in normal pregnancy and with high-altitude residence. The pathologic causes of respiratory alkalosis include various hypoxemic conditions, pulmonary disorders, central nervous system diseases, salicylate intoxication, hepatic failure, sepsis, and the anxiety-hyperventilation syndrome. Respiratory alkalosis is particularly prevalent among the critically ill; in these patients, its presence is a bad prognostic sign, because mortality increases in direct proportion to the severity of the hypocapnia.⁷⁰

Hypocapnia elicits a secondary change in plasma bicarbonate that, as in hypercapnia, has two components. A moderate acute decrease in plasma bicarbonate originates from tissue buffering. A larger decrease accompanies chronic hypocapnia as a result of down-regulation of renal acidification and requires two to three days to reach completion.^{70,81-83} Because blood pH does not exceed 7.55 in most cases of respiratory alkalosis, severe manifestations of alkalemia are usually absent. Marked alkalemia can be observed, however, in certain circumstances, such as with inappropriately set ventilators, some psychiatric conditions, and lesions of the central nervous system. Obviously, clinical manifestations of severe alkalemia are more likely to occur in the acute, rather than the chronic, phase of respiratory alkalosis.

Management of respiratory alkalosis must be di-

rected toward correcting the underlying cause, whenever possible. Because most cases of respiratory alkalosis, especially chronic cases, pose little risk to health and produce few or no symptoms, measures to treat the deranged acid-base composition are not required. The anxiety-hyperventilation syndrome is an exception. An active therapeutic approach that provides reassurance, sedation, and ultimately psychotherapy is most helpful in these cases. Rebreathing into a paper bag or any other closed system provides prompt, but unfortunately short-lived, symptomatic relief. If hypocapnia-induced alkalemia is severe and persistent, sedation may be required.^{60,70}

Pseudorespiratory Alkalosis

Arterial hypocapnia does not necessarily imply respiratory alkalosis or the secondary response to metabolic acidosis but can be observed in an idiopathic form of respiratory acidosis.^{18,19,84} This entity, which we have termed pseudorespiratory alkalosis, occurs in patients with profound depression of cardiac function and pulmonary perfusion but with relative preservation of alveolar ventilation, including patients undergoing cardiopulmonary resuscitation. The severely reduced pulmonary blood flow limits the carbon dioxide delivered to the lungs for excretion, thereby increasing the mixed venous partial pressure of carbon dioxide. By contrast, the increased ventilation:perfusion ratio causes the removal of a larger-than-normal amount of carbon dioxide per unit of blood traversing the pulmonary circulation, thereby creating arterial eucapnia or frank hypocapnia (Fig. 3). Nonetheless, the absolute excretion of carbon dioxide is decreased and the carbon dioxide balance of the body is positive — the hallmark of respiratory acidosis.¹⁹ Such patients may have severe venous acidemia (often due to mixed respiratory and metabolic acidosis) accompanied by an arterial pH that ranges from the mildly acidic to the frankly alkaline. Furthermore, the extreme oxygen deprivation prevailing in the tissues may be completely disguised by the reasonably preserved values of arterial oxygen (Fig. 3). To rule out pseudorespiratory alkalosis in a patient with circulatory failure, blood gas monitoring must include sampling of mixed (or central) venous blood. The management of pseudorespiratory alkalosis must be directed toward optimizing systemic hemodynamics.

Mixed Alkaloses

Extreme alkalemia can occur in patients with metabolic and respiratory alkalosis, even in the presence of only moderate changes in plasma bicarbonate and the partial pressure of arterial carbon dioxide. This disorder can occur in various settings, including among patients with primary hypocapnia associated with chronic liver disease, in whom metabolic alkalosis develops because of vomiting, nasogastric

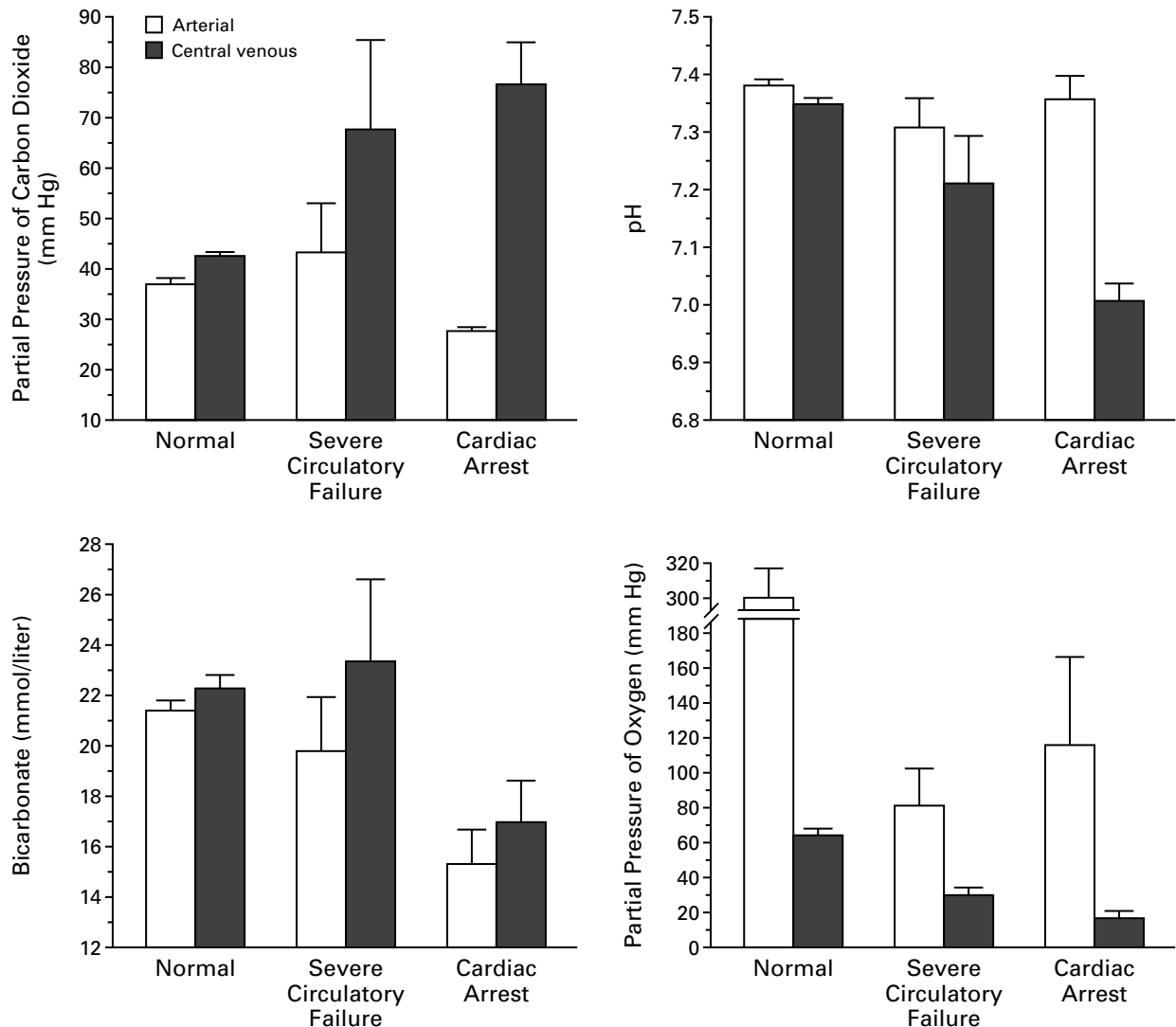


Figure 3. Simultaneous Mean (+SE) Arterial and Central Venous Values for Partial Pressure of Carbon Dioxide, pH, Bicarbonate Concentration, and Partial Pressure of Oxygen in 26 Patients with Normal Hemodynamic Status, 5 Patients with Severe Circulatory Failure, and 5 Patients with Cardiac Arrest Undergoing Cardiopulmonary Resuscitation.

Data were obtained from Adrogué et al.¹⁸

drainage, diuretics, profound hypokalemia, or alkali administration, especially in the context of renal insufficiency.^{68,85} Mixed alkalosis is also observed in patients with end-stage renal disease in whom primary hypocapnia develops; the inappropriately high plasma bicarbonate level reflects the absence of the renal response to the prevailing hypocapnia and the dialysis-induced alkali load. Patients undergoing peritoneal dialysis are more vulnerable than those undergoing hemodialysis, because peritoneal dialysis maintains plasma bicarbonate at a higher level (25 to 26 mmol per liter, as compared with a value of 20 to 21 mmol per liter before hemodialysis). Reducing the

base concentration of the dialysate or switching the patient from peritoneal dialysis to hemodialysis will ameliorate the situation.

REFERENCES

69. Harrington JT, Kassirer JP. Metabolic alkalosis. In: Cohen JJ, Kassirer JP, eds. Acid-base. Boston: Little, Brown, 1982:227-306.
 70. Gennari FJ, Kassirer JP. Respiratory alkalosis. In: Cohen JJ, Kassirer JP, eds. Acid-base. Boston: Little, Brown, 1982:349-76.
 71. Rimmer JM, Gennari FJ. Metabolic alkalosis. *J Intensive Care Med* 1987;2:137-50.
 72. Madias NE, Ayus JC, Adrogué HJ. Increased anion gap in metabolic alkalosis: the role of plasma-protein equivalency. *N Engl J Med* 1979;300:1421-3.
 73. Madias NE, Levey AS. Metabolic alkalosis due to absorption of "non-absorbable" antacids. *Am J Med* 1983;74:155-8.

74. Knutson OH. New method for administration of hydrochloric acid in metabolic alkalosis. *Lancet* 1983;1:953-6.
75. Shires GT, Canizaro PC, Shires GT III, Lowry SF. Fluid, electrolyte, and nutritional management of the surgical patient. In: Schwartz SI, Shires GT, Spencer FC, eds. *Principles of surgery*. 5th ed. New York: McGraw-Hill, 1989:69-103.
76. Bushinsky DA, Gennari FJ. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 1978;89:632-4.
77. Harrington JT, Hulter HN, Cohen JJ, Madias NE. Mineralocorticoid-stimulated renal acidification in the dog: the critical role of dietary sodium. *Kidney Int* 1986;30:43-8.
78. Vinci JM, Gill JR Jr, Bowden RE, et al. The kallikrein-kinin system in Bartter's syndrome and its response to prostaglandin synthetase inhibition. *J Clin Invest* 1978;61:1671-82.
79. Colussi G, Rombola G, De Ferrari ME, Macaluso M, Minetti L. Correction of hypokalemia with antialdosterone therapy in Gitelman's syndrome. *Am J Nephrol* 1994;14:127-35.
80. Hene RJ, Koomans HA, Dorhout Mees EJ, Stolpe AVD, Verhoef GEG, Boer P. Correction of hypokalemia in Bartter's syndrome by enalapril. *Am J Kidney Dis* 1987;9:200-5.
81. Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis: the effect of sustained hyperventilation on renal regulation of acid-base equilibrium. *N Engl J Med* 1991;324:1394-401.
82. Cohen JJ, Madias NE, Wolf CJ, Schwartz WB. Regulation of acid-base equilibrium in chronic hypocapnia: evidence that the response of the kidney is not geared to the defense of extracellular $[H^+]$. *J Clin Invest* 1976;57:1483-9.
83. Hilden SA, Johns CA, Madias NE. Adaptation of rabbit renal cortical Na^+ - H^+ exchange activity in chronic hypocapnia. *Am J Physiol* 1989;257:F615-F622.
84. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med* 1986;315:153-6.
85. Madias NE, Cohen JJ, Adrogue HJ. Influence of acute and chronic respiratory alkalosis on preexisting chronic metabolic alkalosis. *Am J Physiol* 1990;258:F479-F485.