11 Diagnosis and Treatment of Respiratory Alkalosis

Otwell Timmons

Key Points

1. Respiratory alkalosis is defined as a pH above 7.45 due to an arterial carbon dioxide tension less than 35 mmHg.
2. Respiratory alkalosis accompanies pregnancy and the hyperventilation anxiety syndrome, making it the most common acid–base imbalance.
3. Carbon dioxide production and elimination are usually matched, but illness, medication, or injury can decrease production or increase elimination and effect respiratory alkalosis.
4. Among the determinants of carbon dioxide elimination are the cerebral cortex, the brainstem respiratory centers, and the peripheral receptors that sense chemical and physical phenomena.
5. The most common cause of respiratory alkalosis, the hyperventilation anxiety syndrome, arises in the cerebral cortex. It often masquerades as an organic pulmonary or cardiovascular disorder.
6. Hyperventilation constricts the coronary and cerebral circulations and dilates the pulmonary circulation.
7. Metabolic compensation for respiratory alkalosis reaches steady state in about 3 days. Over a longer time, metabolic compensation can return pH to normal despite ongoing hypocarbia.

Key Words: Respiratory alkalosis; respiratory drive; anxiety hyperventilation syndrome; respiratory stimulants; vascular tone

1. DEFINITION

Respiratory alkalosis is the elevation of body pH above 7.45 due to hypocapnia, generally accepted as an arterial partial pressure ($PaCO_2$) less than 35 torr. Respiratory alkalosis may be a primary disturbance, or it may be compensatory to metabolic acidosis. It may be acute or chronic. In chronic cases, metabolic compensation may partially correct the arterial pH or it may normalize the pH.

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2. ETIOLOGY/CAUSATION

All body cells generate carbon dioxide (CO_2) in the course of energy metabolism. All cellular fuels, whether consumed aerobically or anaerobically, generate CO_2. The amount of CO_2 generated varies among fuels. This amount is reflected in the respiratory quotient (RQ), the ratio of moles of CO_2 produced per mole of oxygen consumed. Carbohydrate has the highest RQ, 1. The RQ for protein is about 0.8, and for fat it is 0.7.

From cells, CO_2 diffuses to the capillary blood. There, it initially dissolves in plasma. The solubility of CO_2 in plasma is relatively high, but only a small portion of CO_2 retains the form of a dissolved gas. Gaseous CO_2 is in equilibrium with its hydration product, carbonic acid (H_2CO_3), and the bicarbonate ion (HCO_3^-) in plasma (Fig. 1). H_2CO_3 and HCO_3^- interact to affect pH, as the Henderson–Hasselbalch equation describes:

$$\text{pH} = \text{pK} + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \text{ (when pK} = 6.1\text{)}$$

pK is the dissociation constant of carbonic acid in blood, which is 6.1. pH reflects the hydrogen ion (H^+) concentration in plasma, and it is easily measured. However, clinical utility of the Henderson–Hasselbalch equation is limited by its reliance on logarithms and by the general lack of clinical measures of H_2CO_3 *(1)*. Practical insight into the

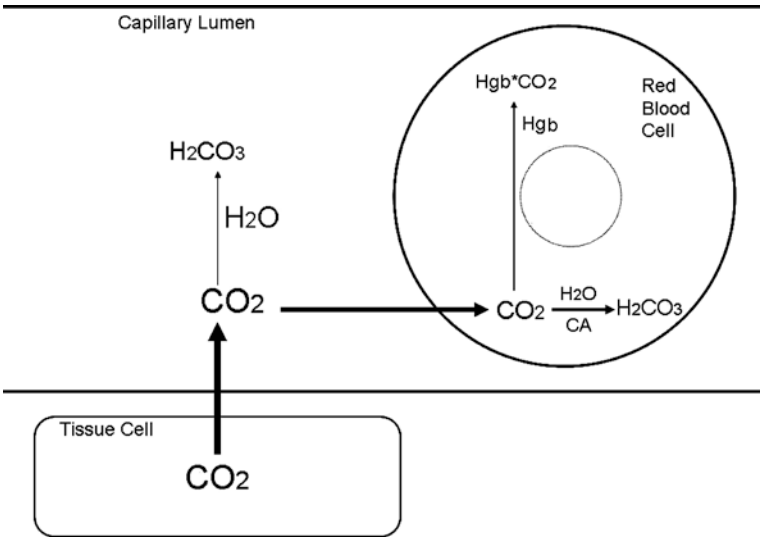

Fig. 1. Transport of CO_2 from tissue cells to the blood. CA, carbonic anhydrase; Hgb, hemoglobin; Hgb∗CO_2, carbaminohemoglobin.

interrelationship of gaseous CO_2 and its metabolic congeners comes from the Henderson equation:

$$H^+ = 24 \times \frac{PCO_2}{HCO_3^-}$$

The Henderson equation points out the relationship of plasma acidity to the ratio of PCO_2 and HCO_3^-.

Larger than the plasma CO_2 stores are intracellular ones. Hydration of CO_2 occurs more rapidly in red blood cells (RBCs) due to the availability of carbonic anhydrase, and most of the CO_2 transported in blood is intracellular (Fig. 1). In RBCs, three storage forms exist. In order of importance from greatest to least, these are hydrated CO_2, hemoglobin-bound CO_2, and dissolved gaseous CO_2 *(2)*.

Maintenance of acid–base homeostasis requires excretion of CO_2 and metabolic acids. The lungs exhale CO_2, and the kidneys secrete most metabolic acids. The kidneys also regulate the concentration of plasma buffers, of which HCO_3^- is the most important. Bases are molecules that can combine with H^+. When the combination produces a weak acid, the base and its corresponding acid are termed a buffer system. Buffers blunt the degree of change in pH when the concentrations of CO_2, other acids, and bases are altered.

Changes in general physiology can rapidly alter CO_2 production (Table 1). Fever, exercise, drug intoxication, and sepsis increase CO_2 production and alter acid–base status. A simple change in the source of non-protein calories from carbohydrate to fat can decrease CO_2 production 43%. Acid–base homeostasis requires, among other actions, that the body match the decrease in CO_2 production with decreased CO_2 excretion.

The circulation delivers CO_2, carbonic acid, and bicarbonate to the lungs. In perfused lung units, CO_2 diffuses from the plasma to the alveolus. Hydrolysis of carbonic acid to gaseous CO_2 maintains the concentration gradient necessary to drive diffusion. From the alveoli, CO_2 is excreted by ventilation (Fig. 2). The amount of CO_2 exhaled per minute is proportional to the minute volume, which is the product of respiratory rate per minute and the effective tidal volume. The arterial partial pressure of CO_2 ($PaCO_2$) is proportional to CO_2 production (VCO_2) and is inversely proportional to alveolar ventilation per unit of time (VA):

$$PaCO_2 \propto \frac{VCO_2}{VA}$$

The lungs excrete the great majority of moles of acid the body produces. Healthy adult lungs exhale 13,000 mEq of carbonic acid daily, where the kidneys excrete 40 to 80 mEq of metabolic acid daily *(2)*. The alveolar ventilation is the most important instantaneous determinant of the body's acid–base status.

Regulation of alveolar ventilation is performed in the brain. The primary drivers of respiratory drive and respiratory pattern are the medullary respiratory centers of the brainstem. These centers take inputs from brain chemoreceptors, from peripheral

Table 1
Causes of Respiratory Alkalosis

Central nervous system
Hyperventilation–anxiety syndrome
Volitional hyperventilation
Pain
Increased intracranial pressure
Brain hypoxia or ischemia
Tumor
Trauma
Stroke
Pharmacologic
Aspirin and other salicylates
Progestational hormones
Methylxanthines
Adrenergic agents
Doxapram
Nikethamide
Ethamivan
Nicotine
Dinitrophenol
Metformin
Pulmonary
Restrictive chest wall disease
Pulmonary edema
Pneumonia
Interstitial pneumonitis
Asthma
Pneumothorax
Hemothorax
Pulmonary embolism
Pulmonary fibrosis
Pulmonary hypertension
Mechanical hyperventilation
General state of the patient
Sepsis
Hypoxemia
Anemia
Exercise
Fever
Carbon monoxide poisoning
Methemoglobinemia

Altitude
Asphyxia
Pregnancy
Liver failure
Inborn errors of metabolism
Heat illness
Cold shock
Change in diet
Thyroid dysfunction

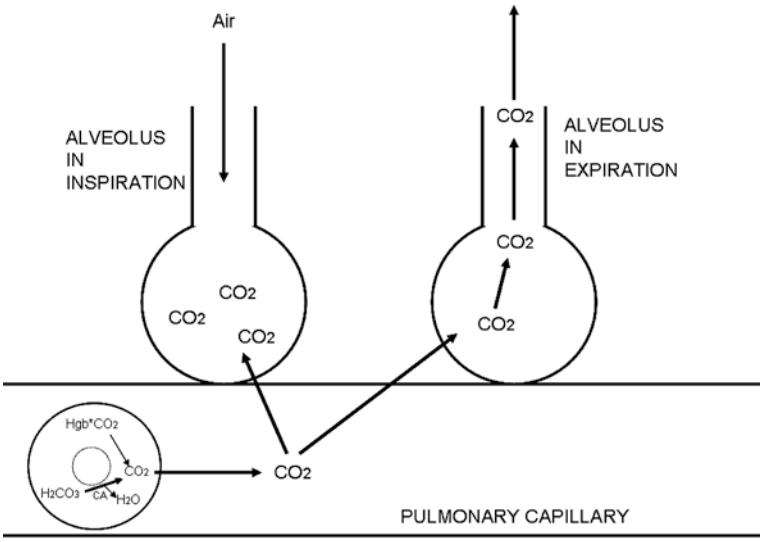

Fig. 2. Transport of CO_2 from blood to expired gas. Hgb∗CO2, carbaminohemoglobin; CA, carbonic anhydrase.

chemoreceptors, from receptors that respond to physical inputs in the lungs, and from other sites in the central nervous system (CNS) (Fig. 3). The interaction of the medullary respiratory centers with their sensors allows feedback control of alveolar ventilation. This control makes extremes of pH unusual in most cases of respiratory alkalosis.

The most active sources of stimuli to the medullary respiratory centers are the central chemoreceptors. These are chemically sensitive areas that are also located in the medulla. These chemoreceptors sense the pH of the cerebrospinal fluid (CSF). As CSF pH varies from physiologic, these receptors signal the medullary respiratory centers to alter alveolar ventilation and restore normal CSF pH.

The pH of CSF does not change instantly after a change in systemic pH. The blood–brain barrier allows equilibration of ions, such as bicarbonate, by relatively slow means. Equilibration of bicarbonate takes hours to days *(3)*. Respiratory compensation for metabolic acidosis or alkalosis will not be at equilibrium in the interim. By contrast, dissolved gases, such as CO_2, cross from the systemic circulation to the CSF and back more rapidly because they can diffuse. Their diffusion, though rapid, is not instantaneous.

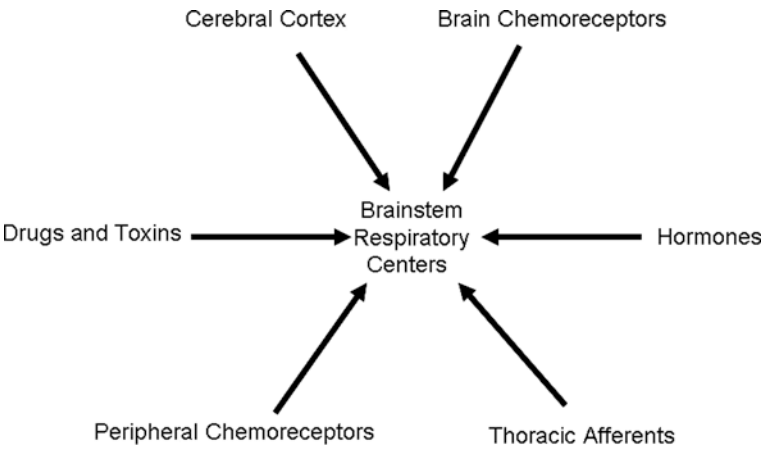

Fig. 3. Inputs to the brainstem respiratory centers.

The response of the chemoreceptors is delayed in congestive heart failure and shock states where arterialized blood may take longer to reach the cerebral circulation.

Augmenting the central chemoreceptors are the peripheral chemoreceptors, which consist of the carotid bodies and the aortic bodies. These receptors sense a wider variety of stimuli, including pH, $PaCO_2$, PaO_2, and oxygen delivery, directly from the blood stream *(4)*. Their contribution to respiratory drive is relatively weak when compared to that of the central chemoreceptors. The ability to sense PaO_2 and stimulate alveolar ventilation in response to hypoxemia is the basis for the hypoxic respiratory drive. Significant respiratory drive in response to hypoxemia is weak until frank hypoxemia, a PaO_2 less than 60 torr, exists.

The central and peripheral chemoreceptors may work together, or they may oppose each other. The receptivity of peripheral receptors to hypoxia and their potential faster response than the central chemoreceptors increase their influence in rapidly changing conditions or when the patient is hypoxemic. At any point, the interaction of chemoreceptors, the cerebral cortex, and neural sensors within the lungs determines the respiratory centers' output.

Lung reflexes are sensed locally and transmitted by vagal afferent fibers to the brain. Together, the inflation and deflation reflexes are considered the Hering–Breuer reflex *(4)*. The inflation reflex ceases inspiration in the presence of lung over distension. It has a protective function, and it helps regulate tidal volume and respiratory rate to minimize breathing work. The deflation reflex stimulates alveolar ventilation when low lung volume is sensed. Individually or together, the inflation and deflation reflexes may promote rapid shallow breathing or, if stimulation of the deflation reflex predominates, deep breathing. Either pattern may produce respiratory alkalosis. Separate from the stretch receptors are pulmonary juxtacapillary (J) receptors. These sense increased thickness of the alveolar–capillary membrane during pulmonary vascular congestion, as in pulmonary edema. Their stimulation increases alveolar ventilation.

As may be expected from the presence of these receptors, lung disease can manifest as hyperventilation. Asthma, emphysema, fibrosing alveolitis, pneumonia, pulmonary

hypertension, and pulmonary embolism have all been associated with hypocapnia. No one pathway explains the resulting hyperventilation in most of these conditions. Hypocapnia likely results from hypoxemia and from stimulation of vagal and chest wall afferents. The breathing pattern may be rapid shallow breathing, or tidal volume may increase in isolation. That these patterns also manifest during changes in lung elasticity implicates the J receptors and the Hering–Breuer reflex *(5–15)*. Air hunger and chest pain may also increase respiratory drive due to volitional or other integrated cortical inputs.

Higher CNS centers also affect respiratory drive. The anxiety–hyperventilation syndrome reflects cerebral cortical inputs that override the usual inhibitory mechanisms. Body pH can rise substantially, and the resulting clinical signs can feed the initial anxiety. Neurological diseases and trauma can produce hyperventilation by disrupting the regularity of breathing or by damaging inhibitory pathways. Damage to the upper midbrain and pons can produce unabated, regular hyperventilation. Lower pontine lesions mediate apneustic breathing: very prolonged inspiration that is sometimes associated with other irregularities of the breathing pattern *(4)*.

Alteration in hormone levels can cause respiratory alkalosis directly or indirectly. The most familiar cause of hormonal hyperventilation occurs in pregnancy. Progesterone, which is necessary to support embryonic implantation and subsequent development of the placenta, is a direct stimulant of the medullary respiratory centers *(16)*. The $PaCO_2$ falls throughout pregnancy, paralleling the rise in progesterone *(17)*. Hypocapnia is also seen in the luteal phase of the menstrual cycle *(17)*, also a response to progesterone levels that are higher than baseline. In menopausal women, hypocapnia has been found to associate with hormone replacement therapy that includes medroxyprogesterone acetate *(18)*. Severe hypothyroidism has caused hypocapnia, probably due to an extremely low basal metabolic rate with relative preservation of minute volume *(19)*.

Numerous drugs directly or indirectly cause respiratory alkalosis. The most commonly used drug with this effect is aspirin. Aspirin at doses of several grams per day in adults directly stimulates the medullary respiratory centers. This primary respiratory alkalosis is distinct from any compensation for the metabolic acidosis aspirin may also cause. Blood gases in aspirin-intoxicated patients may be consistent with respiratory alkalosis, with metabolic acidosis, or with a picture of mixed primary disturbances.

Several drugs have received use as respiratory stimulants in hypoventilatory states. Ingestion of these drugs may cause modest respiratory alkalosis. Among these agents are nikethamide, ethamivan, doxapram, almitrine, progesterone, medroxyprogesterone, and methylxanthines *(20–22)*. Drugs that primarily impact other organ targets but which also can stimulate alveolar ventilation include epinephrine, norepinephrine, angiotensin II, nicotine, dinitrophenol, and metformin *(23–28)*.

Hepatic insufficiency may allow accumulation of toxic products of metabolism. Ammonia is a product of normal protein metabolism that can accumulate in hepatic disease. In pediatric patients, a common cause of chronic, recurrent hyperammonemia is ornithine transcarbamylase deficiency, of which hyperventilation is a clinical sign. The hypocapnia that is characteristic of liver disease correlates well with blood ammonia concentration *(29)*. The mechanism by which ammonia may stimulate respiration has not been elucidated.

Shock due to sepsis, extreme anemia, or cardiogenic failure can cause hyperventilation *(30, 31)*. Theoretically, the spontaneously breathing patient delivers a reduced volume of oxygen to the oxygen-responsive peripheral chemoreceptors. These receptors fire sufficiently to induce hypocapnia. A metabolic acidosis severe enough to offset the respiratory alkalosis is typically present, so a mixed acid–base disturbance or frank acidosis is the usual case. In the particular case of gram-negative sepsis, bacterial lipopolysaccharides may stimulate central chemoreceptors directly, accounting for part of the hypocapnia *(32)*.

Thermal insults, both hypothermia and hyperthermia, can cause respiratory alkalosis. Heat exhaustion and heat stroke both cause hyperventilation through an unknown mechanism. Cold shock occurs after immersion in ice-cold water for more than a few minutes. It elicits a gasp followed by involuntary hyperventilation, cutaneous vasoconstriction, and tachycardia. The hyperventilation is sufficiently severe that it reduces cerebral blood flow by vasoconstricting cerebral arterioles, and disorientation results *(33)*.

Numerous patients receive mechanical ventilation in a variety of settings. Hundreds of thousands of patients receive ventilator support in intensive care units in the United States each year. Patients are also ventilated in step-down units, rehabilitation hospitals, long-term custodial care facilities, and at home. The number of such patients whom are hyperventilated at any time is unknown, but it is likely high. Hyperventilation may be inadvertent. Patients may have normoventilation until a change in physical activity, physiologic dead space, lung compliance, or diet occurs. If such a change reduces the VCO_2 or increases the minute volume, respiratory alkalosis will occur. Intensivists and pulmonologists may favor mild hyperventilation over hypoventilation in routine care because the former offers a "cushion" of stability in case the ventilator ceases to operate.

Therapeutic hyperventilation is offered for a variety of clinical conditions. In each, an attempt is made to capitalize on the pH raising effect of hyperventilation, as in metabolic acidosis states, or to use the influence of pH and PCO_2 on vascular tone.

When metabolic acidosis threatens disability or increases a patient's mortality risk, maintenance of pH is important. Extremes of acidosis may reduce cardiac contractility and alter the kinetics of vital enzyme systems. A very common cause of metabolic acidosis is ketoacidosis in diabetes mellitus (DKA). While DKA itself rarely indicates mechanical ventilation, patients with DKA may have diminished neurological responsiveness or coma that would indicate mechanical ventilation to maintain a patent airway. If ventilation is offered for this reason, particular care must be taken to simulate the minute volume and, thus, the $PaCO_2$ the patient had maintained spontaneously. Whether spontaneous or mechanical, hyperventilation may be the only means to maintain a pH adequate for myocardial contractility and enzyme function. Allowing the $PaCO_2$ to normalize (increase) may also result in increased cerebral blood flow in the setting of existing brain hyperemia, which is known to occur in DKA. Such increased cerebral blood flow may provoke a harmful increase in intracranial pressure *(34, 35)*.

The brain benefits from a complex system to maintain vascular tone. In health and in many disease states, the brain autoregulates its blood flow. The end point of this autoregulation is a matching of cerebral oxygen supply to cerebral oxygen demand. Autoregulation is affected by correlates of oxygen delivery, such as cardiac output, hemoglobin concentration, and arterial oxygen saturation. It can also be affected by

changes in the cerebral oxygen demand. Cerebral perfusion depends on sufficient systemic blood pressure, though blood pressure is not a direct determinant of oxygen delivery. Another determinant of cerebral vascular tone is CO_2. Cerebral blood flow is linearly related to $PaCO_2$ in the normal range of $PaCO_2$. For $PaCO_2$ values between 22 and 60 torr, cerebral blood flow decreases 2% for each 1 torr decline in $PaCO_2$ *(36)*. In short, hypocarbia equals a cerebral vasoconstrictor.

Clinicians have used hyperventilation for several decades to reduce the cerebral blood volume and lower intracranial pressure (ICP). At one time, a low ICP was felt to be a surrogate for successful resuscitation of the brain in a variety of illnesses and injuries, including trauma, stroke, hypoxia-ischemia, and space-occupying lesions of the brain. Recently, instrumentation has been developed to measure brain tissue PO_2. Hemphill et al. showed reduced brain tissue PO_2 as end-tidal CO_2 was lowered between 20 and 60 torr *(37)*. Of concern is that the tissue PO_2 may fall into the ischemic range as therapeutic hyperventilation reduces brain blood volume and brain blood flow. One clinical trial has addressed the potential impact on clinical outcome from hyperventilation of patients with head trauma *(38)*. Those patients hyperventilated to a $PaCO_2$ of 25 torr for 5 days had worse outcome at 3 and 6 months than patients who had $PaCO_2$ tensions above 30 torr. In adult and pediatric guidelines for the initial treatment of traumatic brain injury, hyperventilation is reserved for patients who have neurological instability refractory to less toxic care or for neurologically deteriorating patients *(39*, *40)*.

Pulmonary vascular tone also varies with blood gas and pH values. Alveolar gas tensions and pH appear to be the usual determinants of pulmonary vascular tone. In general, oxygen is a pulmonary vasodilator while hydrogen ion and CO_2 are pulmonary vasoconstrictors. The vasodilation seen in oxygenated and ventilated lung units assures good blood flow to the portions of the lung that are aerated well. The vasoconstriction seen with local hypoxia or hypercarbia reduces blood flow to poorly ventilated lung units. These relationships assure good ventilation–perfusion matching in health and mild lung disease. Pulmonary hypertension includes a failure of lung vasculature to appropriately vasodilate in response to ventilation and oxygenation. In forms of pulmonary hypertension that reflect short-term abnormalities in pulmonary vasomotor response, such as persistent pulmonary hypertension of the newborn, hyperventilation, and hyperoxygenation have been used to vasodilate the pulmonary vasculature. Hyperventilation has not been proven effective in controlled trials, however, and concern exists that it may cause ventilator-associated lung injury. A modern approach is to use selective pulmonary vasodilators, such as inhaled nitric oxide, and sufficient minute ventilation to maintain normocarbia *(41)*.

3. EVALUATION

Respiratory alkalosis itself may be mild and symptomless or it may be sufficiently severe to provoke secondary organ failure. Often, the most prominent findings are those of the inciting condition. Signs of increased alveolar ventilation may predominate. These may include increased respiratory rate, increased depth of respiration, rapid shallow breathing, and increased work of breathing. As a general rule, minute ventilation must increase 10% for significant hypocapnia to result.

By far, the most common cause of respiratory alkalosis is the hyperventilation syndrome, in which hyperventilation and anxiety are associated. In voluntary hyperventilation, patients experience breathlessness as well as the effects of hypocarbia on neuronal excitability and on blood flow to various tissues. Among symptoms of neuronal excitability are paresthesias and tetany in the hands, face, and trunk. Symptoms referable to reduced cerebral blood flow include giddiness, paresthesias, visual disturbance, headache, ataxia, tremor, tinnitus, hallucination, unilateral somatic symptoms that predominate on the left side, and loss of consciousness. Systemic vascular resistance falls during the first several minutes of hyperventilation. Blood pressure falls, and heart rate and cardiac output both increase. Cutaneous vascular resistance increases, accounting for cold extremities and some tingling *(42)*. Coronary blood flow parallels $PaCO_2$, so it falls during respiratory alkalosis. Myocardial oxygen supply falls, but not to a level that would limit myocardial oxygen consumption *(43*, *44)*. Atypical chest pain is commonly seen, and it may worsen anxiety by mimicking coronary disease. Coronary spasm and cardiac arrhythmias may occur in patients who have pre-existing artery disease *(42)*. Air hunger is out of proportion to other clinical signs of pulmonary disease. An effective screening tool for hyperventilation syndrome in adults is the Nijmegen questionnaire (Table 2) *(45)*.

Physical examination may show the increased work of breathing that is associated with the increase in minute ventilation. A patient may sigh frequently. His abdomen may be distended from aerophagia. The breath-hold time may be short, though patient

Table 2
The Nijmegen Questionnaire for Evaluation of the Hyperventilation Syndrome in Adults

Symptom	*Never*	*Seldom*	*Sometimes*	*Often*	*Very often*
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizziness	0	1	2	3	4
Confusion or loss of touch with reality	0	1	2	3	4
Fast or deep breathing	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Tightness across chest	0	1	2	3	4
Bloated sensation in stomach	0	1	2	3	4
Tingling in fingers and hands	0	1	2	3	4
Difficulty in breathing or taking a deep breath	0	1	2	3	4
Stiffness or cramps in fingers and hands	0	1	2	3	4
Tightness around the mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations in the chest	0	1	2	3	4
Anxiety	0	1	2	3	4

Patients circle the frequency with which they experience each symptom. Points are added, and a score equal or greater than 23 indicates hyperventilation with 91% sensitivity and 95% specificity *(45)*. From van Doorn P, Colla P, Folgering H *(56)*.

and operator variability widen the reference range of this test. Anxiety and air hunger may be prominent, and they prompt concern that significant organic respiratory disease exists.

Blood gas criteria for simple respiratory alkalosis are arterial pH above 7.45, $PaCO_2$ less than 35 torr, and no evidence to implicate hypoxia as a drive to breathe, e.g., PaO_2 below 60 torr or arterial blood oxygen saturation less than 0.9. Blood gas sampling may itself be anxiety provoking and may yield data that are not representative of the patient's condition. This might be particularly true in the crying infant. Non-invasive tests in centers experienced with their use may prove more valuable for individual patients. Non-invasive measures include end-tidal CO_2, transcutaneous CO_2, and pulse oximetry.

Acute hypocarbia reduces the ratio of CO_2 to HCO_3^- in the plasma. As per the Henderson equation, H^+ concentration will fall and pH will rise. The degree of pH rise has inherent variability. Plasma and intracellular buffers will blunt some of the rise. Among these buffers, HCO_3^- acutely falls about 0.2 mEq/L for each one torr decrease in $PaCO_2$ *(46)*. This change is a function of equilibria among the elements of the Henderson equation and is not dependent on HCO_3^- excretion by the kidneys. Organic acids, especially lactic acid, may accumulate. The activity of proton and HCO_3^- transporters in the cell membrane changes in the direction necessary to maintain pH *(47)*. Thus, the 95% confidence limits for pH and HCO_3^- after acute onset of hypocarbia are broad bands (Fig. 4) *(46)*.

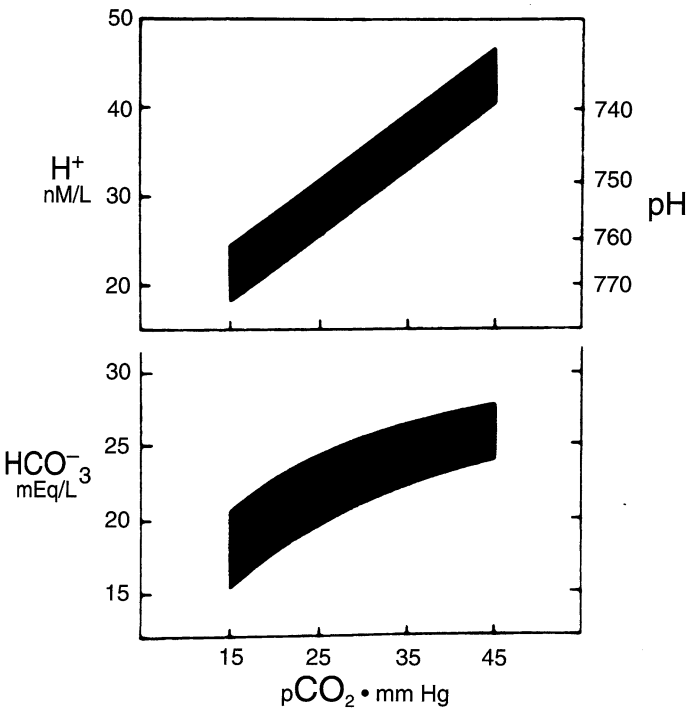

Fig. 4. Ninety-five percent confidence bands for pH and HCO_3^- across varying levels of $PaCO_2$ in patients undergoing acute hyperventilation. From Madias and Adrogue *(57)*. Modified from Arbus et al. *(46)*.

Within hours of the onset of hypocarbia, the kidneys reduce acid excretion and increase HCO_3^- excretion to begin renal compensation for respiratory alkalosis. In about 3 days, a new steady state occurs during which pH has returned about half-way to normal. Plasma HCO_3^- declines approximately 0.4 mEq/L and H^+ increases about 0.4 nEq/L for each 1 torr decrement in $PaCO_2$ *(47, 48)*. Chronic hypocarbia can elicit sufficient metabolic compensation that pH returns to normal in the absence of an obvious source of metabolic acidosis. Chronic respiratory alkalosis is the only simple acid–base disturbance known to be compatible with a normal pH *(1)*.

In the setting of cardiopulmonary resuscitation, arterial blood gases may falsely show respiratory alkalosis despite an increased total body burden of CO_2. The low pulmonary blood flow inherent in cardiac arrest diminishes the delivered volume of CO_2 from the venous blood to the alveoli. If ventilation is supported, ordinary minute volume provides more than sufficient ventilation to eliminate this small volume of CO_2 and the end-tidal CO_2 and the pulmonary capillary CO_2 plummet. Blood from the pulmonary capillaries determines the makeup of arterial blood, and arterial blood gases may appear very alkalotic. At the same time, venous blood may show a significant respiratory acidosis. This venous acidosis more accurately reflects the total body acid–base balance. It normalizes after the return of spontaneous circulation. The discrepancy between arterial and venous CO_2 tension limits the value of arterial blood gas sampling during cardiopulmonary resuscitation. Venous blood gases may be needed to show the patient's true acid–base status *(49, 50)*.

4. TREATMENT

The most common cause of respiratory alkalosis is the hyperventilation syndrome. Treatment must focus on reassurance, reducing the minute volume, and relieving the symptoms of hypocarbia. When a single source for the anxiety can be found, counseling can be structured to improve the patient's response to the provocation. There are cases, however, when such counseling focuses such thought on the breathing process that the patient may worsen *(42)*. Rebreathing from a paper sack may normalize the $PaCO_2$, but it has no demonstrated benefit to control the anxiety. Its value may mostly be educational in those patients who can accept their diagnosis.

Drugs are of limited usefulness in hyperventilation syndrome. Anxiolytics include benzodiazepines, beta-adrenergic blockers, and anti-depressants. Benzodiazepines may only be given within a limited time because of dependence and withdrawal potential. Beta blockers may exacerbate mild asthma, which is among the differential diagnoses of the anxiety–hyperventilation syndrome. Anti-depressants may normalize CO_2 in panicked patients *(51)*.

Relief of mechanical hyperventilation is usually straightforward. The approach differs based on the nature of the hyperventilation. Inadvertent hypocarbia of patients receiving complete mechanical support should respond to reduction of minute ventilation, through use of either a lower tidal volume or a lower respiratory rate. Notably, high-frequency oscillatory ventilation differs from conventional ventilation in that lower minute volume occurs at higher, rather than lower, respiratory rates. If an anomaly of ventilator triggering causes numerous controlled or assisted breaths, the use of

intermittent mandatory ventilation without assisted spontaneous breaths may resolve the problem *(52)*. Such anomalies include air-leak syndromes of the airway or the lungs, pressure waves generated by splashes of condensate within the ventilator circuit, and excessive sensitivity of the demand valve. Patients in controlled ventilatory modes receive full volume breaths whenever they breathe spontaneously. They may benefit from intermittent mandatory ventilation or from measures to reduce the spontaneous respiratory rate. Effective measures may include optimizing inspiratory flow to match patient demand, sedating patients, or pharmacologically paralyzing patients. Finally, adding dead space to the ventilator circuit may reduce the effective tidal volume.

5. MIXED ACID–BASE DISORDERS INVOLVING RESPIRATORY ALKALOSIS

Mixed acid–base disturbances occur when a metabolic disorder coexists with a respiratory disorder, when two metabolic disorders coexist, or when three disorders occur together. Most diagnoses are made by taking a history, and this should be true in the diagnosis of mixed acid–base disorders. When laboratory methods must be called on to establish the diagnosis, the following discussion may be helpful.

Simple acid–base disorders have predictable biochemical effects. Most of these involve pH, blood gas tensions, and total CO_2, which is the sum of HCO_3^- and H_2CO_3. Others include the anion gap and the serum potassium concentration. The anion gap is the difference between the concentration of sodium, the major extracellular cation, and the sum of the concentrations of the major measured anions, chloride and HCO_3^-. The anion gap measures the influence of minor, usually unmeasured anions on body chemistry. The anion gap is elevated after intake of exogenous acids, generation of unmeasured endogenous acids, and by several acid–base disturbances. Potassium is a predominantly intracellular cation. Its extracellular (plasma) concentration varies with pH, increasing with acidosis and decreasing with alkalosis. In simple acid–base disorders, the pH is defended by compensatory mechanisms. These include renal actions on the balance of electrolytes in the plasma to compensate for primary respiratory disturbances. They also include changes in the respiratory drive, usually in response to a change in cerebrospinal fluid pH that has occurred due to a primary metabolic disturbance. Respiratory compensation can occur quickly because of the large capacity of the lungs to excrete acid as CO_2. Metabolic compensation, controlled in the kidneys, occurs more slowly and may take days to weeks to complete.

A simple way to assess for complex acid–base disturbances is to inspect an acid–base nomogram. Acid–base nomograms vary, but they commonly relate $PaCO_2$, pH, and either HCO_3^- or measured base excess. Use of a nomogram allows interpretation of the acid–base status without the need for mathematical calculations *(53)*. An interactive acid–base map is available on the World Wide Web at http://www.acid–base.com/diagram.php *(54)*. Its usual ranges were established by meta-analysis of 35 years of human case reports. A simple paper-based acid–base map is also available (Fig. 5) *(55)*.

Mixed acid–base disorders may include one or two metabolic disturbances with or without a single respiratory disturbance. Multiple respiratory disturbances are not

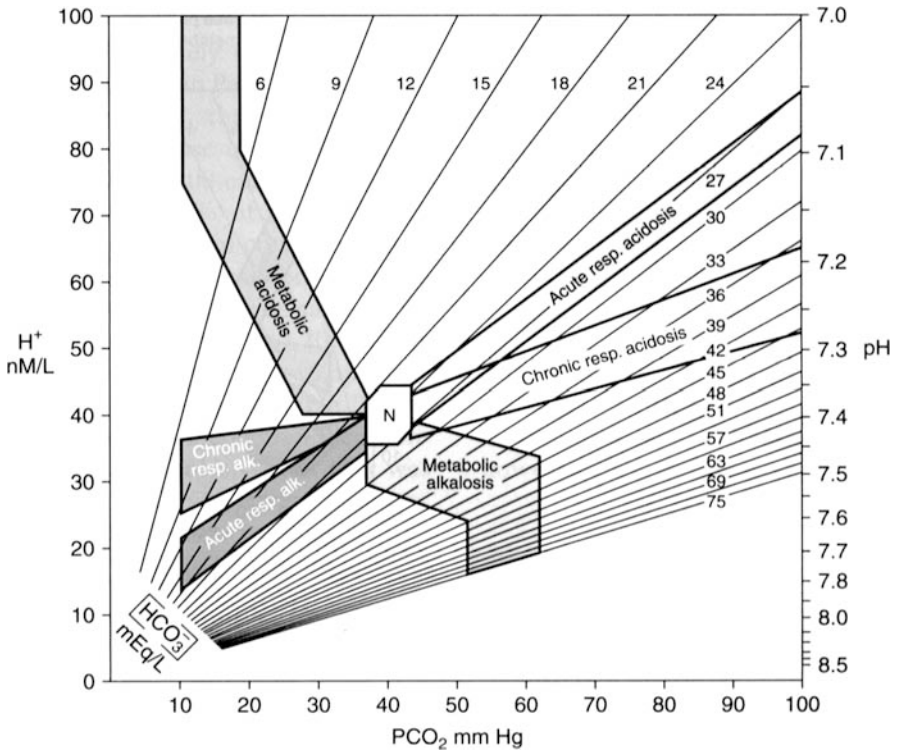

Fig. 5. An acid–base map. This graph relates pH, PCO_2, and H^+ across concentrations of HCO_3 to suggest proper assessment of acid–base status. The user plots a patient's blood gas data to find the point where pH, PCO_2, and HCO_3^- intersect. The central area, N, denotes normal acid–base status. Labeled bands reflect single acid–base derangements. Patients whose points of intersection lay outside the labeled areas likely have a mixed acid–base disturbance. From Malley *(55)*.

possible because a patient cannot have hypocarbia and hypercarbia at the same time. Diagnosis of the acid–base state relies on history, physical examination, and interpretation of electrolytes and blood gases. Use of an acid–base nomogram may simplify diagnosis.

CASE SCENARIOS

Case Scenario 1. A 20-year-old patient is ventilated for a pulmonary contusion. His lung compliance improved markedly 4 days ago, and for 3 days his pH has been above 7.5 with $PaCO_2$ 30–34 torr. When you reduce his mandatory breath rate, he is apneic. You should expect this patient's respiratory drive to improve

1. in 12 min
2. in 12 h
3. in 72 h

This patient has an uncompensated acute respiratory alkalosis of 3 days duration. Though his $PaCO_2$ may normalize within minutes, the pH of the cerebrospinal fluid and

brain extracellular fluid will take hours to normalize. In the absence of active treatment with systemic acid or other measures, the respiratory drive will likely stay depressed for 12–24 h.

Case Scenario 2. A 13-year-old girl is found unresponsive with an open bottle of aspirin. Perhaps 200 tablets, each containing 325 mg aspirin, are missing. After initial stabilization, an arterial blood gas shows pH 7.3, PCO_2 20 torr, PO_2 350 torr, and base deficit 16 mEq/L. Based on the acid–base derangement, the next steps in medically managing this girl should include the following:

1. Decrease the minute volume to prevent cerebral vasoconstriction
2. Increase minute volume to normalize the pH
3. Hemodialyze to remove aspirin
4. Treat metabolic acidosis with intravenous fluid containing bicarbonate

The high base deficit and low PCO_2 indicate this patient's acid–base derangement is acute metabolic acidosis with acute respiratory alkalosis. The respiratory alkalosis is a direct effect of aspirin on the respiratory centers. The metabolic acidosis is due to aspirin's block of the electron transport chain in mitochondria. Aerobic metabolism cannot occur, and the body becomes anaerobic despite elevated oxygen tension. This results in excessive generation of heat and lactic acid. Though the first choice may prevent cerebral vasoconstriction and the second choice may raise the pH, neither will prevent death or disability from this potentially lethal aspirin overdose. The patient will likely die unless timely hemodialysis can remove the aspirin and restore aerobic cellular metabolism. Because the acidosis is not due to hypovolemia or bicarbonate loss, fluid repletion with bicarbonate solutions will help only transiently.

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