Objectives

1. Recognize the features that define respiratory acidosis and respiratory alkalosis.

2. Understand the adaptations that occur to respiratory acid-base disturbances.

3. Appreciate the diagnostic approaches and therapeutic interventions to such disorders.

I. Disorders

Respiratory acid-base disorders are those abnormalities in acid-base equilibrium initiated by a change in the arterial carbon dioxide tension ($PaCO_2$)--the respiratory determinant of acidity in the Henderson equation:

$$H^+ = 24 \text{ x } PaCO_2 / [HCO_3^-] \qquad \text{(Equation 1)}$$

There are two respiratory acid-base disorders: respiratory acidosis and respiratory alkalosis.

II. Respiratory Acidosis

A. Definition - Respiratory acidosis is the acid-base disturbance initiated by an increase in $PaCO_2$. Primary hypercapnia is a synonymous term.

B. Pathophysiology - The level of $PaCO_2$ is determined by the interaction of two factors, the rate of carbon dioxide production (V_{CO2}) and the rate of alveolar ventilation (V_A), as follows:

$$PaCO_2 = K \text{ x } V_{CO2} / V_A \qquad \text{(Equation 2)}$$

where K is a constant.

1. By far, most cases of respiratory acidosis reflect a decrease in alveolar ventilation.
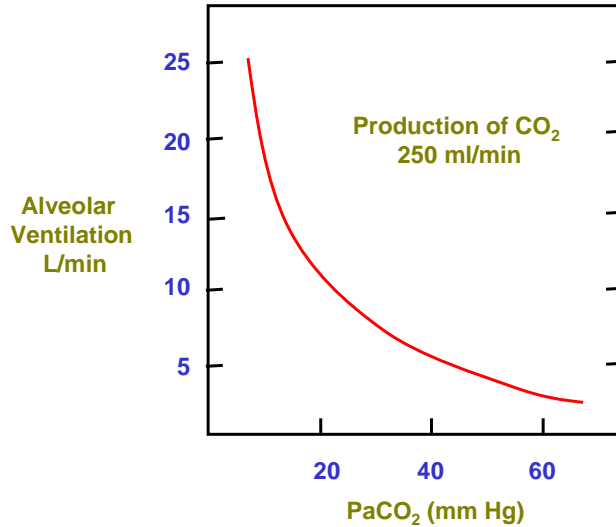

Figure 1

2. Overproduction of carbon dioxide is usually matched by increased excretion (due to increased alveolar ventilation) such that hypercapnia is prevented. However, increased production of carbon dioxide can cause respiratory acidosis in patients with marked limitation in pulmonary reserve or those receiving constant mechanical ventilation. Clinical circumstances of overproduction of carbon dioxide include increased physical activity, augmented work of breathing by the respiratory muscles, shivering, seizures, fever, hyperthyroidism, and administration of large loads of carbohydrate or bicarbonate.

3. The major threat to life from CO_2 retention in subjects breathing room air (FiO_2, 21%) is the associated obligatory hypoxemia, as indicated by the alveolar gas equation:

$$P_AO_2 = 150 – 1.25 \text{ x } PaCO_2 \qquad \text{(Equation 3)}$$

where P_AO_2 is alveolar oxygen tension. Thus, in the absence of supplemental oxygen, it is not possible for $PaCO_2$ to reach values much higher than 80 mm Hg while the level of PaO_2, the arterial oxygen tension, is still compatible with life. Extreme hypercapnia can only be seen in subjects receiving oxygen supplementation.

C. Secondary physiologic response - Respiratory acidosis acidifies body fluids (Equation 1). It elicits adaptive increments in plasma bicarbonate concentration that attenuate the impact of hypercapnia on systemic acidity; these increments in plasma bicarbonate should be viewed as an integral part of the respiratory acidosis. Consequently, the absence of the appropriate level of this secondary hyperbicarbonatemia for the prevailing

level of primary hypercapnia (see below) constitutes a complicating metabolic acid-base disorder.

1. Acute adaptation

    a. It is completed within 5-10 min from onset of hypercapnia.

    b. It originates exclusively from acidic titration of the body's nonbicarbonate buffers (hemoglobin, intracellular proteins and phosphates, plasma proteins):

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

    $$H^+ + Buf^- \leftrightarrow HBuf$$
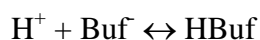
    where Buf^- refers to the base component and HBuf to the acid component of nonbicarbonate buffers.

    c. On average, plasma bicarbonate concentration increases by about 0.1 mEq/L for each 1 mmHg acute increment in $PaCO_2$; as a result, plasma hydrogen ion concentration increases by about 0.75 nEq/L for each mm Hg acute rise in $PaCO_2$.

2. Chronic adaptation

    a. It requires 3-5 days of sustained hypercapnia for completion.

    b. It originates from upregulation of renal acidification mechanisms (both in the proximal and distal segments of the nephron) that result in:

        i.   a transient increase in urinary net acid excretion (mostly a rise in ammonium excretion) that generates new bicarbonate for the body fluids; and

        ii. a persistent increase in the rate of renal bicarbonate reabsorption that maintains the increased plasma bicarbonate level.

    c. On average, plasma bicarbonate concentration increases by about 0.3 mEq/L for each mm Hg chronic increment in $PaCO_2$; as a result, plasma hydrogen ion concentration increases by about 0.3 nEq/L for each mm Hg chronic rise in $PaCO_2$. Thus, at a given $PaCO_2$ value, chronic adaptation provides better defense of systemic acidity than acute adaptation. As an example, acute or chronic adaptation to a $PaCO_2$ of 60 mm Hg in a subject with a normal baseline of acid-base status will yield, on average, the following values:

	$PaCO_2$ mm Hg	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L	pH
Normal	40	24	40	7.40
Respiratory acidosis				
Acute	60	26	55	7.26
Chronic	60	30	48	7.32

Empiric observations have been used for construction of 95% confidence intervals for graded degrees of acute or chronic respiratory acidosis.

d. The renal response to chronic hypercapnia includes a transient increase in chloride excretion and generation of hypochloremia. This reduction in plasma chloride concentration balances the increase in plasma bicarbonate concentration, plasma anion gap remaining unchanged.
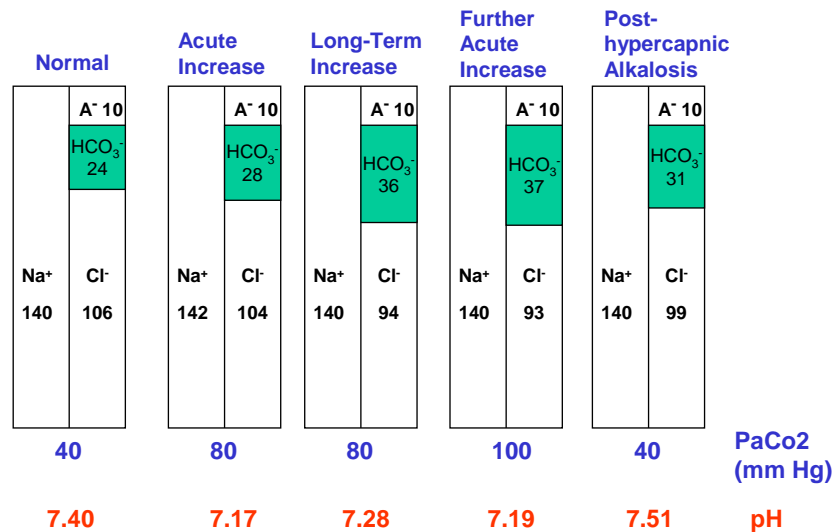

Figure 2

D. Etiology (**Knowledge of the specific causes of acute and chronic respiratory acidosis is not required for the Pathophysiology Course; the material is provided for clinical correlation in subsequent years of study**) - Respiratory acidosis can develop in patients with normal or abnormal airways and lungs as shown in Tables 1 and 2. The classification into causes of acute or chronic respiratory acidosis takes into consideration the usual mode of onset and duration of the various causes and emphasizes the biphasic time course of the secondary physiologic response to hypercapnia. Primary hypercapnia can result from disease or malfunction within any element of the regulatory system controlling respiration, including the central and peripheral nervous system, the respiratory muscles, the thoracic cage, the pleural space, the airways, and the lung parenchyma. Not infrequently, more than one cause contributes to the development of respiratory acidosis in a given patient. Chronic lower

airways obstruction resulting from bronchitis and emphysema is the most common cause of chronic hypercapnia.

Table 1

Causes of Acute Respiratory Acidosis		Causes of Chronic Respiratory Acidosis	
Normal airway and lungs	*Abnormal airway and lungs*	*Normal airway and lungs*	*Abnormal airway and lungs*
Central nervous system depression	**Upper airway obstruction**	**Central nervous system depression**	**Upper airway obstruction**
General anesthesia	Coma induced hypopharyngeal obstruction	Sedative overdose	Tonsillar and peritonsillar hypertrophy
Sedative overdose	Aspiration of foreign body or vomitus	Methadone/heroin addiction	Paralysis of vocal cords
Head trauma	Laryngospasm or angioedema	Primary alveolar hypoventilation	Tumor of the cords or larynx
Cerebrovascular accident	Obstructive sleep apnea	Obesity-hypoventilation syndrome	Airway stenosis post prolonged intubation
Central sleep apnea	Inadequate laryngeal intubation	Brain tumor	Thymoma, aortic aneurysm
Cerebral edema	Laryngeal obstruction post intubation	Bulbar poliomyelitis	**Lower airway obstruction**
Brain tumor encephalitis	**Lower airway obstruction**	**Neuromuscular impairment**	Chronic obstructive lung disease (bronchitis, bronchiolitis, bronchiectasis, emphysema)
Neuromuscular impairment	Generalized bronchospasm	Poliomyelitis	
High spinal cord injury	Severe asthma	Multiple sclerosis	**Disorders involving pulmonary alveoli**
Guillain-Barre syndrome	Bronchiolitis of infants and adults	Muscular dystrophy	Severe chronic pneumonitis
Status epilepticus	**Disorders involving pulmonary alveoli**	Amyotrophic lateral sclerosis	Diffuse infiltrative disease
Botulism, tetanus	Severe bilateral pneumonia	Diaphragmatic paralysis	Interstitial fibrosis
Crisis in myathenia gravis	Acute respiratory distress syndrome	Myxedema	
Hypokalemic myopathy	Severe pulmonary edema	Myopathic disease	
Familial hypokalemic periodic paralysis	**Pulmonary perfusion defect**	**Ventilatory restriction**	
Drugs or toxic agents (curare, succinylcholine, aminoglycosides, organophosphates)	Cardiac arrest	Kyphoscoliosis, spinal arthritis	
Ventilatory restriction	Severe circulatory failure	Obesity	
Rib fractures with flail chest	Massive pulmonary thromboembolism	Fibrothorax	
Pneumothorax	Fat or air embolus	Hydrothorax	
Hemothorax		Impaired diaphragmatic function	
Impaired diaphragmatic function			
Iatrogenic events			
Misplacement or displacement of airway cannula during anesthesia or mechanical ventilation			
Bronchoscopy associated hypoventilation or respiratory arrest			
Increased CO_2 production with constant mechanical ventilation			

E. Clinical manifestations and pathophysiologic consequences (**Knowledge of this section is not required for the Pathophysiology Course; the material is provided for clinical correlation in subsequent years of study**).

1. Neurological: Clinical manifestations of respiratory acidosis arising from the central nervous system are collectively known as "hypercapnic encephalopathy" and include irritability, inability to concentrate, headache, anorexia, apathy, confusion, combativeness, hallucinations, delirium, transient psychosis, progressive narcosis, and coma. Frank papilledema (pseudotumor cerebri) and motor disturbances (myoclonic jerks, flapping tremor, and seizures) might also develop. The occurrence

and severity of neurological manifestations depend on the magnitude of hypercapnia, the rapidity with which it develops, the severity of the acidemia, and the degree of the accompanying hypoxemia.

2. Cardiovascular: Respiratory acidosis causes inhibition of myocardial contractility, direct systemic vasodilation (especially in the cerebral circulation), but also beta-adrenergic stimulation. The composite effect is such that mild to moderate hypercapnia is usually associated with increased cardiac output, normal or increased blood pressure, and increased cerebral blood flow. When hypercapnia is severe or considerable hypoxemia is present, decreases in both cardiac output and blood pressure might be observed.

3. Renal: Salt and water retention often attends chronic hypercapnia, especially in the presence of cor pulmonale. In addition to the effects of heart failure on the kidney, contributing factors include the stimulation of the beta-adrenergic system and the renin-angiotensin-aldosterone axis, and the increased levels of antidiuretic hormone and cortisol.

F. Diagnosis - Simple respiratory acidosis is characterized by hypercapnia, acidemia, and a secondary increase in plasma bicarbonate concentration. However, respiratory acidosis is frequently associated with other acid-base disorders. Examples of such mixed acid-base disorders follow:

	$PaCO_2$ mm Hg	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L	pH
Example #1	50	20	60	7.22
Example #2	80	24	80	7.10
Example #3	60	37	39	7.41

In example #1, hypercapnia is associated with a decreased, rather than an increased, level of plasma bicarbonate, indicating the presence of mixed respiratory acidosis and metabolic acidosis (e.g., a patient with respiratory insufficiency due to chronic obstructive pulmonary disease causing respiratory acidosis, and concomitant circulatory failure from an acute myocardial infarction resulting in lactic acidosis). Similarly, the absence of any increment in plasma bicarbonate concentration despite the prevailing hypercapnia (as in example #2 in which plasma bicarbonate is normal) signifies the presence of mixed respiratory acidosis and metabolic acidosis. In example #3, the increase in plasma bicarbonate level is considerably higher than that appropriate for this level of hypercapnia (even for chronic adaptation) and thus defines the coexistence of respiratory acidosis and metabolic alkalosis (e.g., a patient with respiratory failure due to severe bilateral pneumonia causing respiratory acidosis, and nasogastric suction resulting in metabolic alkalosis).

G. Therapeutic principles

1. Acute respiratory acidosis: Treatment must be directed at prompt removal of the underlying cause, whenever possible. Efforts should focus on establishing and securing a patent airway, restoring adequate oxygenation by delivering an oxygen-rich inspired mixture, and providing adequate ventilation.

2. Chronic respiratory acidosis: Only rarely one can remove the underlying cause in patients with chronic respiratory acidosis. Such patients frequently develop episodes of acute decompensation due to further reduction in alveolar ventilation as a result of pulmonary infection, use of narcotics, or uncontrolled oxygen therapy (in general the hypoxic drive to ventilation remains adequate if PaO_2 does not exceed 60 mm Hg) (Fig. 2). A number of measures can be used to improve alveolar ventilation, including treatment with antibiotics, bronchodilators, or diuretics; avoidance of irritant inhalants, tranquilizers, or sedatives; elimination of retained secretions; and gradual reduction of supplemental oxygen aiming at a PaO_2 of about 60 mm Hg. Administration of adequate quantities of chloride (usually as the potassium salt) will correct a complicating element of Cl^- sensitive metabolic alkalosis (commonly diuretic-induced) that can further dampen the ventilatory drive. In contrast to acute respiratory acidosis, ventilator assistance is used more conservatively in decompensated chronic hypercapnia, because of the great difficulty often encountered in weaning such patients from ventilators. If mechanical ventilation is instituted, restoration of the patient's $PaCO_2$ level to near its chronic baseline should proceed gradually over a period of many hours to a few days to allow a commensurate decrease in plasma bicarbonate level. Overly rapid reduction in $PaCO_2$ in such patients risks the development of sudden post-hypercapnic alkalosis with potential serious consequences (Fig. 2).

III. Respiratory Alkalosis

A. Definition - Respiratory alkalosis is the acid-base disturbance initiated by a reduction in $PaCO_2$. Primary hypocapnia is a synonymous term.

B. Pathophysiology

1. By far, most cases of respiratory alkalosis reflect an increase in alveolar ventilation (Equation 2 and Fig. 1).

2. Primary decreases in carbon dioxide production are generally attended by parallel decreases in alveolar ventilation, thus preventing expression of respiratory alkalosis. However, in the presence of constant alveolar ventilation (i.e., mechanical ventilation), decreased carbon dioxide production (e.g., sedation, skeletal muscle paralysis, hypothermia, hypothyroidism) can cause respiratory alkalosis.

C. Secondary physiologic response - Respiratory alkalosis alkalinizes body fluids (Equation 1). It elicits adaptive decrements in plasma bicarbonate concentration that attenuate the impact of hypocapnia on systemic acidity; these decrements in plasma bicarbonate should be viewed as an integral part of the respiratory alkalosis. Consequently, the absence of the appropriate level of this secondary hypobicarbonatemia for the prevailing level of primary hypocapnia (see below) constitutes a complicating metabolic acid-base disorder.

1. Acute adaptation

   a. It is completed within 5-10 min from onset of hypocapnia

   b. It originates principally from alkaline titration of the body's nonbicarbonate buffers (hemoglobin, intracellular proteins and phosphates, plasma proteins):

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

   $$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$
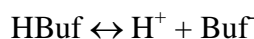
   where HBuf refers to the acid component and Buf$^-$ to the base component of nonbicarbonate buffers.

   c. On average, plasma bicarbonate concentration falls by about 0.2 mEq/L for each mm Hg acute decrement in $PaCO_2$; as a result, plasma hydrogen ion concentration decreases by about 0.75 nEq/L for each mm Hg acute reduction in $PaCO_2$.

2. Chronic adaptation

   a. It requires 2-3 days of sustained hypocapnia for completion.

   b. It originates from downregulation of renal acidification mechanisms (both in the proximal and distal segments of the nephron) that result in

      i. a transient decrease in urinary net acid excretion (mostly a fall in ammonium excretion and an early component of increased bicarbonate excretion) that reduces the body's bicarbonate stores; and

      ii. a persistent decrease in the rate of renal bicarbonate reabsorption that maintains the decreased plasma bicarbonate level.

   c. On average, plasma bicarbonate concentration decreases by about 0.4 mEq/L for each mm Hg chronic decrement in $PaCO_2$; as a result, plasma hydrogen ion concentration decreases by about 0.4 nEq/L for each mm Hg chronic reduction in $PaCO_2$. Thus, at a given $PaCO_2$ value, chronic adaptation provides better defense of systemic acidity than acute adaptation. As an example, acute or chronic

adaptation to a $PaCO_2$ of 20 mm Hg in a subject with a normal baseline of acid-base status will yield, on average, the following values:

	$PaCO_2$ mm Hg	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L	pH
Normal	40	24	40	7.40
Respiratory acidosis				
Acute	20	20	24	7.62
Chronic	20	15	32	7.49

Empiric observations have been used for construction of 95% confidence intervals for graded degrees of acute or chronic respiratory alkalosis.

d.   Chronic hypocapnia is characterized by an increase in plasma chloride concentration that balances most of the fall in plasma bicarbonate concentration, the remainder reflecting a small increase in the plasma anion gap.

D.   Etiology **(Knowledge of the specific causes of respiratory alkalosis is not required for the Pathophysiology Course; the material is provided for clinical correlation in subsequent years of study) -** Primary hypocapnia is the most frequent acid-base disturbance encountered, occurring in normal pregnancy and high-altitude residence. Table 3 lists the major causes of respiratory alkalosis. Most are associated with the abrupt appearance of hypocapnia but, in many instances, the process might be sufficiently prolonged to permit full chronic adaptation to occur. Consequently, no attempt has been made to separate these conditions into acute and chronic categories. Increased ventilatory drive can result from signals arising from the lung, the peripheral chemoreceptors (carotid and aortic), the brain stem chemoreceptors, or influences originating in other centers of the brain. Hypoxemia is a major stimulus of alveolar ventilation, but PaO_2 values lower than 50 mm Hg are required to consistently elicit this effect. Some of the major causes of respiratory alkalosis are benign, whereas others are life threatening. Primary hypocapnia is particularly common among the critically ill and its presence constitutes an ominous prognostic sign.

Table 2

Causes of Respiratory Alkalosis	
Hypoxemia or tissue hypoxia	**Central nervous system stimulation**
Decreased inspired O_2 tension	Voluntary
High altitude	Pain
Bacterial or viral pneumonia	Anxiety
Aspiration of food, foreign body, or vomitus	Psychosis
Larygospasm	Fever
Drowning	Subarachnoid hemorrhage
Cyanotic heart disease	Cerebrovascular accident
Severe anemia	Meningoencephalitis
Left shift deviation of HbO2 curve	Tumor
Hypotension	Trauma
Severe ciurculatory failure	**Drugs or hormones**
Pulmonary embolism	Nikethamide, ethamivan
Stimulation of chest receptors	Doxapram
Pneumonia	Xanthines
Asthma	Salicylates
Pneumothorax	Catecholamines
Hemothorax	Angiotensin II
Flail chest	Vasopressor agents
Infant or adult respiratory distress syndrome	Progesterone
Cardiac failure	Medroxyprogesterone
Noncardiogenic pulmonary edema	Dinitrophenol
Pulmonary embolism	Nicotine
Interstitial lung disease	**Miscellaneous**
	Pregnancy
	Sepsis
	Hepatic failure
	Mechanical hyperventilation
	Heat exposure
	Recovery form metabolic acidosis

E. Clinical manifestations and pathophysiologic consequences **(Knowledge of this section is not required for the Pathophysiology Course; the material is provided for clinical correlation in subsequent years of study).**

1. Neurological: Rapid decrements in $PaCO_2$ to half the normal values or lower are typically accompanied by paresthesias of the extremities, chest discomfort, circumoral numbness, lightheadedness, confusion, and infrequently, tetany or generalized seizures. These manifestations are seldom present in the chronic phase. Acute hypocapnia causes cerebral vasoconstriction and decreases cerebral blood flow (in severe cases it can reach values less than 50% of normal) but flow essentially normalizes during sustained hypocapnia.

2. Cardiovascular: No appreciable changes in cardiac output, systemic blood pressure, or cardiac rhythm occur in actively hyperventilating subjects. However, major reductions in cardiac output and blood pressure, and substantial hyperlactatemia frequently occur in passively hyperventilating subjects (i.e., during mechanical ventilation) most likely reflecting the decreased venous return associated with mechanical ventilation. In addition, patients with coronary artery disease might suffer

hypocapnia-induced coronary vasoconstriction, resulting in angina pectoris and arrhythmias.

F. Diagnosis - Simple respiratory alkalosis is characterized by hypocapnia, alkalemia, and secondary decrease in plasma bicarbonate concentration. However, respiratory alkalosis is frequently associated with other acid-base disorders. Examples of such mixed acid-base disorders follow:

	$PaCO_2$ mm Hg	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L	pH
Example #1	30	36	20	7.70
Example #2	20	24	20	7.70
Example #3	15	9	40	7.40

In example #1, hypocapnia is associated with an increased, rather than a decreased, level of plasma bicarbonate, indicating the presence of mixed respiratory alkalosis and metabolic alkalosis (e.g., a patient with hepatic failure causing respiratory alkalosis, and ongoing nasogastric suction resulting in metabolic alkalosis). Similarly, the absence of any decrement in plasma bicarbonate concentration despite the prevailing hypocapnia (as in example #2 in which plasma bicarbonate is normal) signifies the presence of mixed respiratory alkalosis and metabolic alkalosis. In example #3, the decrease in plasma bicarbonate level is considerably greater than that appropriate for this level of hypocapnia (even for chronic adaptation) and thus defines the coexistence of respiratory alkalosis and metabolic acidosis (e.g., a patient with salicylate intoxication in whom stimulation of the ventilatory center in the brain stem accounts for the respiratory alkalosis, whereas the accelerated production of organic acids is responsible for the metabolic acidosis).

G. Therapeutic principles - Management of respiratory alkalosis must be directed toward correcting the underlying cause, whenever possible. Taking measures to treat the respiratory alkalosis itself is not commonly required, because the disorder, especially in its chronic form, leads to minimal or no symptoms and poses little risk to health. A notable exception is the patient with the anxiety-hyperventilation syndrome; in addition to reassurance or sedation, rebreathing into a closed system (e.g., a paper bag) might prove helpful by interrupting the vicious cycle that can result from the reinforcing effects of the symptoms of hypocapnia. Administration of acetazolamide can be beneficial in the management of signs and symptoms of high-altitude sickness, a syndrome characterized by hypoxemia and respiratory alkalosis. Considering the risks of severe alkalemia, sedation or, in rare instances, skeletal muscle paralysis and mechanical ventilation might be required to temporarily correct marked respiratory alkalosis. Of course, patients undergoing mechanical ventilation lend themselves to an effective correction of hypocapnia (whether due to maladjusted ventilator or other causes) by resetting the device or increasing the dead space of the system.

IV. References

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