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CHAPTER • II

RESPIRATORY ACID-BASE DISORDERS

Rebecca A. Johnson and Helio Aufran de Moraes

"Life is a struggle, not against sin, not against the Money Power, not against malicious animal magnetism, but against hydrogen ions."

Henry Louis Mencken (1919)

Respiratory acid-base disorders are those abnormalities in acid-base equilibrium initiated by a change in arterial carbon dioxide tension (P_{aCO_2}). P_{aCO_2} is regulated by respiration; a primary increase in P_{aCO_2} acidifies body fluids and initiates the acid-base disturbance called respiratory acidosis, whereas a decrease in P_{aCO_2} alkalinizes body fluids and is known as respiratory alkalosis. The primary responsibility of the lungs is to exchange gases at the blood-gas interface. In the mammalian lung, oxygen and carbon dioxide move by diffusion from areas of high to low partial pressure. Diffusion of gases is directly proportional to the surface area of the interface and inversely proportional to the thickness of membrane (Fick's law). With a relatively large surface

area and a very thin ($<1 \mu\text{m}$) blood-gas interface, the lungs are well suited for their role in gas exchange.

GAS TRANSPORT DURING RESPIRATION

OXYGEN

Contraction of the diaphragm moves gases down the continually branching airways until they reach the transitional and respiratory bronchioles, alveolar ducts, and alveoli. Within this respiratory zone, alveolar ventilation and gas exchange occur as oxygen moves down its concentration gradient and into the red blood cells. The

partial pressure of oxygen in the red blood cells approximates that of alveolar gas within the first third of the lung capillaries, primarily because of the lung's considerable diffusion capabilities. Oxygen then is carried in the blood to meet the oxygen demand of the tissues in two forms: dissolved and combined with hemoglobin. Most of the delivered oxygen is bound by hemoglobin with only a small contribution from the dissolved oxygen (0.003 mL dissolved O_2 per 100 mL of blood per mm Hg P_{O_2}). The maximal amount of oxygen that can be combined with hemoglobin is called the oxygen capacity. Approximately 1.36 mL of O_2 can combine with 1 g of hemoglobin. Assuming 15 g of hemoglobin per 100 mL of blood, this results in approximately 21 mL O_2 per 100 mL blood carried to the tissues. As determined by the oxygen-hemoglobin dissociation curve (Fig. 11-1), at low P_{O_2} , the amount of oxygen carried by hemoglobin increases rapidly with increases in P_{O_2} . However, at higher P_{O_2} (>60 to 70 mm Hg), the curve flattens off, and little additional hemoglobin loading occurs. Unloading of large amounts of oxygen from hemoglobin is facilitated in the tissues where oxygen pressures are much lower (10 to 60 mm Hg) and the curve is very steep. Several factors shift this curve to the right and aid in the unloading of oxygen to the tissues, including increased H^+ ion and carbon dioxide concentrations (as seen in respiratory acidosis), increased temperature, and increased 2,3-diphosphoglycerate (2,3-DPG), a compound that competes with oxygen for its binding site on hemoglobin.

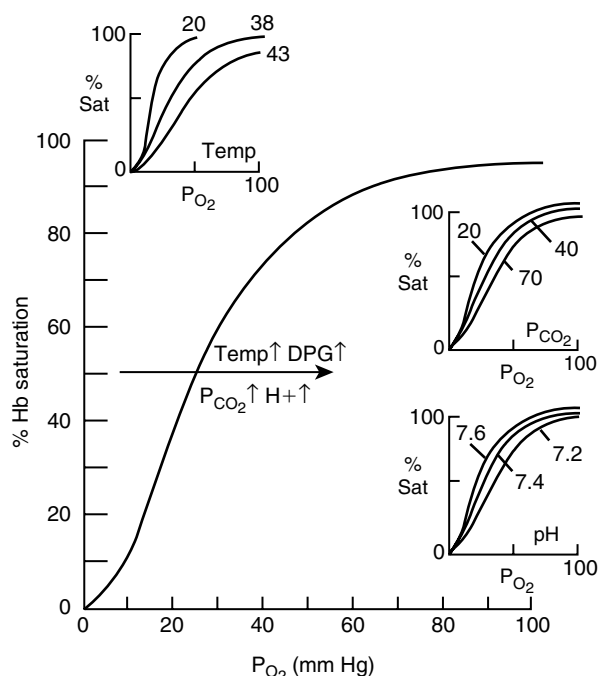
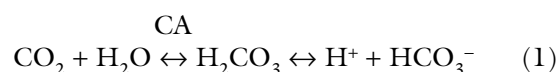


Fig. 11-1 Rightward shift of the O_2 dissociation curve by increase of H^+ , PCO_2 , temperature, and 2,3-diphosphoglycerate (DPG). (Adapted from West JB: *Respiratory physiology. The essentials*, ed 7, Philadelphia, 2005, Lippincott Williams & Wilkins, p. 79.)

CARBON DIOXIDE

As oxygen is transported to and used by tissues, metabolic processes in the body normally produce approximately 15,000 mmol of carbon dioxide daily. The lungs are responsible for excreting a great deal more carbonic acid (H_2CO_3 and dissolved carbon dioxide) each day than the kidneys.⁵³ Hence, alveolar ventilation and carbon dioxide removal have a large influence on acid-base balance. Dissolved carbon dioxide is 20 times more soluble than oxygen. It is so diffusible that we can assume complete equilibration of PCO_2 across membranes. As the tissues produce carbon dioxide, equilibrium is achieved rapidly between intracellular and extracellular compartments. Thus CO_2 diffuses rapidly from the tissues into red blood cells. Within the red blood cell, carbonic anhydrase (CA) hydrates CO_2 forming carbonic acid:



As shown in Fig. 11-2, carbonic acid spontaneously dissociates into H^+ and HCO_3^- at intracellular pH. The HCO_3^- ions diffuse from the red cells into plasma. The cell membrane is relatively impermeable to cations, and chloride (Cl^-) ions diffuse into the red cells from plasma to maintain electroneutrality (so-called "chloride shift"). In the lungs, the shift of chloride out of red cells is facilitated by the high intracellular concentration of chloride (~60 mEq/L) when compared with other cells. Most of the carbon dioxide (~81%) is transported to the lung as bicarbonate. A small amount is transported still dissolved in plasma (~8%), and some is combined with amino groups of blood proteins (~11%), the most important of which is carbaminohemoglobin.⁶⁷

CONTROL OF ALVEOLAR VENTILATION AND CHEMOSENSITIVITY

The drive to breathing originates within respiratory centers of the brainstem (i.e., ventral respiratory group), which comprises a network responsible for respiratory rhythm generation and respiratory pattern formation. These central respiratory areas receive input from chemoreceptors in the periphery and from areas throughout the central nervous system (CNS) while sending efferent signals to the muscles of respiration, such as the diaphragm and accessory muscles (i.e., intercostal and upper airway muscles) (Fig. 11-3).

Inputs from CO_2^- , O_2^- , and pH-sensitive chemoreceptors alter alveolar ventilation.^{6,17,47} The primary stimuli for changes in alveolar ventilation are hypoxemia ($Pa_{O_2} < 60$ mm Hg) and carbon dioxide-induced changes in intracellular and extracellular pH. In the normal animal,

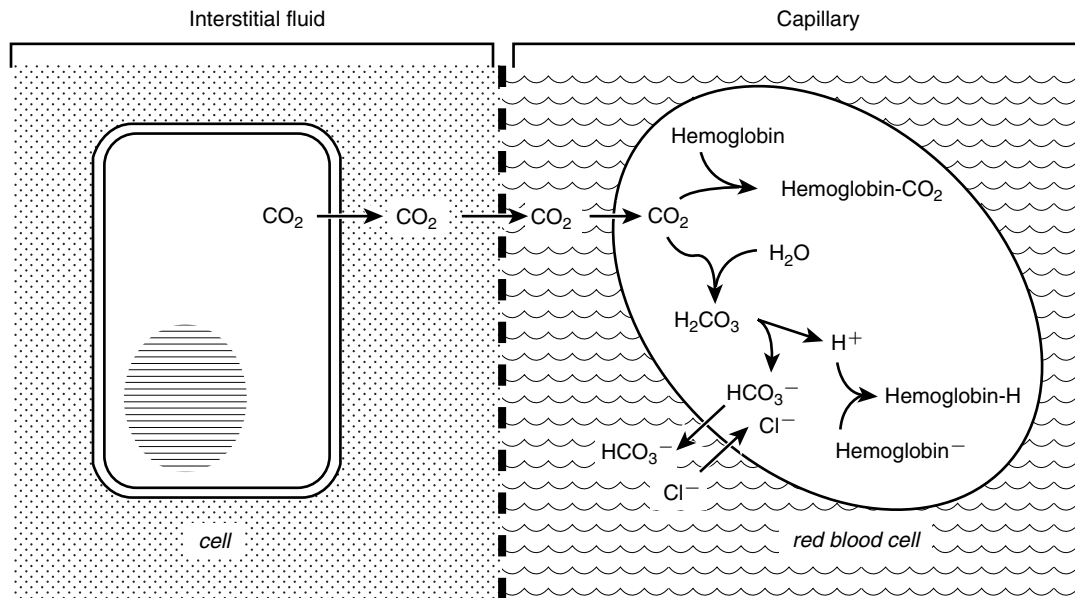


Fig. 11-2 The chloride shift. Increased CO_2 from cell metabolism leaves plasma and enters red blood cells, where it combines with hemoglobin and forms carbaminohemoglobin. The largest amount of CO_2 inside red blood cells is hydrated to form carbonic acid, which dissociates into bicarbonate and hydrogen ions. Bicarbonate diffuses out of the red blood cells into plasma in exchange for chloride ions.

peripheral chemoreceptors primarily are found within the carotid and aortic bodies; these organs are influenced by changes in O_2 and CO_2 and pH. In addition to the periphery, O_2 -sensitive chemoreceptors also are present in the CNS, but their contribution to ventilatory responses to hypoxia remains unclear.⁶² As a result, peripheral chemoreceptors at the bifurcation of the carotid bodies dominate the hypoxic ventilatory response and are responsible for approximately 90% of the increase in minute ventilation seen with hypoxemia.^{12,16} Along with peripheral CO_2 chemoreceptors, CO_2 /pH-sensitive receptors also are located centrally throughout the brainstem (i.e., nucleus tractus solitarius, locus ceruleus, midline medullary raphe, rostral ventral respiratory group, fastigial nucleus, retrotrapezoid nucleus; for review, see Putnam et al⁵⁴). Although both peripheral and central chemoreceptors contribute to CO_2 -induced ventilatory responses, the central receptors appear to be quantitatively more important for producing changes in ventilation mediated by CO_2 ; resection of the peripherally located carotid bodies only leads to a small increase in resting PaCO_2 levels (2 to 4 mm Hg) secondary to a decrease in alveolar ventilation.^{37,54} The CO_2 -sensitive chemoreceptors are extremely responsive, and small changes in CO_2 /pH affect breathing dramatically. For example, in resting awake humans, a 1-mm increase in PCO_2 increases ventilation by approximately 20% to 30%.¹⁷

The lungs are the only avenue for CO_2 elimination. Carbon dioxide efficiently diffuses across the alveolar

capillary wall. Thus under most circumstances, the CO_2 partial pressure is essentially the same in the alveoli (PACO_2) and arteries (PaCO_2). In the steady state, PaCO_2 is inversely proportional to alveolar ventilation (V_A) based on the alveolar ventilation equation:

$$\text{PaCO}_2 = 0.863 \left(\frac{V_{\text{CO}_2}}{V_A} \right) \quad (2)$$

where V_{CO_2} is the metabolic production of carbon dioxide and 0.863 is a constant that equates dissimilar units for V_{CO_2} and V_A .⁷² The V_A is the fraction of the total minute ventilation (V_E) that is produced at the gas exchange units of the lung. The portion of gas not reaching the gas exchange areas of the lung is termed dead space gas. The dead space to tidal volume ratio (V_D/V_T) refers to the portion of each tidal volume that ventilates dead space and is “wasted.” Therefore the alveolar gas equation can be rewritten as:

$$\text{PaCO}_2 = 0.863 \left(\frac{V_{\text{CO}_2}}{V_E [1 - (V_D/V_T)]} \right) \quad (3)$$

As determined by equations (2) and (3), measuring the PaCO_2 provides direct information about the adequacy of alveolar ventilation. Many primary respiratory acid-base disorders consequently result from alveolar hypoventilation (increased PaCO_2) or alveolar hyperventilation (decreased PaCO_2).

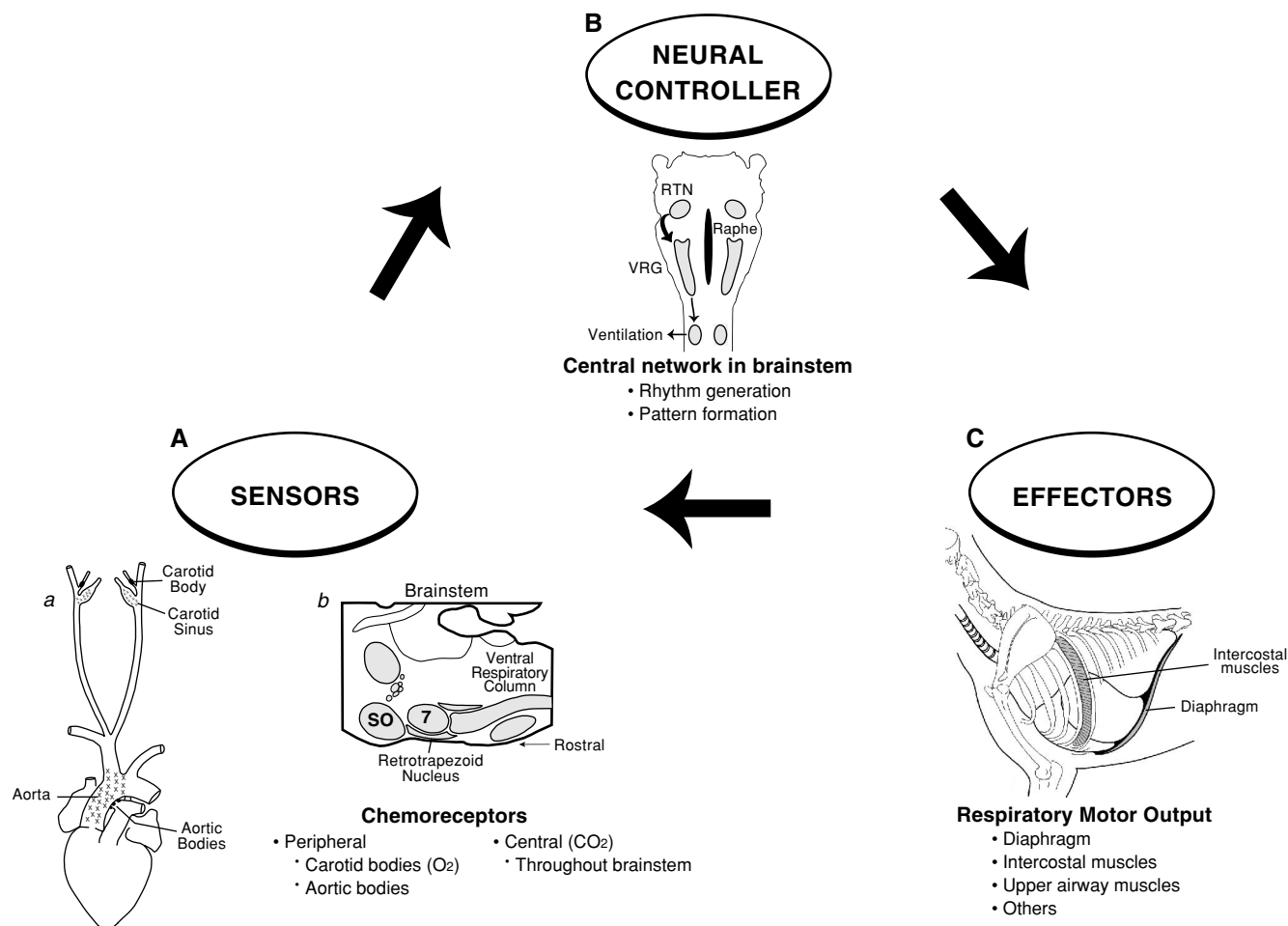


Fig. 11-3 Schematic representation of the respiratory control system. **A**, Sensors. Chemosensory and mechanosensory information originates from peripheral (carotid and aortic bodies) and central receptors (chemosensitive areas throughout the brainstem, **b**). **a**, A representation of peripheral receptors is found in **a**. The carotid bodies located at the bifurcation of the external and internal carotid arteries are responsible for the majority of the hypoxemic ventilatory response in mammals. A stylized view of the lateral aspect of the brainstem is shown in **b**. Chemosensitive areas found throughout the brainstem are the primary receptors mediating the hypercapnic ventilatory response. Many CO₂-sensitive neurons are found in the retrotrapezoid nucleus (RTN) located rostral to the ventral respiratory column, ventral to the facial nucleus (7) and caudal to the superior olive (SO). **B**, Neural controller: a stylized view of the ventral aspect of rat brainstem with RTN neurons is shown. Information from peripheral and central receptors is relayed centrally to ventral brainstem structures. Stimulation of the RTN activates premotor neurons in the ventral respiratory group (VRG), which then activate cranial and spinal motor neurons to modulate respiratory rhythm and pattern of breathing. **C**, Effectors: output from motor neurons reaches the respiratory effector muscles (e.g., diaphragm, intercostal muscles) producing a breath. Information from the effectors feeds back to the sensors to modulate breathing. (**A** redrawn from Mitchell's 2004 adaptation from Alheid GF, Gray PA, Jiang MC, et al: Parvalbumin in respiratory neurons of the ventrolateral medulla of the adult rat, *J Neurocytol* 31:693-717, 2002. **B** redrawn from Mitchell GS: Back to the future: carbon dioxide chemoreceptors in the mammalian brain, *Nat Neurosci* 7:1288-1290, 2004.)

THE ALVEOLAR-ARTERIAL OXYGEN GRADIENT

Frequently, patients with respiratory acidosis or alkalosis also are hypoxemic. When determining management options, it is important to discern between hypoxia from

primary lung disease (e.g., ventilation-perfusion mismatching) and alveolar hypoventilation. If breathing room air, the alveolar gas equation dictates that, at steady state, arterial or alveolar (PAO₂) oxygen tension will decrease with an increase in PCO₂:

$$PAO_2 = PIO_2 - \frac{PACO_2}{R} \quad (4)$$

where R is the respiratory exchange ratio that accounts for the difference between CO₂ production and O₂ consumption at steady state, PIO₂ is the inspired oxygen tension, and PACO₂ is the alveolar PCO₂. In normal animals, R is approximately 0.8. Because of the high solubility of CO₂, PACO₂ can be substituted for PaCO₂ in equation (4) under the assumption that PaCO₂ will equal PACO₂.

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} \quad (5)$$

Thus the difference between PAO₂ and PaO₂ can be calculated as:

$$(A - a) O_2 \text{ gradient} = PAO_2 - PaO_2 \\ = \left[PIO_2 - \left(\frac{PaCO_2}{R} \right) \right] - PaO_2 \quad (6)$$

Considering R = 0.8, and 1/0.8 = 1.25:

$$(A - a) O_2 \text{ gradient} = (PIO_2 - 1.25PaCO_2) - PaO_2 \quad (7)$$

At sea level in a patient breathing room air, PIO₂ is approximately 150 mm Hg. This can be substituted in equation (7):

$$(A - a) O_2 \text{ gradient} = (150 - 1.25PaCO_2) - PaO_2 \quad (7)$$

Values less than 15 mm Hg generally are considered normal.¹⁴ If the (A - a) O₂ ratio is widened, a component of the hypoxemia results from ventilation-perfusion mismatching. It should be remembered that FiO₂ is dependent on barometric pressure and will be lower at higher altitudes. At an altitude of 500 m (~1640 feet), PIO₂ equals 140 mm Hg, whereas at 1000 m (3280 feet), PIO₂ equals 130 mm Hg. Although it has long been thought that in the hypercapnic patient the alveolar-arterial oxygen difference differentiates hypoxemia caused by pure hypoventilation from hypoxemia in which other lung factors play a role, this idea has been seriously challenged^{23,30} because the (A - a) O₂ gradient may be increased in some patients with extrapulmonary disorders. Clinically, a normal gradient excludes pulmonary disease and suggests some form of central alveolar hypoventilation or an abnormality of the chest wall or inspiratory muscles.⁵⁷ To increase the specificity of the test to diagnose ventilation/perfusion mismatch, only patients with (A - a) O₂ gradient values more than 25 mm Hg¹⁴ should be considered abnormal. These patients are likely to have primary pulmonary disease, but extrapulmonary disorders cannot be completely ruled out.

HYPOXEMIA

Arterial blood gas analysis is not only essential for determining PaCO₂ levels and the acid-base condition of a

patient but it also provides information pertaining to a patient's oxygenation status. There are five main reasons for hypoxemia, including low fraction of inspired oxygen, hypoventilation, diffusion impairment, ventilation-perfusion mismatching, and shunt (Box 11-1).

LOW PARTIAL PRESSURE OF INSPIRED O₂ (PIO₂)

Low levels of inspired oxygen produce patient hypoxemia by reductions in mean alveolar oxygen levels (PAO₂), subsequently reducing PaO₂. Although relatively uncommon in veterinary medicine, this type of hypoxemia can result from a decrease in barometric pressure (i.e., residence at high altitudes or nonpressurized airline flights) or improper inhalant anesthetic technique (e.g., administration of N₂O without O₂). In these cases, there is an increase in alveolar ventilation secondary to hypoxemia, which in turn decreases PaCO₂. The (A - a) O₂ difference remains within normal limits because of the concomitant decrease in PIO₂.

HYPOVENTILATION

As previously discussed, the prevailing PAO₂ is determined by the balance between the removal of oxygen by the blood and replenishment of oxygen by alveolar ventilation. According to equations (4) and (5) above, as alveolar ventilation decreases, PAO₂ and PaO₂ decrease, whereas PACO₂ and PaCO₂ must increase. As a result, the (A - a) O₂ gradient does not change. If the (A - a) difference is widened, there may be a component of the hypoxemia attributable to primary lung disease such as ventilation-alveolar perfusion mismatching or right-to-left shunting. In addition, the alveolar gas equation also predicts that although increases in alveolar ventilation can change PAO₂ considerably, they can only moderately increase PaO₂. Because of the sigmoid shape of the oxygen-hemoglobin dissociation curve, the effect of increasing alveolar ventilation on arterial oxygen saturation is minimal above a PaO₂ of 55 to 60 mm Hg.^{24,41} Clinically important causes of hypoventilation include CNS disease, respiratory depressant drugs, neuromuscular diseases affecting the respiratory muscles, chest wall injury, upper airway obstruction, and severe diffuse pulmonary disease.

Box 11-1

Mechanisms of Derangement in Arterial Oxygenation

- Low fraction of inspired oxygen (FiO₂)
- Diffusion barrier
- Hypoventilation
- Ventilation-perfusion mismatch (V̇-Q mismatch)
- Right-to-left shunt

DIFFUSION IMPAIRMENT

Diffusion impairment occurs whenever there is incomplete equilibration of alveolar gas and pulmonary end-capillary blood. Equilibration of oxygen between the alveolus and red blood cell is extremely rapid under normal conditions, and this type of hypoxemia infrequently is observed in small animal medicine. However, a diffusion impairment leading to hypoxemia may be seen with thickening of the alveolar-capillary membrane (e.g., “alveolar-capillary block” seen in diffuse pulmonary interstitial disease) or loss of alveolar or capillary surface area (e.g., emphysema or vasculitis). Although hypoxemia caused by a diffusion impairment may occur as a consequence of the aforementioned disease states, it also may be detected under certain circumstances of high cardiac output that markedly decrease transit time of red cells (e.g., exercise). In any case, its contribution to hypoxemia usually is negligible, and a diffusion impairment seldom is the limiting factor in oxygen transfer to arterial blood.

VENTILATION-ALVEOLAR PERFUSION MISMATCH (\dot{V} - \dot{Q} MISMATCH)

Despite regional differences in \dot{V} - \dot{Q} ratios throughout the mammalian lung, the heterogeneity of individual lung units is relatively limited, resulting in a \dot{V} - \dot{Q} ratio of approximately 0.8.⁴¹ This ratio enables mixed venous blood to become fully oxygenated and CO_2 to be eliminated without increases in minute ventilation.⁷⁴

\dot{V} - \dot{Q} mismatch is one of the most commonly encountered causes of hypoxemia. It is present in areas of the lung in which perturbations in ventilation or perfusion occur and result in inefficient gas exchange. For example, low \dot{V} - \dot{Q} units have low PaO_2 and high alveolar PCO_2 , resulting in hypercapnic and hypoxemic blood. In fact, when breathing room air, the blood leaving a gas exchange unit with a \dot{V} - \dot{Q} ratio of less than 0.1 is essentially unoxygenated. Low \dot{V} - \dot{Q} (poorly ventilated, adequately perfused) units can be found in patients with increased airway resistance (e.g., asthma, bronchitis, chronic obstructive pulmonary disease). High \dot{V} - \dot{Q} (poorly perfused, adequately ventilated) units have high PaO_2 and a low PaCO_2 . In lung areas with \dot{V} - \dot{Q} ratios greater than 1, additional increases in ventilation do not improve oxygenation.^{50,74} High \dot{V} - \dot{Q} ratios are found in diseases with increased compliance (e.g., emphysema) or in low output states (e.g., pulmonary embolism).

Final blood gas tensions are determined by mixing of gas contents from different gas units. Thus \dot{V} - \dot{Q} mismatch will produce hypoxemia based on the actual O_2 and CO_2 levels in each lung area and the amount of blood flow to each unit.^{50,74} The severity of \dot{V} - \dot{Q} mismatch can be assessed using the $(A - a) \text{O}_2$ gradient because both abnormally low and high \dot{V} - \dot{Q} ratios increase the gradient. Patients with \dot{V} - \dot{Q} mismatch usually are hypoxemic but have normal or decreased PaCO_2

because chemoreceptors respond to and minute ventilation is altered by changes in carbon dioxide levels.^{49,74} Hypoxemia resulting from \dot{V} - \dot{Q} mismatch can be corrected by increasing the fraction of inspired oxygen (FiO_2) by use of 100% O_2 .

RIGHT-TO-LEFT SHUNT

Right-to-left shunting is a severe form of \dot{V} - \dot{Q} mismatch and results when mixed venous blood completely bypasses ventilated pulmonary alveoli and returns to the arterial circulation. A small amount (2% to 3%) of shunting is present in normal animals through the bronchial and thebesian circulations. In pathologic states, shunt results from perfusion of lung areas that receive no ventilation because of atelectasis or consolidation (\dot{V} - $\dot{Q} = 0$) or from deoxygenated blood flow through anatomic right-to-left channels. Thus shunting is the main cause for hypoxemia in pulmonary edema, atelectasis, pneumonia, and in congenital abnormal cardiac communications between the systemic and pulmonary circulations (e.g., patent ductus arteriosus, ventricular septal defect, atrial septal defect, tetralogy of Fallot) with right-to-left blood flow bypassing the lungs.

Even small amounts of shunt result in clinically relevant hypoxemia because venous blood oxygen content is extremely low and mixed venous blood is being added directly to arterial blood without alveolar gas exchange. Similar to \dot{V} - \dot{Q} mismatch, patients with right-to-left shunting have a decreased PaO_2 with normal or decreased PaCO_2 and widened $(A - a) \text{O}_2$ gradients. However, one major difference is that the PaO_2 levels in animals with increased shunting fail to return to normal even with 100% O_2 supplementation. In contrast, animals with \dot{V} - \dot{Q} mismatch, hypoventilation, or diffusion impairment exhibit pronounced increases in PaO_2 with oxygen enrichment (Table 11-1).

RESPIRATORY ACIDOSIS

Respiratory acidosis, or primary hypercapnia, results when carbon dioxide production exceeds elimination via the lung (for reviews, see Epstein and Singh¹⁵ and Markou et al⁴¹). Respiratory acidosis almost always is a result of respiratory failure with resultant alveolar hypoventilation and is characterized by an increase in PaCO_2 , decreased pH, and a compensatory increase in blood HCO_3^- concentration.

METABOLIC COMPENSATION IN RESPIRATORY ACIDOSIS

Acute Respiratory Acidosis

Acute increases in PCO_2 cause intracellular CO_2 levels to increase. An increase in CO_2 concentration shifts the reaction $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+$ to the right. Bicarbonate and H^+ concentrations slightly increase within 10 minutes because of dissociation of

TABLE 11-1 Theoretical Effect of Breathing 21% and 100% Oxygen on Mean P_{O_2} Values in Alveolar Gas, Arterial Blood, and Mixed Venous Blood

F_{iO_2}	Ideal Gas Exchange		$\dot{V}-\dot{Q}$ Mismatch		Right-to-Left Shunt	
	21%	100%	21%	100%	21%	100%
P_{O_2} (venous in mm Hg)	40	51	40	51	40	42
P_{O_2} (alveolar in mm Hg)	101	673	106	675	114	677
P_{O_2} (arterial in mm Hg)	101	673	89	673	59	125
(A - a) P_{O_2} gradient in mm Hg	0	0	17	2	55	552

From Murray JF: *Gas exchange and oxygen transport*. In Murray JF, editor: *The normal lung*, Philadelphia, 1986, WB Saunders, p. 194.

H_2CO_3 into HCO_3^- and H^+ . Bicarbonate ions are released from erythrocytes in exchange for chloride, increasing plasma strong ion difference (SID). An increase in CO_2 concentration also shifts the general buffer reaction ($A^- + H^+ \leftrightarrow HA$) to the left. Intracellular buffers (e.g., hemoglobin, $hemoglobin^- + H^+ \leftrightarrow$ reduced hemoglobin) play a critical role in acute buffering of hypercapnia, handling 97% of the H^+ load in dogs.^{21,39} Only 3% of the H^+ load is handled by extracellular buffers (i.e., plasma proteins). As a result, for each 1-mm Hg increase in PCO_2 , these buffers increase HCO_3^- 0.15 mEq/L in dogs¹³ and cats⁶⁴ (Box 11-2). Presence of moderate hypoxemia does not alter the adaptive response to acute respiratory acidosis.³⁸

Box 11-2 Predicted Metabolic Compensations in Respiratory Blood Gas Disorders

Acute Respiratory Acidosis

$[HCO_3^-]$ increases 0.15 mEq/L for every 1-mm Hg increase in PCO_2 in dogs

Same for cats

Chronic Respiratory Acidosis

$[HCO_3^-]$ increases 0.35 mEq/L for every 1-mm Hg increase in PCO_2 in dogs

Degree of compensation is not known for cats

Acute Respiratory Alkalosis

$[HCO_3^-]$ decreases 0.25 mEq/L for every 1-mm Hg decrease in PCO_2 in dogs

Same for cats

Chronic Respiratory Alkalosis

$[HCO_3^-]$ decreases 0.55 mEq/L for every 1-mm Hg decrease in PCO_2 in dogs

Degree of compensation is not known for cats, but pH is usually normal or slightly alkalemic

Chronic Respiratory Acidosis

If hypercapnia persists, renal compensation occurs to stabilize plasma HCO_3^- at a higher concentration within 5 days.^{31,52,59,68} Chronic hypercapnia causes intracellular H^+ to increase in the renal tubular cells. Up-regulation of the Na^+H^+ antiporter of the renal brush border occurs,⁶⁵ and hydrogen ions are exchanged for sodium and then excreted largely as $NH_4^+Cl^-$.^{57,69} Intracellular HCO_3^- is reabsorbed and exchanged for Cl^- , resulting in an increase in plasma SID, chloruresis, and negative chloride balance.¹⁸ The chloride lost in the urine decreases urine SID because the chloride is accompanied by NH_4^+ rather than sodium ions. A new steady state is reached when the increased filtered load of HCO_3^- resulting from the increased plasma concentration of HCO_3^- is balanced by increased renal reabsorption of HCO_3^- . The net effect is buffering of the respiratory acidosis and hypochloremic hyperbicarbonatemia caused by chronic hypercapnia. For each 1-mm Hg increase in PCO_2 , HCO_3^- will increase 0.35 mEq/L in dogs (see Box 11-2).¹³ The renal response to chronic hypercapnia is not altered by moderate hypoxemia, dietary sodium or chloride restriction, alkali loading, or adrenalectomy.³⁸ The renal compensation in chronic respiratory acidosis typically is considered to be incomplete, not returning pH completely to normal.⁷⁵ In stable human patients with chronic respiratory acidosis, however, a 0.51-mEq/L increase in $[HCO_3^-]$ is expected for each 1-mm Hg increase in PCO_2 .⁴² Thus arterial pH appears to remain near reference ranges in human patients with long-standing respiratory acidosis.⁴ Similar results have been observed in dogs with chronic respiratory acidosis and no identifiable reason for the increase in HCO_3^- concentration other than renal compensation (Goodman and de Moraes, unpublished observations).²⁶ These observations suggest that the kidneys may be able to bring arterial pH back to normal in dogs with longstanding (>30 days) respiratory acidosis. Renal compensation in cats with chronic respiratory acidosis is not known. Cats do not increase renal ammoniogenesis during experimental metabolic acidosis.³⁴ Cats may not

be able to compensate adequately in chronic respiratory acidosis because an increase in ammoniogenesis is the most adaptive factor.

Hypochloremia is a common finding in dogs with experimentally induced chronic hypercapnia.^{40,52,59,68} During recovery from chronic hypercapnia, chloride restriction hinders the return of plasma HCO_3^- concentration to normal. Thus the kidney needs chloride to preferentially resorb chloride with sodium, excrete excess HCO_3^- in the urine, and reestablish normal SID in the plasma.

CAUSES OF RESPIRATORY ACIDOSIS

Respiratory acidosis and hypercapnia can occur with any disease process involving the neural control of ventilation, mechanics of ventilation, or alveolar gas exchange resulting in hypoventilation, ventilation-perfusion mismatches, or both. **Acute respiratory acidosis** usually results from sudden and severe primary parenchymal (e.g., fulminant pulmonary edema), airway, pleural, chest wall, neurologic (e.g., spinal cord injury), or neuromuscular (e.g., botulism) disease.¹⁵ **Chronic respiratory acidosis** results in sustained hypercapnia and has many etiologies including alveolar hypoventilation, abnormal respiratory drive, abnormalities of the chest wall and respiratory muscles, and increased dead space.¹⁵ In patients with neuromuscular disease leading to muscular weakness, the degree of hypercapnia appears to be out of proportion to the severity of muscle disease and may be underestimated without blood gas analysis. In these patients, muscle weakness and elastic load are responsible for modulation of central respiratory output. This results in a rapid shallow breathing pattern that leads to chronic CO_2 retention.⁴³ A more detailed list of causes of respiratory acidosis is found in Box 11-3.

As determined by the alveolar gas equations (1) and (2) above, hypercapnia can result from a decrease in alveolar ventilation (either through a decrease in total minute ventilation or increase in the dead space to tidal volume ratio) or an increase in metabolic production of carbon dioxide. In small animal clinical practice, increased CO_2 production infrequently results in hypercapnia. In normal circumstances (e.g., exercise), an increase in CO_2 production usually is matched by an increase in CO_2 elimination via the lung.⁷¹ However, if CO_2 production is increased with impaired or fixed alveolar ventilation that is unable to effectively remove CO_2 , acute respiratory acidosis may develop, as is observed in a few conditions such as heat stroke and malignant hyperthermia.^{10,63}

Decreased alveolar ventilation produces hypercapnia from either a reduction in total minute ventilation (also termed global hypoventilation) or abnormal ventilation-perfusion ratios in the lung. In global hypoventilation,

Box 11-3

Causes of Respiratory Acidosis

Large Airway Obstruction

- Aspiration (e.g., foreign body, vomitus)
- Mass (e.g., neoplasia, abscess)
- Tracheal collapse
- Chronic obstructive pulmonary disease
- Asthma
- Obstructed endotracheal tube
- Brachycephalic syndrome
- Laryngeal paralysis/laryngospasm

Respiratory Center Depression

- Drug induced (e.g., narcotics, barbiturates, inhalant anesthesia)
- Neurologic disease (e.g., brainstem or high cervical cord lesion)

Increased CO_2 Production with Impaired Alveolar Ventilation

- Cardiopulmonary arrest
- Heatstroke
- Malignant hyperthermia

Neuromuscular Disease

- Myasthenia gravis
- Tetanus
- Botulism
- Polyradiculoneuritis
- Tick paralysis
- Electrolyte abnormalities (e.g., hypokalemia)
- Drug induced (e.g., neuromuscular blocking agents, organophosphates, aminoglycosides with anesthetics)

Restrictive Extrapulmonary Disorders

- Diaphragmatic hernia
- Pleural space disease (e.g., pneumothorax, pleural effusion)
- Chest wall trauma/flail chest

Intrinsic Pulmonary and Small Airway Diseases

- Acute respiratory distress syndrome
- Chronic obstructive pulmonary disease
- Asthma
- Severe pulmonary edema
- Pulmonary thromboembolism
- Pneumonia
- Pulmonary fibrosis
- Diffuse metastatic disease
- Smoke inhalation

Ineffective Mechanical Ventilation (e.g., Inadequate Minute Ventilation, Improper CO_2 Removal)

Marked Obesity (Pickwickian Syndrome)

CO₂ is delivered to the lung but ventilation is inadequate, and hypercapnia and hypoxemia develop. Global hypoventilation results from either an abnormal ventilatory drive or alterations in respiratory pump mechanics.

In normal animals, carbon dioxide is a marked stimulus for ventilation that subsequently increases central respiratory drive to offset any potential increase in blood CO₂ levels. However, animals with profound reductions in their drive to breathe do not respond to such stimuli and become hypercapnic. Conditions that may result in central hypoventilation include CNS trauma, neoplasia, infection, general anesthesia, narcotics, and cerebral edema. Global hypoventilation also results from failure of respiratory mechanics. In these cases, the respiratory muscles, chest wall, or both are ineffective in maintaining adequate ventilation, and the central respiratory drive usually is increased. Examples of diseases that affect respiratory mechanics are severe obesity, spinal cord injury, and myasthenia gravis.

Maintaining normal ventilation to alveolar perfusion ratios is essential for preserving eucapnia and normoxemia.⁷³ Areas of lung that are ventilated but ineffectively perfused increase the dead space to tidal volume ratio (V_D/V_T). When a normal breathing pattern shifts to a pattern consisting of very fast respiratory rates and small, inadequate tidal volumes (as seen in some patients with acute respiratory distress syndrome), V_D/V_T increases. In some disease states (e.g., shock), there may be areas of the lung with minimal or no alveolar perfusion. The normal lung has great reserve capabilities, and additional alveoli usually can compensate to keep the PaCO₂ within normal limits. However, if other alveolar units cannot be hyperventilated to remove the CO₂, an increased dead space will result in hypercapnia. Disorders resulting in this type of respiratory acidosis include pulmonary thromboembolism, emphysema, and fibrosis.

DIAGNOSIS AND CLINICAL FEATURES OF RESPIRATORY ACIDOSIS

Most clinical signs in animals with respiratory acidosis reflect the underlying disease process responsible for hypercapnia rather than the hypercapnia itself, and subjective clinical evaluation of the patient alone is not reliable in making a diagnosis of respiratory acidosis. In fact, patients with chronic, compensated respiratory acidosis may have very mild clinical signs. One should consider respiratory acidosis in a patient presented with a disorder likely to be associated with hypercapnia (see Box 11-3). Definitive diagnosis of respiratory acidosis is established by arterial blood gas analysis.

In extremely acute hypoventilation (e.g., cardiopulmonary arrest, airway obstruction), hypoxemia is the immediate threat to life, and a laboratory diagnosis of acute respiratory acidosis is not made in small animal practice. Frequently, the patient dies from hypoxemia before hypercapnia can become severe. Abrupt cessation

of ventilation is fatal within 4 minutes, whereas severe hypercapnia would not develop for 10 to 15 minutes in such a setting.³⁹ Many small animals presented to veterinarians have been ill long enough to develop a chronic steady state (i.e., 2 to 5 days), and their blood gas results reflect adaptation to chronic hypercapnia. However, if a patient with chronic respiratory acidosis acutely decompensates, life-threatening consequences may develop, and the patient may die quickly.

Although many clinical signs are subtle, especially in chronic respiratory acidosis, investigations in humans and experimental animals show that cardiovascular, metabolic, and neurologic consequences arise after acute hypercapnic acidemia.⁶⁹ Hypercapnia stimulates the sympathetic nervous system and causes release of catecholamines.^{9,36} Tachyarrhythmias (including ventricular fibrillation) are common and result from increased sympathetic tone, electrolyte fluctuations, associated hypoxemia, and acidemia.^{15,32,51} In experimental canine models, acute respiratory acidosis increases heart rate and cardiac output but decreases myocardial contractility and systemic vascular resistance with no change in blood pressure.⁷⁰ Thus on physical examination of the patient, one sees a hyperdynamic state, with an increased heart rate and cardiac output, increased or normal blood pressure, and “flushed” or “brick-red” mucous membranes associated with vasodilatation. Hypercapnia also causes a rightward shift of the oxygen-hemoglobin dissociation curve (see Fig. 11-1), promoting unloading of oxygen at the tissues and enhancing oxygen delivery and carrying capacity.⁵⁵

Metabolic consequences of acute hypercapnia include retention of both sodium and water, possibly as a result of increased antidiuretic hormone release, increased cortisol secretion, and activation of the renin-angiotensin system.³⁹ Respiratory, as well as metabolic, acidosis also may lead to gastroparesis by altering gastric muscle activity and fundic tone.⁶⁶

The nature of the neurologic signs seen depends on the magnitude of hypercapnia, rapidity of change in CO₂ and pH, and amount of concurrent hypoxemia. Acute hypercapnia causes cerebral vasodilatation, subsequently increasing cerebral blood flow and intracranial pressure.^{3,33,46,76} Clinically, the CNS effects of hypercapnia can result in signs ranging from anxiety, restlessness, and disorientation to somnolence and coma, especially when PCO₂ approaches 70 to 100 mm Hg.^{2,39,49,69}

TREATMENT OF RESPIRATORY ACIDOSIS

The most effective treatment of respiratory acidosis consists of rapid diagnosis and elimination of the underlying cause of alveolar hypoventilation. For example, airway obstruction should be identified and relieved, and medications that depress ventilation should be discontinued if possible. Pleurocentesis should be performed to remove fluid or air when pleural effusion or pneumothorax is present. Although at times it is not possible to

remove the underlying cause of hypoventilation (e.g., chronic pulmonary disease), appropriate treatment of the primary disease should be initiated along with supportive therapeutic measures. The primary goal is to remove the CO_2 , and consequently mechanical ventilation often is necessary.

According to the alveolar gas equation, a patient breathing room air at sea level (P_{IO_2} , ~150 mm Hg) will develop life-threatening hypoxia ($\text{PaO}_2 < 55$ to 60 mm Hg) before life-threatening hypercapnia. Thus supplemental oxygen and assisted ventilation are needed in treating acute respiratory acidosis. Although oxygen therapy may aid in the treatment of acute respiratory acidosis, oxygen may suppress the drive for breathing in patients with chronic hypercapnia. In chronic hypercapnia, the central chemoreceptors become progressively insensitive to the effects of CO_2 , and O_2 becomes the primary stimulus for ventilation. As a result, oxygen therapy may further suppress ventilation, worsening respiratory acidosis. If oxygen is administered, PaO_2 should be kept between 60 and 65 mm Hg because the hypoxic drive to breathing remains adequate up to this level.⁵⁷

In respiratory acidosis, the goals of treatment are to ensure adequate oxygenation and to provide adequate alveolar ventilation. Patients approaching respiratory muscle fatigue or respiratory failure or those experiencing progressive acidemia or hypoxemia will need mechanical or assisted ventilation to accomplish these objectives. Respiratory failure in the face of concurrent hypoxemia is diagnosed when PaCO_2 is more than 50 mm Hg in a nonsedated or nonanesthetized patient, when PaO_2 is less than 50 mm Hg with a FIO_2 of 0.21, or when a poor response of PaO_2 is less than 50 mm Hg with a FIO_2 of more than 0.5.⁸ When mechanical or assisted ventilation is begun, care must be taken to decrease PaCO_2 slowly. In human patients, rapid decreases in PCO_2 can result in cardiac arrhythmias, decreased cardiac output, and reduced cerebral blood flow.³⁹ A sudden decrease in blood PCO_2 also may result in posthypercapnic metabolic alkalosis and rapid diffusion of CO_2 from cerebrospinal fluid into blood, thus quickly increasing cerebrospinal pH.

Therapy with NaHCO_3 or other alkalinizing solutions is not indicated in respiratory acidosis. Administration of NaHCO_3 increases SID and may decrease $[\text{H}^+]$ and ventilatory drive, thus worsening hypoxemia. The resulting decrease in respiratory drive as a result of NaHCO_3 administration additionally may increase CO_2 and worsen respiratory failure, especially if alveolar ventilation cannot be increased to balance out the increased CO_2 production. NaHCO_3 itself is not innocuous. NaHCO_3 may alter hemodynamics, causing hypotension, decreased contractility, and cardiac arrest,⁴⁸ as well as decreased cerebral blood flow and cerebrovenous oxygen tension.⁵ Thus NaHCO_3 treatment is not warranted. In addition, the use of the strong organic base tris(hydroxymethyl)

aminomethane (THAM) has been investigated.¹⁵ THAM promotes CO_2 removal as HCO_3^- is generated. However, the amount of CO_2 removed is very small, and thus THAM has marginal clinical benefit at best.

Administration of a parenteral solution with adequate amounts of Cl^- facilitates recovery from chronic hypercapnia and prevents development of metabolic alkalosis after PaCO_2 has returned to normal. Dogs recovering from chronic hypercapnia and receiving a low-salt diet had persistently increased plasma HCO_3^- concentrations.⁶⁰ Addition of sodium or potassium chloride to the diet allowed full correction of the acid-base disturbances. Provision of sufficient Cl^- allows the kidney to reabsorb Na^+ in conjunction with Cl^- and to excrete the excess HCO_3^- retained during compensation for chronic hypercapnia.

RESPIRATORY ALKALOSIS

Respiratory alkalosis or primary hypocapnia is characterized by decreased PCO_2 , increased pH, and a compensatory decrease in HCO_3^- concentration in the blood. Respiratory alkalosis occurs whenever the magnitude of alveolar ventilation exceeds that required to eliminate the CO_2 produced by metabolic processes in the tissues.

METABOLIC COMPENSATION IN RESPIRATORY ALKALOSIS

Acute Respiratory Alkalosis

When PCO_2 is acutely decreased, CO_2 leaves the cells to achieve a new equilibrium point. Chloride ions leave red blood cells in exchange for HCO_3^- , causing a decrease in plasma HCO_3^- concentration. This results in decreased plasma SID and increases intracellular SID. Furthermore, H^+ translocation into the extracellular space in exchange for sodium and potassium also decreases plasma SID. As in respiratory acidosis, intracellular phosphates and proteins are the major buffers in the acute adaptive response. Extracellular buffering by release of H^+ from plasma proteins constitutes only 1% of the acute response, whereas intracellular buffering accounted for the remaining 99%.²¹ In dogs and cats, a compensatory decrease of 0.25 mEq/L in HCO_3^- concentration for each 1-mm Hg decrease in PCO_2 is expected (see Box 11-2).^{13,25}

Chronic Respiratory Alkalosis

During chronic respiratory alkalosis, a 0.55-mEq/L decrease in HCO_3^- is expected for each 1-mm Hg decrease in PCO_2 in dogs (see Box 11-2).¹³ This represents effective compensation, and the pH is normal or near normal in dogs with chronic respiratory alkalosis. However, normalization of pH may take up to 4 weeks to be achieved.¹¹ Cats chronically exposed to a hypoxic environment ($\text{FIO}_2 = 10\%$) for 28 days also were able to maintain a normal arterial pH.⁷ Expected compensation

in cats cannot be inferred from this study, but based on the ability to maintain a normal pH, it may be reasonable to assume that cats can compensate to chronic respiratory alkalosis, as well as dogs and humans. As a result, abnormal PCO_2 and HCO_3^- concentration with normal pH does not necessarily imply a mixed acid-base disorder in both dogs and cats.

CAUSES OF RESPIRATORY ALKALOSIS

Common causes of respiratory alkalosis include stimulation of peripheral chemoreceptors by hypoxemia, primary pulmonary disease, direct activation of the brainstem respiratory centers, overzealous mechanical ventilation, and situations that cause pain, anxiety, or fear. In addition, respiratory alkalosis can occur during recovery from metabolic acidosis because hyperventilation persists for 24 to 48 hours after correction of metabolic acidosis. A more detailed list of causes is found in Box 11-4.

When PO_2 decreases to less than 60 mm Hg, the peripheral chemoreceptors mediate an increase in rate and depth of breathing, resulting in hypocapnia. Decreased oxygen delivery also results in hypocapnia (e.g., severe anemia, cardiovascular shock). The effect of the resulting hypocapnia and decreased $[\text{H}^+]$ on the central chemoreceptors is to negatively feedback on the respiratory control system and blunt this initial hyperventilation. As renal compensation occurs, plasma HCO_3^- decreases, $[\text{H}^+]$ increases, and central inhibition of further hyperventilation is removed. A steady state results when the peripherally mediated hypoxic drive to ventilation is balanced by the central effect of the alkalemia resulting from renal adaptation to hypocapnia. If PCO_2 is held constant in the presence of hypoxemia (as seen in patients with pulmonary disease), the dampening effect of hypocapnia does not occur, and a lesser degree of hypoxemia may stimulate ventilation.

Pulmonary diseases such as pneumonia, diffuse interstitial lung disease, and thromboembolism may cause respiratory alkalosis. The hyperventilation seen with primary lung disease may be a result, at least in part, of the concurrent hypoxemia. However, pulmonary diseases may cause hyperventilation without hypoxemia as a result of stimulation of stretch receptors and nociceptive receptors.^{20,58} The stretch receptors are located in the smooth muscle of the tracheobronchial tree. The nociceptive receptors include irritant receptors in the epithelium of small airways and juxtacapillary receptors (J receptors) lining capillaries in the interstitium. These receptors respond to stimuli such as irritants, interstitial edema, fibrosis, or pulmonary capillary congestion.

DIAGNOSIS AND CLINICAL FEATURES OF RESPIRATORY ALKALOSIS

It is difficult to attribute specific clinical signs to respiratory alkalosis in the dog and cat. The clinical signs usually

Box 11-4

Causes of Respiratory Alkalosis

Hypoxemia (Stimulation of Peripheral Chemoreceptors by Decreased Oxygen Delivery)

- Right-to-left shunting
- Decreased $\text{P}\text{I}\text{O}_2$ (e.g., high altitude)
- Congestive heart failure
- Severe anemia
- Severe hypotension
- Decreased cardiac output
- Pulmonary diseases with ventilation-perfusion mismatch
 - Pneumonia
 - Pulmonary thromboembolism
 - Pulmonary fibrosis
 - Pulmonary edema
 - Acute respiratory distress syndrome

Pulmonary Disease (Stimulation of Stretch/nociceptors Independent of Hypoxemia)

- Pneumonia
- Pulmonary thromboembolism
- Interstitial lung disease
- Pulmonary edema
- Acute respiratory distress syndrome

Centrally Mediated Hyperventilation

- Liver disease
- Hyperadrenocorticism
- Gram-negative sepsis
- Drugs
 - Salicylates
 - Corticosteroids
 - Progesterone (pregnancy)
 - Xanthines (e.g., aminophylline)
- Recovery from metabolic acidosis
- Central neurologic disease
 - Trauma
 - Neoplasia
 - Infection
 - Inflammation
 - Cerebrovascular accident
- Exercise
- Heatstroke

Muscle Metaboreceptor Overactivity

- Heart failure

Overzealous Mechanical Ventilation

Situations Causing Pain, Fear, or Anxiety

are caused by the underlying disease process and not by the respiratory alkalosis itself. However, in humans, headache, light-headedness, confusion, paresthesias of the extremities, tightness of the chest, and circumoral numbness have been reported in acute respiratory alkalosis.^{1,20} In any case, clinical signs in small animals are uncommon because of efficient metabolic compensation,

and tachypnea may be the only clinical abnormality found, especially with chronic hypocapnia.

If the pH exceeds 7.6 in respiratory alkalosis, neurologic, cardiopulmonary, and metabolic consequences may arise.¹ Such a pH only can be achieved in acute respiratory alkalosis before renal compensation ensues. Alkalemia results in arteriolar vasoconstriction that can decrease cerebral and myocardial perfusion. In addition, hyperventilation ($PCO_2 < 25$ mm Hg) causes decreased cerebral blood flow, potentially resulting in clinical signs such as confusion and seizures.

Hypocapnia decreases blood pressure and cardiac output in anesthetized but not awake subjects, possibly because anesthetics blunt reflex tachycardia. For example, in anesthetized dogs, acute hypocapnia decreased blood pressure as a result of reduced cardiac output together with an ineffective increase in total peripheral resistance and no change in heart rate.^{35,44} Although alkalemia exerts a small positive inotropic effect on the isolated heart, alkalemia also predisposes to refractory supraventricular and ventricular arrhythmias, especially in patients with preexisting cardiac disease.¹

Acute alkalemia shifts the oxygen-hemoglobin dissociation curve to the left, reducing the release of oxygen to the tissues by increasing affinity of hemoglobin for oxygen (see Fig. 11-1).²⁸ However, chronic alkalemia negates this effect by increasing the concentration of 2,3-DPG in red cells.^{20,27,56}

Hypokalemia may occur as a result of the translocation of potassium into cells and renal and extrarenal losses in patients with acute respiratory alkalosis.^{20,27,56} In anesthetized, hyperventilated dogs, potassium is expected to decrease 0.4 mEq/L for each 10-mm Hg decrease in PCO_2 .⁴⁴ Similar changes (0.6 mEq/L for each 10-mm Hg decrease in PCO_2) were observed in awake dogs with acute respiratory acidosis induced by hypoxemia²⁹ or by simulating a high altitude environment (30,000 feet).⁶¹ Hypokalemia can result in neuromuscular weakness, sensitization to digitalis-induced arrhythmias, polyuria, and increased ammonia production that amplifies the effects of hepatic encephalopathy.¹ However, the hypokalemia induced by respiratory alkalosis is mild and short-lived. Hypokalemia is not present in patients with chronic respiratory alkalosis.^{2a,19,22}

TREATMENT OF RESPIRATORY ALKALOSIS

Treatment should be directed toward relieving the underlying cause of the hypocapnia; no other treatment is effective. Respiratory alkalosis severe enough to cause clinical consequences for the animal is uncommon. Hypocapnia itself is not a major threat to the well-being of the patient. Thus the underlying disease responsible for hypocapnia should receive primary therapeutic attention.

SUMMARY

Respiratory acid-base disorders and derangements in arterial blood gases are common entities that may lead to increased morbidity and mortality in small animal patients. Early and proper diagnosis of these disease states is essential in providing correct and effective therapy. Recent, more widespread availability of “bedside” portable blood gas analyzers in small animal practice has allowed the practitioner to monitor the acid-base and oxygenation status of the patient, thus providing more efficient, high quality care for the compromised small animal patient.

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CHAPTER • 12

MIXED ACID-BASE DISORDERS

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"A patient will have as many diseases as he/she pleases."

Anonymous

A mixed acid-base disturbance is characterized by the presence of two or more separate primary acid-base abnormalities occurring in the same patient. An acid-base disturbance is said to be simple if it is limited to the primary disturbance and the expected

compensatory response. Box 12-1 shows a classification of mixed acid-base disorders.

Recognition of a mixed acid-base disorder is important from a diagnostic and a therapeutic point of view. It permits early detection of complications (e.g., the