



CHAPTER • 11

Respiratory Acid-Base Disorders

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“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 alveolar ventilation; 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 neural pathways controlling respiration initiate and coordinate respiratory muscle contraction, thereby generating adequate alveolar ventilation in the lungs. The primary responsibility of the mammalian lung is then to exchange gases at the alveolar blood-gas interface where carbon dioxide and oxygen 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 the membrane (Fick’s law). With a relatively large surface area and a very thin (<1 micron) blood-gas interface, the lungs are well suited for their role in gas exchange and thus, greatly influence respiratory acid-base regulation.

CONTROL OF ALVEOLAR VENTILATION

The drive to breathe originates within respiratory centers of the medulla (i.e., ventral respiratory column, VRC), which consist of a network responsible for respiratory rhythm generation and respiratory pattern formation. Although supramedullary brain structures, such as the pons, cerebellum and forebrain, modulate breathing, they are not required to breathe. Respiratory rhythm generation and pattern formation are altered by homeostatic control mechanisms that permit flexibility in the respiratory control system (i.e., plasticity). For example, the medullary respiratory centers are modified by sensory (i.e., chemoreceptors and mechanoreceptors) and modulatory projections (i.e., serotonergic neurons), as well as

many other processes that affect breathing (i.e., cortical inputs, cardiovascular alterations, etc.). These inputs collectively establish the spatiotemporal efferent signals that project to respiratory pump muscles such as the diaphragm and upper airway muscles involved in airway resistance regulation. Altogether, these pathways result in muscular contraction, which subsequently drives alveolar ventilation⁵⁰ (Figure 11-1).

CHEMORECEPTORS AND CHEMOREFLEXES

Chemoreceptors provide sensory inputs to the respiratory control system concerning changes in CO_2 or O_2 . As a result, alveolar ventilation is altered via negative feedback mechanisms to minimize variations in normal gas levels.^{6,19,50,55} The primary stimuli for changes in alveolar ventilation are hypoxemia ($P_{aO_2} < 60$ mm Hg) and carbon dioxide-induced changes in intracellular and extracellular pH, although the magnitude of these changes is dependent on the specific chemoreflex. For example, arterial CO_2 levels are tightly regulated under normal ventilatory control; increases in arterial CO_2 levels (P_{aCO_2}) of 1 to 3 mm Hg will double alveolar ventilation. In contrast, arterial O_2 pressures (P_{aO_2}) can change up to 20 mm Hg with little alteration in ventilation.⁵⁰

In adult mammals, chemoreceptors are located in both the peripheral and central nervous systems. The most significant oxygen-sensitive chemoreceptors are primarily found within the carotid body at the bifurcation of the internal and external carotid arteries. Although carotid body chemoreceptors sense changes in CO_2 and pH as well, these chemoreceptors dominate the hypoxic ventilatory response and are responsible for approximately 90% of the increase in minute ventilation seen with hypoxemia.^{14,18} Oxygen-sensitive receptors are also found in the aortic bodies within the aortic arch. However, they appear to play a minimal role during normal ventilation.⁵⁰ In addition to the periphery, O_2 -sensitive chemoreceptors

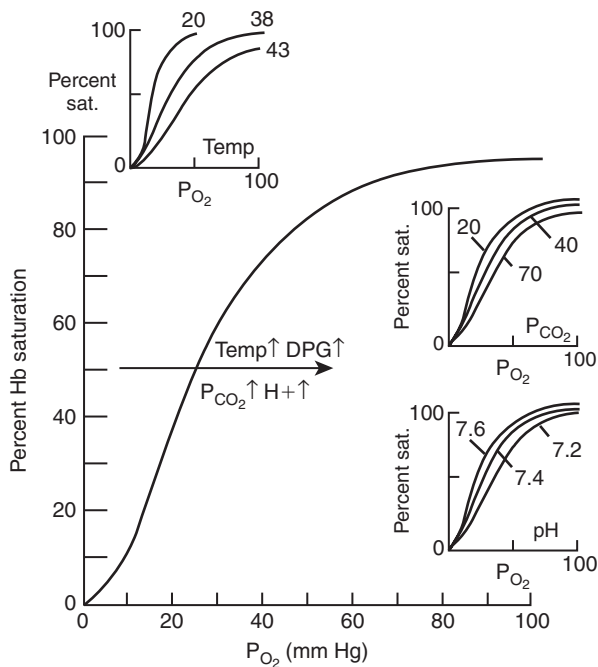


Figure 11-1 Schematic representation of the respiratory control system. Sensors. Chemosensory and mechanosensory information originates from peripheral (carotid and aortic bodies) and central (brainstem) chemoreceptors. The carotid bodies located at the bifurcation of the external and internal carotid arteries are responsible for the majority of the hypoxemic ventilatory response in mammals, whereas chemosensitive areas found throughout the brainstem are the primary receptors mediating the hypercapnic ventilatory response. Central controller. Information from peripheral and central receptors is relayed centrally to ventral brainstem structures. Stimulation of the retrotrapezoid nucleus activates premotor neurons in the ventral respiratory group, which then activate cranial and spinal motor neurons to initiate respiratory rhythm and modulate pattern of breathing. 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.

are also present in the CNS, but their contribution to ventilatory control remains unclear.⁷³

In contrast to O₂-sensitive receptors, the primary CO₂/pH-sensitive receptors are located in the CNS throughout the brainstem (i.e., retrotrapezoid nucleus [RTN], serotonergic and GABAergic neurons in the raphe nuclei, noradrenergic neurons in the locus coeruleus, nucleus of the solitary tract [NTS], pre-Bötzinger complex, and cerebellar fastigial nucleus).⁵⁰ Although both peripheral and central chemoreceptors contribute to CO₂-induced ventilatory responses, the central receptors appear to be quantitatively more significant for producing changes in ventilation mediated by CO₂; resection of the peripherally-located carotid bodies only leads to a small increase in resting PaCO₂ levels (2 to 4 mm Hg) secondary to a decrease in alveolar ventilation.^{41,64} The CO₂-sensitive chemoreceptors are

extremely responsive as small changes in CO₂/pH affect breathing dramatically. For example, in resting awake humans, a 1-mm increase in PCO₂ increases ventilation by approximately 20% to 30%.¹⁹

The lungs are the only avenue for CO₂ elimination. Carbon dioxide efficiently diffuses across the alveolar capillary wall. Thus, under most circumstances, the CO₂ partial pressure is essentially the same in the alveoli (PaCO₂) and arteries (Paco₂). In the steady state, PaCO₂ is inversely proportional to alveolar ventilation (V_A) based on the alveolar ventilation equation:

$$PaCO_2 = 0.863 \left(\frac{\dot{V}CO_2}{\dot{V}_A} \right) \quad (1)$$

where CO₂ is the metabolic production of carbon dioxide and 0.863 is a constant that equates dissimilar units for CO₂ and A.⁸³ The A is the fraction of the total minute ventilation (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:

$$PaCO_2 = 0.863 \left(\frac{\dot{V}CO_2}{\dot{V}_E [1 - (V_D / V_T)]} \right) \quad (2)$$

As determined by equations (1) and (2), measuring the PaCO₂ provides direct information about the adequacy of alveolar ventilation. Many primary respiratory acid-base disorders subsequently result from alveolar hypoventilation (increased PaCO₂) or alveolar hyperventilation (decreased PaCO₂).

MECHANOREFLEXES

In addition to chemoafferent alterations of ventilatory control, ventilation is also influenced by sensory inputs originating from the chest wall, pulmonary and airway receptors*. Many receptors located throughout the airways are activated in response to changes in pressure, cold, irritation, and stretch. For example, laryngeal stimulation by negative pressure or cold results in reflex activity directed at maintaining upper airway patency whereas airways below the larynx contain slowly (SAR) and rapidly (RAR) adapting stretch receptors and bronchopulmonary C fibers which, upon activation, result in many reflex events including bronchoconstriction or bronchodilation, protective reflexes (i.e., cough), and alterations in respiratory timing.³⁷

As discussed, the essential function of the ventilatory control system is to maintain blood gas regulation and many factors regulate its homeostasis. Although

*For review see: Kubin et al., 2006.

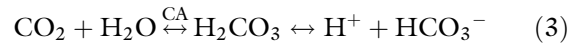
conscious factors (i.e., speaking, smelling, breath holding) can purposely alter respiration, ventilatory regulation is mainly controlled by the autonomic nervous system. As such, the CNS receives afferent inputs from chest wall, airway and lung parenchyma receptors as well as chemoafferent information from arterial blood and pH. Altogether, sensory information from mechanoreceptors and chemoreceptors is integrated within brainstem breathing centers to generate the neural respiratory rhythm and pattern. The respiratory output is further modulated by neurochemical signals (i.e., serotonergic inputs) with subsequent contraction of effector inspiratory muscles (e.g., diaphragm). Oxygen is then taken into the lungs, alveolar ventilation results, and blood gas levels of oxygen and carbon dioxide are regulated as the respiratory control cycle continues.

GAS DIFFUSION AND TRANSPORT DURING RESPIRATION

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.⁶³ Hence, alveolar ventilation and carbon dioxide removal have a large influence in acid-base balance. Dissolved carbon dioxide is approximately 20 to 24 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 rapidly achieved between intracellular and

extracellular compartments. Thus CO_2 diffuses rapidly from the tissues into red blood cells. In the blood, bicarbonate is formed through the following reaction:



The first reaction is quite slow in plasma but fast within the erythrocyte due to the presence of carbonic anhydrase (CA), which quickly hydrates CO_2 to form carbonic acid. As shown in Figure 11-2, carbonic acid spontaneously dissociates into H^+ and HCO_3^- at intracellular pH. When the concentration rises, HCO_3^- ions diffuse from the red cells into the plasma. However, the cell membrane is relatively impermeable to cations (H^+), 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 (approximately 60 mEq/L) when compared with other cells. Most of the carbon dioxide (approximately 81%) is subsequently transported to the lung as bicarbonate. A small amount is transported still dissolved in plasma (approximately 8%), and some is combined with terminal amino groups of blood proteins (approximately 11%), the most important of which is carbaminohemoglobin.⁷⁸

OXYGEN

Although respiratory blood-gas disorders primarily result from alterations of CO_2 levels, consideration must be also be given to alterations in O_2 levels as patients with respiratory acid-base disorders may also become hypoxemic. Oxygen transport is initiated by contraction of the diaphragm with consequent movement of inspired gas down the continually branching airways until the transitional and respiratory bronchioles, alveolar ducts, and alveoli

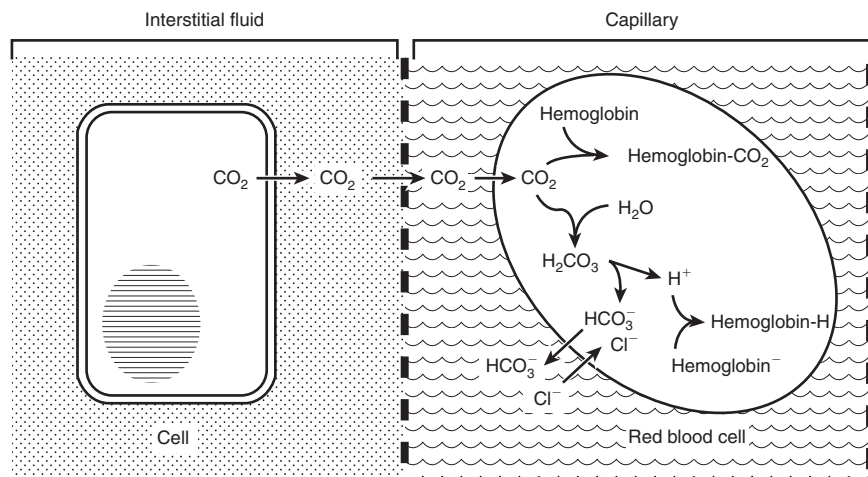


Figure 11-2 The chloride shift. Increased CO_2 from cell metabolism leaves plasma and enters red blood cells, where it combines with hemoglobin and forms carbaminohemoglobin. The largest amount of CO_2 inside red blood cells is hydrated to form carbonic acid, which dissociates into bicarbonate and hydrogen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

are reached. 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 due to the lung's considerable diffusion capabilities. Oxygen is then 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/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, approximately 21 mL O_2 per 100 mL blood is carried to the tissues. As determined by the oxygen-hemoglobin dissociation curve (Figure 11-3), at low P_{O_2} , the amount of oxygen carried by hemoglobin increases rapidly with increases in P_{O_2} .

However, at a 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.

THE ALVEOLAR-ARTERIAL OXYGEN GRADIENT

When patients present with hypoxemia associated with respiratory acid-base disorders, it is important to discern between hypoxia from primary lung disease (e.g., ventilation-perfusion mismatching) and alveolar hypoventilation to manage the patient appropriately.

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Figure 11-3 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, 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2005: 75–89.)

If breathing room air, the alveolar gas equation dictates that, at steady state, arterial or alveolar (PAO_2) oxygen tension will decrease with an increase in PCO_2 :

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

where R is the respiratory exchange ratio that accounts for the difference between CO_2 production and O_2 consumption at steady state, PIO_2 is the inspired oxygen tension, and $PACO_2$ is the alveolar PCO_2 . In normal animals, R is approximately 0.8. Because of the high solubility of CO_2 , $PACO_2$ can be substituted for $PaCO_2$ in [equation \(4\)](#) under the assumption that $PACO_2$ will equal $PaCO_2$.

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

Thus the difference between PAO_2 and PaO_2 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, PIO_2 is approximately 150 mm Hg. This can be substituted in [equation 7](#):

$$(A - a)O_2 \text{ gradient} = (150 - 1.25PaCO_2) - PaO_2 \quad (8)$$

Values below 15 mm Hg are generally considered normal.¹⁶ If the $(A - a) O_2$ ratio is widened, a component of the hypoxemia results from ventilation-perfusion mismatching. It should be remembered that FI_{O_2} is dependent on barometric pressure and will be lower at higher altitudes. At an altitude of 500 m (approximately 1640 feet), $PIO_2 = 140$ mm Hg, whereas at 1000 m (3280 feet), $PIO_2 = 130$ 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 factors play a role, this idea has been seriously challenged,^{26,33} because the $(A - a) O_2$ 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.⁶⁷ To increase the specificity of the test to diagnose the ventilation/perfusion mismatch, only patients with $(A - a) O_2$ gradient values greater than 25 mm Hg should be considered abnormal.¹⁶

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 $Paco_2$ levels and acid-base condition of a patient; 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 O_2 (PIO_2)

Low levels of inspired oxygen produce patient hypoxemia by reductions in mean alveolar oxygen levels (PAO_2), subsequently reducing PaO_2 . 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 an improper inhalant anesthetic technique (e.g., administration of N_2O without O_2). In these cases, there is a subsequent increase in alveolar ventilation secondary to hypoxemia, which in turn decreases $PACO_2$. The $(A - a) O_2$ difference remains within normal limits because of the concomitant decrease in PIO_2 .

HYPOVENTILATION

As previously discussed, the prevailing PAO_2 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, PAO_2 and PaO_2 decrease while $PACO_2$ and $PaCO_2$ must increase. As a result, the $(A - a) O_2$ 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 PAO_2 considerably, they can only moderately increase PaO_2 . Due to the sigmoid shape of the oxygen-

BOX 11-1

Mechanisms of Derangement in Arterial Oxygenation

- Low fraction of inspired oxygen (FI_{O_2})
- Diffusion barrier
- Hypoventilation
- Ventilation-perfusion mismatch ($\dot{V} - \dot{Q}$ mismatch)
- Right-to-left shunt

hemoglobin dissociation curve, the effect of increasing alveolar ventilation on arterial oxygen saturation is minimal above a P_{aO_2} of 55 to 60 mm Hg.^{27,46} Clinically, important causes of hypoventilation include CNS disease, respiratory depressant pharmacologic agents, neuromuscular diseases affecting the respiratory muscles, chest wall injury, upper airway obstruction, and severe diffuse pulmonary disease.

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 the erythrocyte 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 from 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 is usually 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 0.8.⁴⁶ This ratio enables the mixed venous blood to become fully oxygenated and the CO_2 to be eliminated without increases in minute ventilation.⁸⁵

$\dot{V}-\dot{Q}$ mismatch is one of the most commonly encountered causes of hypoxemia. It is present in areas of the lung where there are perturbations in ventilation or perfusion resulting in inefficient gas exchange. For example, low $\dot{V}-\dot{Q}$ units have a low P_{aO_2} and high alveolar P_{CO_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 $\dot{V}-\dot{Q}$ units (poorly ventilated, adequately perfused) can be found in patients with increased airway resistance (e.g., asthma, bronchitis, chronic obstructive pulmonary disease). High $\dot{V}-\dot{Q}$ units (poorly perfused, adequately ventilated) have a high P_{aO_2} and a low P_{aCO_2} . In lung areas with $\dot{V}-\dot{Q}$ ratios greater than 1, additional increases in ventilation do not improve oxygenation.^{59,85} High $\dot{V}-\dot{Q}$ ratios are found in diseases with increased compliance (e.g., emphysema) or low output states (e.g., pulmonary embolism).

Final blood gas tensions are determined by the 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.^{59,85} The severity of $\dot{V}-\dot{Q}$ mismatch can be assessed using the $(A - a) O_2$ gradient as 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 P_{aCO_2} because chemoreceptors respond to, and minute ventilation is altered by, changes in carbon dioxide levels.^{58,85} Hypoxemia resulting from $\dot{V}-\dot{Q}$ mismatch can be corrected by increasing the fraction of inspired oxygen (F_{IO_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 thesbian 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 or 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 P_{aO_2} with a normal or decreased P_{aCO_2} and widened $(A - a) O_2$ gradients. However, one major difference is that the P_{aO_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 P_{aO_2} with oxygen enrichment (Table 11-1).

RESPIRATORY ACIDOSIS

Respiratory acidosis, or primary hypercapnia, results when carbon dioxide production exceeds elimination via the lung*. Respiratory acidosis is almost always a result of respiratory failure with resultant alveolar hypoventilation and is characterized by an increase in P_{aCO_2} , decreased pH, and a compensatory increase in blood HCO_3^- concentration.

*For reviews see: Epstein and Singh, 2001¹⁷ and Markou et al. 2004⁴⁶.

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: WB Saunders, 1986: 194.

METABOLIC COMPENSATION IN RESPIRATORY ACIDOSIS

Acute Respiratory Acidosis

Acute increases in P_{CO_2} cause intracellular CO_2 levels to increase. An increase in CO_2 concentration shifts the reaction $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$ to the right. Bicarbonate and H^+ concentrations slightly increase within 10 minutes because of dissociation of H_2CO_3 into HCO_3^- and H^+ . Bicarbonate ions are released from erythrocytes in exchange for chloride, increasing the 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.^{24,43} 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 P_{CO_2} , these buffers increase HCO_3^- 0.15 mEq/L in dogs¹⁵ and cats⁷⁵ (Box 11-2). Presence of moderate hypoxemia does not alter the adaptive response to acute respiratory acidosis.⁴⁴

Chronic Respiratory Acidosis

If hypercapnia persists, renal compensation occurs to stabilize plasma HCO_3^- at a higher concentration within 5 days.^{34,62,69,79} Chronic hypercapnia causes intracellular H^+ to increase in the renal tubular cells. Upregulation of the $Na^+ - H^+$ antiporter of the renal brush border occurs,⁷⁶ and hydrogen ions are exchanged for sodium and then excreted as $NH_4^+ Cl^-$.^{67,80} Intracellular HCO_3^- is reabsorbed and exchanged for Cl^- , resulting in an increase in plasma SID, chloruresis, and negative chloride balance.²⁰ 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

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 P_{CO_2} in dogs
Same for cats

Chronic Respiratory Acidosis

$[HCO_3^-]$ increases 0.35 mEq/L for every 1-mm Hg increase in P_{CO_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 P_{CO_2} in dogs
Same for cats

Chronic Respiratory Alkalosis

$[HCO_3^-]$ decreases 0.55 mEq/L for every 1-mm Hg decrease in P_{CO_2} in dogs
Degree of compensation is not known for cats, but pH is usually normal or slightly alkalemic

P_{CO_2} , HCO_3^- will increase 0.35 mEq/L in dogs.¹⁵ (see Box 11-2). The renal response to chronic hypercapnia is not altered by moderate hypoxemia, dietary sodium or chloride restriction, alkali loading, or adrenalectomy.⁴⁴ The renal compensation in chronic respiratory acidosis typically is considered to be incomplete, not returning pH completely to the normal value.⁸⁶ 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 P_{CO_2} .⁴⁷ 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.²⁹ 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.³⁸ 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.^{44,62,69,79} 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., fulminate pulmonary edema), airway, pleural, chest wall, neurologic (e.g., spinal cord injury), or neuromuscular (e.g., botulism) disease.¹⁷ **Chronic respiratory acidosis** results in sustained hypercapnia and has many causes, including alveolar hypoventilation, abnormal respiratory drive, abnormalities of the chest wall and respiratory muscles, and increased dead space.¹⁷ 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 the modulation of central respiratory output. This results in a rapid shallow or dyspneic breathing pattern that leads to chronic CO_2 retention.⁴⁹ 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 is matched by an increase in CO_2 elimination via the lung.⁸² 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.^{12,74}

Decreased alveolar ventilation produces hypercapnia from either a reduction in total minute ventilation (also

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)

termed global hypoventilation) or abnormal ventilation-perfusion ratios in the lung. In global hypoventilation, 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 rise in blood CO₂ levels. Animals with profound reductions in their drive to breathing, however, do not respond to such stimuli and become hypercapnic. Conditions that may result in central hypoventilation include CNS trauma, neoplasia, infection, inhalant anesthetics, 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 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.⁸⁴ Areas of lung that are ventilated but are ineffectively perfused increase the dead space to tidal volume ratio (V_D/V_T). When a normal breathing pattern shifts to a dyspneic pattern (see Dyspnea section) consisting of very fast respiratory rates and small, inadequate tidal volumes (as that seen in some patients with acute respiratory distress syndrome), the 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 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

Because most clinical signs in animals with respiratory acidosis reflect the underlying disease process responsible for hypercapnia rather than the hypercapnia itself, 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 having 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.⁴² 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, dyspnea (see Dyspnea section) and 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 following acute hypercapnic acidemia.⁸⁰ Hypercapnia stimulates the sympathetic nervous system and causes release of catecholamines.^{11,40} Tachyarrhythmias (including ventricular fibrillation) are common and result from increased sympathetic tone, electrolyte fluctuations, associated hypoxemia, and acidemia.^{17,35,60} 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.⁸¹ 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 vasodilation. Hypercapnia also causes a rightward shift of the oxygen-hemoglobin dissociation curve (see Figure 11-3), promoting unloading of oxygen at the tissues and enhancing oxygen delivery and carrying capacity.⁶⁵

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.⁴³ Respiratory, as well as metabolic, acidosis may also lead to gastroparesis by altering gastric muscle activity and fundic tone.⁷⁷

The nature of the neurologic signs seen depends on the magnitude of hypercapnia, rapidity of change in CO₂ and pH, and the amount of concurrent hypoxemia. Acute hypercapnia causes cerebral vasodilation, subsequently increasing cerebral blood flow and intracranial pressure.^{3,36,54,87} 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.^{1,43,58,80}

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, whereas 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 still be initiated along with supportive therapeutic measures. The primary goal is to remove the CO_2 , and consequently mechanical ventilation is often necessary.

According to the alveolar gas equation, a patient breathing room air at sea level (P_{IO_2} , approximately 150 mm Hg) will develop life-threatening hypoxia ($P_{\text{aO}_2} < 55$ to 60 mm Hg) before life-threatening hypercapnia. Thus supplemental oxygen and assisted ventilation is needed in treating acute respiratory acidosis. Although oxygen therapy may aid in the treatment of acute respiratory acidosis, in patients with chronic hypercapnia, 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 the respiratory acidosis. If oxygen is administered, P_{aO_2} should be kept between 60 and 65 mm Hg because the hypoxic drive to breathing remains adequate up to this level.⁶⁷

In respiratory acidosis, the goals of treatment are to ensure adequate oxygenation and 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 the P_{aCO_2} is more than 50 mm Hg in a nonsedated or nonanesthetized patient, when P_{aO_2} is less than 50 mm Hg with F_{IO_2} of 0.21, or when P_{aO_2} is less than 50 mm Hg with a F_{IO_2} of more than 0.5.⁸ When mechanical or assisted ventilation is begun, care must be taken to decrease P_{aCO_2} slowly. In human patients, rapid decreases in P_{CO_2} can result in cardiac arrhythmias, decreased cardiac output, and reduced cerebral blood flow.⁴³ A sudden decrease in blood P_{CO_2} may also 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,⁵⁷ 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.¹⁷ 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 the development of metabolic alkalosis after P_{aCO_2} has returned to normal. Dogs recovering from chronic hypercapnia and receiving a low-salt diet had persistently increased plasma HCO_3^- levels.⁷⁰ 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 excrete the excess HCO_3^- retained during compensation for chronic hypercapnia.

RESPIRATORY ALKALOSIS

Respiratory alkalosis or primary hypocapnia is characterized by decreased P_{CO_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 P_{CO_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%.²⁴ In dogs and cats, a compensatory decrease of 0.25 mEq/L in HCO_3^- concentration for each 1-mm Hg decrease in P_{CO_2} is expected^{15,28} (see Box 11-2).

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 P_{CO_2} in dogs¹⁵ (see Box 11-2). 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.¹³ Cats chronically exposed to a hypoxic environment ($F_{iO_2} = 10\%$) 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 P_{CO_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 $[H^+]$ 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, $[H^+]$ 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 P_{CO_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.^{23,68} 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

BOX 11-4

Causes of Respiratory Alkalosis

Hypoxemia (Stimulation of Peripheral Chemoreceptors by Decreased Oxygen Delivery)

- Right-to-left shunting
- Decreased P_{iO_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 (ARDS)

Pulmonary Disease (stimulation of Stretch/Nociceptors Independent of Hypoxemia)

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

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

(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 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.^{23,1} In any case, clinical signs in small animals are uncommon due to efficient metabolic compensation and tachypnea may be the only clinical abnormality found, especially with chronic hypocapnia.

If the pH is greater than 7.6 in respiratory alkalosis, neurologic, cardiopulmonary, and metabolic consequences may arise.¹ Such a pH can only 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 ($P_{CO_2} < 25$ 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.^{39,52} 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 oxygen³¹ (see Figure 11-3). However, chronic alkalemia negates this effect by increasing the concentration of 2,3-DPG in red cells.^{30,23,66}

Hypokalemia may occur due to the translocation of potassium into cells and renal and extrarenal losses in patients with acute respiratory alkalosis.^{23,30,66} In anesthetized, hyperventilated dogs, potassium is expected to decrease 0.4 mEq/L for each 10-mm Hg decrease in P_{CO_2} .⁵² Similar changes (0.6 mEq/L for each 10-mm Hg decrease in P_{CO_2}) were observed in awake dogs with acute respiratory acidosis induced by hypoxemia³² or by simulating a high altitude environment (30,000 feet).⁷² Hypokalemia can result in neuromuscular weakness, sensitization to digitalis-induced arrhythmias, polyuria, and increased ammonia production that amplifies the effects of hepatic encephalopathies.¹ However, the hypokalemia induced by respiratory alkalosis is mild and short-lived. Hypokalemia is not present in patients with chronic respiratory alkalosis.^{2,22,25}

TREATMENT OF RESPIRATORY ALKALOSIS

Treatment should be directed towards 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.

DYSPNEA

In small animal practice, dyspnea is an important clinical sign associated with acute or severe respiratory dysfunction and abnormal acid-base regulation. In animals, dyspnea is defined as difficult or labored breathing. However, dyspnea in humans is further described as an unpleasant sensory experience of breathing discomfort or "pain." With the recent advances in veterinary pain recognition and management, it is appropriate to assume veterinary patients have similar negative sensory experiences associated with disorders that result in dyspnea in humans. There are at least three types of dyspnea that are pertinent to veterinary patients: air hunger, increased work of breathing, and thoracic tightness*. Air hunger results from an imbalance in the *perception* of an increased drive to breathe from chemoreceptors (e.g., hypoxemia and hypercapnia) relative to the afferent signaling from stretch receptors in the thoracic cavity and lungs.⁵¹ Although air hunger does not require abnormal arterial concentrations of oxygen or carbon dioxide, it is the balance of the patient's actual alveolar ventilation compared with the ventilation needed to maintain normal acid-base regulation of the patient that determines if dyspnea occurs. A second type of dyspnea occurs with an increased work or effort of breathing. Increased respiratory pressures generated to breathe in the face of decreased pulmonary compliance, airway obstruction, or alterations in respiratory muscle length result in dyspnea.^{21,71} A common example of this type is seen in dynamic upper airway obstructions in which cognitive awareness of the inability to breathe can reach distressing levels. Lastly, in humans, and presumably in animals, asthmatic chest tightness results in dyspnea secondary to bronchoconstriction. The primary afferent signals responsible for this type of dyspnea are generated from intrapulmonary afferent receptors and not respiratory muscle afferents.^{9,45}

Treatment specifically directed at relieving dyspneic sensations associated with respiratory disorders is challenging. Although therapy should initially be directed at removing the inciting cause, newer treatments such

*For review see Mellema, 2008.⁴⁸

as nebulized furosemide,⁵⁶ opioids[†], corticosteroids,⁶¹ and application of chest wall vibration¹⁰ have been suggested to relieve dyspnea and any associated respiratory acid-base disturbances. In any case, the recognition of dyspnea in our veterinary patients as an abnormal, unpleasant stimulus associated with respiratory abnormalities may alter our future medical management of disorders associated with respiratory acid-base abnormalities.

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. More widespread availability of cost-effective, "bedside" portable blood gas analyzers in small animal practice allows the practitioner to monitor 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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[†]For review see: Zebraski et al, 2000.⁸⁸

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