Respiratory Acid–Base Disorders in the Critical Care Unit

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KEYWORDS

• Oxygenation • Ventilation • Blood gas • Potassium • Brain injury

KEY POINTS

- Changes in carbon dioxide tension (P_{CO_2}) can have a variety of physiologic effects; some may be beneficial, while others can cause harm.
- Respiratory acid–base disorders can have particular relevance to specific patient populations, such as those with brain injury.
- Increased P_{CO_2} on venous blood gas analysis can be due to low cardiac output.
- Treatment of most respiratory acid–base abnormalities is based on resolution of the underlying disease.
- Mechanical ventilation is indicated in the management of severe or progressive respiratory acidosis.

INTRODUCTION

There are a variety of causes of respiratory acid–base disorders in critically ill and injured animals, although the incidence of these abnormalities is unknown in veterinary patients and not well described in people. Given the underlying causes for respiratory acid–base disorders, it is likely that they are common in the critical care patient population. The recognition of respiratory acid–base disorders is important from both a diagnostic and therapeutic perspective, emphasizing the role of blood gas evaluation in critical care.

Respiratory acid–base disorders are marked by changes in carbon dioxide tension (P_{CO_2}). The terminology associated with changes in P_{CO_2} can be confusing and lacks standardization. Respiratory acidosis is characterized by an increase in P_{CO_2} above the reference range for that species. The terms hypoventilation, hypercapnia, and hypercarbia are synonymous with respiratory acidosis and can be used

interchangeably. Similarly, a decrease in Pco_2 can be labeled respiratory alkalosis, hyperventilation, hypocapnia, or hypocarbia. For the purpose of this discussion, the terms respiratory acidosis or hypercapnia and respiratory alkalosis or hypocapnia will be used.

CONTROL OF CARBON DIOXIDE TENSION

Arterial Pco_2 is proportional to carbon dioxide production ($\dot{V}CO_2$) and inversely proportional to alveolar minute ventilation ($\dot{V}_A$), as outlined by the following formula:

$$Paco_2 \propto \dot{V}CO_2/\dot{V}_A$$

From this formula, it can be appreciated that changes in Pco_2 can be divided into those that change $\dot{V}CO_2$ and those that change $\dot{V}_A$. Carbon dioxide is a product of cellular metabolism, and steady-state $\dot{V}CO_2$ is related to metabolic rate. In the normal state, the respiratory center of the brain regulates $\dot{V}_A$ in response to changes in $\dot{V}CO_2$ to target a preset Pco_2.[1] Metabolic acid–base abnormalities will override the Pco_2 set point, and the respiratory center will alter $\dot{V}_A$ to change Pco_2 in a manner that will minimize the overall change in extracellular pH. This is known as respiratory compensation for a metabolic acid–base disorder.

Titration of bicarbonate by metabolic acids will also increase the production of CO_2. Hence bicarbonate administration can be a cause of respiratory acidosis if the animal is unable to maintain appropriate increases in $\dot{V}_A$. Carbon dioxide is transported to the alveoli via the pulmonary capillaries, where it is eliminated by $\dot{V}_A$. Alveolar minute ventilation is the product of respiratory rate and the portion of tidal volume that reaches perfused gas exchange units. This can be written as:

$$\dot{V}_A = f \times (V_T - V_D)$$

where f = respiratory frequency; V_T = tidal volume, and V_D = dead space volume.[2] For patients connected to a breathing circuit, such as ventilator patients, increases in the fraction of inspired CO_2 can also be a cause of respiratory acidosis.

Respiratory acid–base disorders are classically identified on arterial blood gas analysis. The reader is reminded that on venous blood gas analysis, decreased cardiac output can cause an increase in venous Pco_2 that does not reflect decreased $\dot{V}_A$.[3,4] As a result, perfusion abnormalities need to be considered as a potential cause of respiratory acidosis when evaluating venous blood gas results.

CLINICAL EFFECTS OF RESPIRATORY ACID–BASE ABNORMALITIES

The clinical effects of respiratory acid–base abnormalities may be due to either the change in Pco_2 or the change in the pH, or both. Investigations into the impact of respiratory acid–base disorders often struggle to separate these 2 effects.

Respiratory Effects

Respiratory acidosis can have fatal consequences as a result of hypoxemia rather than the associated acidemia. Increases in $Paco_2$ reflect an increased alveolar Pco_2, which in turn causes a decrease in alveolar Po_2. If breathing room air, $Paco_2$ greater than 80 mm Hg can cause life-threatening hypoxemia.[5] Oxygen supplementation is recommended in all patients with severe hypercapnia ($Paco_2$ >60 mm Hg). It should be noted that increased venous Pco_2 due to decreased cardiac output will not be a cause of hypoxemia, if $\dot{V}_A$ is adequate. Hypercapnia also has pulmonary effects including bronchodilatation and enhancement of hypoxic pulmonary vasoconstriction.

These changes will improve ventilation/perfusion matching and optimize gas exchange. Respiratory acidosis may also improve oxygen delivery to the tissues by shifting the oxyhemoglobin dissociation curve to the right (Bohr effect).[5,6]

Hypocapnia will have the opposite effects on the respiratory system. It increases Pa_{O_2}, which is a benefit of increasing $\dot{V}_A$ in the face of hypoxemia. It will also be associated with bronchodilatation and inhibition of hypoxic pulmonary vasoconstriction. Respiratory alkalosis will shift the oxyhemoglobin curve to the left, potentially decreasing tissue oxygen delivery.[5,6]

Nervous System

Neurologic effects of abnormal P_{CO_2} are primarily described with relevance to hypercapnia. Respiratory acidosis can have several effects on the nervous system including changes in cerebral blood flow, changes in neuronal function, alterations in consciousness, and seizures.[1] Increases in P_{CO_2} will cause cerebral vasodilatation, increased cerebral blood flow, and may potentiate intracranial hypertension in at-risk animals. In contrast, hypocapnia will cause cerebral vasoconstriction and decreases in intracranial pressure. Severe hypercapnia can cause obtundation, and loss of consciousness (hypercapnic narcosis) can occur at Pa_{CO_2} greater than 90 to 120 mm Hg.[1,7]

Cardiovascular System

The effect of respiratory acidosis on the cardiovascular system may be unpredictable. Hypercapnia causes an increase in catecholamine release leading to systemic vasoconstriction and increased cardiac output, while acidemia may impair cardiac contractility and promote vasodilatation.[1,8] The net effect on the cardiovascular system may be minimal.

Electrolyte Changes

Acidemia can impact the concentrations of extracellular fluid potassium and ionized calcium. Respiratory acidosis and some forms of metabolic acidosis will promote potassium ion translocation from the intracellular space to the extracellular space, in exchange for hydrogen ions.[9] Changes in pH can also alter blood ionized calcium concentration. Free ionized calcium exists in equilibrium with a pool of calcium bound to albumin. With acidemia, such as respiratory acidosis, more ionized calcium is released from albumin, and the free (measured) ionized calcium concentration will increase. Respiratory alkalosis will cause a decreased ionized calcium concentration.[10]

Immunomodulatory Effects

Respiratory acidosis alters immune function through several mechanisms including impairment of white blood cell migration and phagocytosis and inhibition of proinflammatory cytokine release.[11,12] It is yet to be determined if these effects result in a net benefit or net harm to the patient. Preliminary investigations suggest that the influence of respiratory acidosis on the immune system may vary depending on the nature and severity of the primary disease process.[13]

SPECIFIC CLINICAL SCENARIOS IN THE CRITICAL CARE UNIT
Brain Disease

Carbon dioxide should be monitored frequently in animals with severe brain disease, as they can lose central control of ventilation and be at risk of hypercapnia or hypocapnia. As changes in P_{CO_2} can alter cerebral blood flow, it can be of great clinical significance in these patients. Hypercapnia can have devastating consequences in patients with intracranial hypertension, and control of P_{CO_2} by mechanical ventilation may be

indicated. Therapeutic hypocapnia (also known as therapeutic hyperventilation) has been used to treat life-threatening intracranial hypertension. It may be an option to salvage a patient not responding to therapy, but it is a temporary measure, and more definitive treatment will be required. Studies in people have associated therapeutic and spontaneous hypocapnia with brain ischemia and poor clinical outcomes in brain-injured patients, and the role of hypocapnia in brain injury remains controversial. Current clinical practice guidelines for people support the use of transient therapeutic hypocapnia for intracranial hypertension, but recommend against hyperventilation to Pa_{CO_2} less than 25 mm Hg.[14]

Mechanical Ventilation

Specific mechanical ventilation protocols developed for people with acute respiratory distress syndrome (ARDS), known as lung-protective ventilation, are based on small tidal volumes and moderate-to-high positive end expiratory pressure. This approach limits $\dot{V}_A$ and is associated with development of respiratory acidosis. As the benefits of this ventilation protocol are often considered to outweigh the potential adverse effects of respiratory acidosis, a higher Pa_{CO_2} may be tolerated in these patients. This is known as permissive hypercapnia. There is some suggestion in the literature that permissive hypercapnia may provide an outcome benefit in ARDS patients, although more investigation is required to better evaluate this issue. Currently, permissive hypercapnia is a common component of ventilation strategies for people with ARDS, asthma, and chronic obstructive airway disease.[12,15]

RESPIRATORY ACIDOSIS

Respiratory acidosis occurs when $\dot{V}_A$ is inadequate relative to $\dot{V}_{CO_2}$. It can be a primary acid–base disorder or occur as compensation for metabolic alkalosis. Specific studies of respiratory acidosis in the small animal critical care setting are lacking. In a population of 624 dogs that had venous blood gas analysis on presentation to an emergency room, 5% had primary respiratory acidosis, and 16% had respiratory acidosis as part of a mixed acid–base disorder (Hopper, unpublished data, 2015). These results suggest respiratory acidosis maybe less common than respiratory alkalosis.

   Causes of respiratory acidosis are outlined in **Box 1**. In the CCU, abnormalities in $\dot{V}_A$ are of particular concern. Sedative and anesthetic drug administration is common in these patients, and monitoring of P_{CO_2} is advised when drugs known to cause respiratory depression are used, especially in higher doses, such as animals on high-dose fentanyl constant rate infusions. Respiratory muscle fatigue can occur in any animal with sustained increased respiratory rate and effort. In the author's experience, hypercapnia secondary to respiratory muscle fatigue from severe pulmonary parenchymal disease such as pneumonia is a common clinical scenario. This may be indicative of respiratory failure and can be a warning sign of impending respiratory arrest.

Diagnostic Approach

In the management of CCU patients, there are 2 aspects to the diagnosis of respiratory acidosis. The first is recognition of patients in which P_{CO_2} should be monitored in the event that respiratory acidosis develops. These include all the patients that are described in **Box 1**. In addition, P_{CO_2} monitoring is recommended for any critically ill patient, as numerous changes associated with severe systemic disease have the potential to impact P_{CO_2}. Furthermore, P_{CO_2} monitoring should be frequent, as $\dot{V}_A$ can be dynamic. If venous blood gases are being monitored, changes in P_{CO_2} may also reflect sudden changes in cardiac output.[3,4] In additional to blood gas analysis, continuous

Box 1
Causes of respiratory acidosis

Compensation for metabolic alkalosis

Increased inspired CO_2
- Animals on a breathing circuit

Decreased alveolar minute ventilation
- Central respiratory depression
  ○ Drugs (eg, opioids)
  ○ Brain disease
- Cervical spinal cord injury
- Neuromuscular disease
- Respiratory muscle fatigue
- Obstructive airway disease

Increased CO_2 production
- Sepsis
- Malignant hyperthermia
- Thyroid crisis
- Overfeeding
- Sodium bicarbonate administration
- Citrate anticoagulation

Venous blood gas
- Decreased cardiac output

end tidal CO_2 monitoring is recommended in any intubated patient. Once respiratory acidosis has been identified, the second aspect of diagnosis is to determine the underlying cause. Consideration of the history, signalment, and physical examination should indicate the diagnosis in most cases.

Treatment of Respiratory Acidosis

As previously mentioned, supplemental oxygen is indicated in patients with significant hypercapnia (Pa_{CO_2} >60 mm Hg). Resolution of respiratory acidosis is primarily focused on resolution of the underlying disease, whenever possible. If the primary disease has no specific therapy or clinical improvement is likely to be slow, consideration for the respiratory stability of the patient is important. If the cause of respiratory acidosis is a mechanism of inadequate $\dot{V}_A$ (see **Box 1**), respiratory failure may be a concern, and mechanical ventilation may be indicated. Patients with respiratory acidosis from other causes may be managed with supplemental oxygen alone in many circumstances. As a general guideline, for respiratory acidosis of any cause, if it is severe (Pa_{CO_2} >60 mm Hg), sustained, or progressive in nature, mechanical ventilation to maintain appropriate $\dot{V}_A$ is indicated.

If respiratory acidosis has been of sufficient duration to allow substantial metabolic compensation to occur, it will be accompanied by a significant increase in serum bicarbonate concentration. If the respiratory acidosis is rapidly resolved with therapy, the patient will be left with a metabolic alkalosis, as renal excretion of bicarbonate will take hours to days to achieve.[16]

RESPIRATORY ALKALOSIS

Respiratory alkalosis occurs when carbon dioxide elimination ($\dot{V}_A$) is excessive relative to $\dot{V}_{CO_2}$.

It can be a primary acid–base disorder or occur as compensation for a metabolic acidosis. Common causes of hypocapnia include many common disease states in critically ill animals (**Box 2**) suggesting that respiratory alkalosis occurs frequently. This is supported by an evaluation of a population of 624 dogs that had venous blood gas analysis on presentation to an emergency room, in which 10% had primary respiratory alkalosis, and 51% had respiratory alkalosis as part of a mixed acid–base disorder (Hopper, unpublished data).

Increased $\dot{V}_A$ is the most likely mechanism of respiratory alkalosis (see **Box 2**). Decreased $\dot{V}CO_2$ is unlikely to occur, and, if the animal has appropriate respiratory control, $\dot{V}_A$ should be decreased accordingly to maintain a normal P_{CO_2}. Alveolar minute ventilation will be increased in response to severe hypoxemia (Pa_{O_2} <60 mm Hg) via chemoreceptor stimulation.[2] Pulmonary diseases such as pneumonia, edema, and fibrosis can also stimulate increases in $\dot{V}_A$ without severe hypoxemia. Other causes of increased $\dot{V}_A$ occur through peripheral chemoreceptor stimulation or direct stimulation of the central respiratory center.

Diagnostic Approach

Many CCU patients should have P_{CO_2} monitored, as discussed in the respiratory acidosis section. Blood gas analysis in respiratory distress patients is particularly important when considering respiratory alkalosis. When respiratory alkalosis is identified, concurrent evaluation of oxygenation with arterial blood gas or pulse oximetry measurement is recommended. **Box 2** outlines the major causes of respiratory alkalosis.

Treatment of Respiratory Alkalosis

In general, there is no specific treatment for respiratory alkalosis. Recognition of hypocapnia is important as a diagnostic and monitoring tool, and therapy is focused on resolution of the primary disease. Spontaneous hypocapnia in human brain-injured patients has been associated with greater severity of injury and higher mortality, although the role of interventions to normalize P_{CO_2} in these patients has yet to be defined.[17]

Box 2
Causes of respiratory alkalosis

Compensation for metabolic acidosis

Increased alveolar minute ventilation
- Hypoxemia
- Pulmonary disease
- Low cardiac output
  ○ Hypovolemic shock, cardiogenic shock
- Pain and anxiety
  ○ Not a consistent cause of respiratory alkalosis
- Central respiratory stimulation
  ○ Mass lesion, meningitis
- Sepsis
- Drugs
  ○ Salicylates

Decreased CO_2 production
- Extremely unlikely to occur clinically

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