Secondary Responses to Altered Acid-Base Status: The Rules of Engagement

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ABSTRACT

Each of the four canonical acid-base disorders expresses as a primary change in carbon dioxide tension or plasma bicarbonate concentration followed by a secondary response in the countervailing variable. Quantified empirically, these secondary responses are directional and proportional to the primary changes, run a variable time course, and tend to minimize the impact on body acidity engendered by the primary changes. Absence of an appropriate secondary response denotes the coexistence of an additional acid-base disorder. Here we address the expected magnitude of the secondary response to each cardinal acid-base disorder in humans and offer caveats for judging the appropriateness of each secondary response.

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The physiologic approach to acid-base disorders views blood pH as determined by the prevailing levels of carbonic acid ($Paco_2$, the respiratory component) and plasma bicarbonate concentration ($[HCO_3^-]$, the metabolic component), as stipulated by the Henderson equation, $[H^+] = 24 \times Paco_2/[HCO_3^-]$.[1] The four canonical acid-base disorders include the respiratory disorders (acidosis and alkalosis) and the metabolic disorders (acidosis and alkalosis). Whereas the respiratory disorders are expressed as primary changes in $Paco_2$, the metabolic disorders are expressed as primary changes in plasma $[HCO_3^-]$.[2,3]

Each primary change in either the respiratory or the metabolic component elicits *in vivo* a secondary response in the countervailing component that is directional and proportional to the primary change, albeit fractionally smaller, thus tending to minimize the change in body acidity. These secondary responses originate from physicochemical buffering and change in ventilation, organic-acid metabolism, and renal acidification. They have been quantified in dogs and humans, are consistent in presence and predictable in magnitude, and are viewed as an integral part of each canonical disorder. Absence of an appropriate secondary response denotes the coexistence of an additional acid-base disturbance.[1–3]

A popular, alternative epithet of the secondary responses is compensatory. We discourage use of this term, because it evokes confusing pronouncements about partial *versus* complete compensation; secondary responses generally ameliorate the impact of primary changes on blood acidity but never completely restore blood acidity to control levels. Moreover, under certain circumstances, secondary responses yield a maladaptive effect on blood pH (see next section).[1,3] We term the secondary responses to respiratory acidosis (primary increase in $Paco_2$) and respiratory alkalosis (primary decrease in $Paco_2$) secondary hyperbicarbonatemia and secondary hypobicarbonatemia, respectively. The alternative terms secondary or compensatory metabolic alkalosis and secondary or compensatory metabolic acidosis, respectively, are also confusing and objectionable. Similarly, the secondary responses to metabolic acidosis (primary decrease in plasma $[HCO_3^-]$) and metabolic alkalosis (primary increase in plasma $[HCO_3^-]$) are termed secondary hypocapnia and secondary hypercapnia, respectively; we discourage use of the alternative terms secondary or compensatory respiratory alkalosis and secondary or compensatory respiratory acidosis, respectively.[3]

MAGNITUDE AND TIME COURSE OF THE SECONDARY RESPONSES

Here we examine the mean slope of the secondary response to each cardinal acid-base disorder (Table 1) and the time interval required for each secondary response to reach completion. Toward this end, we reviewed all available human

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Table 1. Secondary responses to alterations in acid-base status

Disorder	Primary Change	Secondary Response	Mean Slope of the Secondary Response
Respiratory acidosis	$\uparrow Pa_{CO_2}$	$\uparrow [HCO_3^-]$	
acute			$\Delta[HCO_3^-]/\Delta Pa_{CO_2} = 0.1$ mEq/L per mmHg
chronic			$\Delta[HCO_3^-]/\Delta Pa_{CO_2} = 0.35$ mEq/L per mmHg
Respiratory alkalosis	$\downarrow Pa_{CO_2}$	$\downarrow [HCO_3^-]$	
acute			$\Delta[HCO_3^-]/\Delta Pa_{CO_2} = 0.2$ mEq/L per mmHg
chronic			$\Delta[HCO_3^-]/\Delta Pa_{CO_2} = 0.4$ mEq/L per mmHg
Metabolic acidosis	$\downarrow [HCO_3^-]$	$\downarrow Pa_{CO_2}$	$\Delta Pa_{CO_2}/\Delta[HCO_3^-] = 1.2$ mmHg per mEq/L
Metabolic alkalosis	$\uparrow [HCO_3^-]$	$\uparrow Pa_{CO_2}$	$\Delta Pa_{CO_2}/\Delta[HCO_3^-] = 0.7$ mmHg per mEq/L

The term "acute" refers to a duration of minutes to several hours. The term "chronic" refers to a duration of several days or longer.

studies for each disorder and weighed study design, methods, and evidence of a steady state. One can think of these as general rules for secondary responses. Because of space constraints, we cite only limited references.

Respiratory Acidosis

Hypercapnia acidifies body fluids and titrates nonbicarbonate buffers, yielding a small increase in plasma $[HCO_3^-]$. This secondary hyperbicarbonatemic response is completed within 5 to 10 minutes and remains stable for several hours. Observations in unanesthetized normal humans studied in an environmental chamber (inspired CO_2 7 and 10%) reveal a mean $\Delta[HCO_3^-]/\Delta Pa_{CO_2}$ slope of 0.1 mEq/L per mmHg; expected $[HCO_3^-] = 24 + [(\text{current } Pa_{CO_2} - 40) \times 0.1]$.[4] An essentially identical slope is obtained in humans in whom respiratory acidosis is induced by endogenous hypercapnia.[5]

Sustained hypercapnia causes an additional, larger increase in plasma $[HCO_3^-]$ owing to stimulation of renal acidification. In dogs, a new steady state emerges within 3 to 5 days.[6,7] Whether this temporal pattern applies to humans is unknown. In patients, chronic hypercapnia often reflects gradual deterioration in pulmonary function; consequently, the secondary response might keep pace with the slowly rising Pa_{CO_2} without a perceptible delay. Careful observations of patients with chronic hypercapnia as a result of chronic obstructive pulmonary disease allowed estimation of a mean $\Delta[HCO_3^-]/\Delta Pa_{CO_2}$ slope of 0.35 mEq/L per mmHg; expected $[HCO_3^-] = 24 + [(\text{current } Pa_{CO_2} - 40) \times 0.35]$. This slope functions up to a Pa_{CO_2} of approximately 70 mmHg. Beyond that level, the slope of $\Delta[HCO_3^-]/\Delta Pa_{CO_2}$ seems to flatten.[8,9] More recently, a substantially larger slope was reported, but the small number of blood gas measurements, one for each of 18 patients, calls into question the validity of the conclusion reached.[10]

Respiratory Alkalosis

Hypocapnia alkalinizes body fluids and titrates nonbicarbonate buffers, yielding a decrease in plasma $[HCO_3^-]$. This secondary hypobicarbonatemic response is completed within 5 to 10 minutes and remains stable for several hours. Hypocapnia of 20 to 120 minutes' duration resulting from either voluntary hyperventilation in normal individuals or controlled hyperventilation in anesthetized patients undergoing minor surgical procedures yielded a mean $\Delta[HCO_3^-]/\Delta Pa_{CO_2}$ slope of 0.2 mEq/L per mmHg; expected $[HCO_3^-] = 24 - [(40 - \text{current } Pa_{CO_2}) \times 0.2]$.[11,12]

Sustained hypocapnia causes an additional decrease in plasma $[HCO_3^-]$ owing to suppression of renal acidification. A new steady state emerges within 2 to 3 days.[13,14] Studies of normal volunteers who were exposed to hypobaric hypoxia (6 days) and unanesthetized patients who had spinal cord or head injuries and were undergoing controlled hyperventilation (7 to 11 days) revealed a mean $\Delta[HCO_3^-]/\Delta Pa_{CO_2}$ slope of 0.4 mEq/L per mmHg; expected $[HCO_3^-] = 24 - [(40 - \text{current } Pa_{CO_2}) \times 0.4]$.[14,15]

Metabolic Acidosis

Primary hypobicarbonatemia engenders acidemia that stimulates central and peripheral chemoreceptors, causing increases in tidal volume and, usually, respiratory rate. This secondary hypocapnic response consistently attends metabolic acidosis, whether induced in normal volunteers who are administered ammonium chloride or observed in patients with various disorders, such as diarrhea, disturbances of intermediary metabolism, or renal failure. Although the magnitude of the ventilatory response varies considerably among studies, it seems to be independent of the cause of the acidosis. Compiling most published studies, a mean $\Delta Pa_{CO_2}/\Delta[HCO_3^-]$ slope of 1.2 mmHg per mEq/L is obtained; expected $Pa_{CO_2} = 40 - [(24 - \text{current } HCO_3) \times 1.2]$.[16–20]

The secondary response appears within 30 to 120 minutes from onset of metabolic acidosis; the time interval for its completion (and its disappearance after correction of the metabolic acidosis) depends on the pace of development of the disorder.[21,22] In patients with cholera, when plasma $[HCO_3^-]$ falls or corrects slowly, such as by 6 mEq/L in 24 hours, the ventilatory response keeps pace with the level of plasma $[HCO_3^-]$. Conversely, when metabolic acidosis develops or corrects rapidly, 11 to 24 hours is required for the ventilatory response to reach completion or vanish.[16]

Metabolic Alkalosis

Contrary to the wide recognition of metabolic acidosis–induced secondary hypocapnia, the very existence of secondary hypercapnia in response to metabolic alkalosis is controversial.[23,24] Absence of hypercapnia in some early studies can be traced to methodologic problems and inclusion of patients who have disorders that stimulate ventilation.[23] In addition, confusion arises from the seemingly paradoxic stimulation of ventilation observed during rapid intravenous infusion of sodium bicarbonate, a model of acute metabolic alkalosis; this hyperventilatory response, caused by decomposition of bicarbonate into CO_2, is short-lived and converts to alkalemia-induced hypoventilation.[25]

Subsequent studies established that the alkalemia engendered by metabolic alkalosis consistently suppresses alveolar ventilation, an effect primarily caused by

reduction in tidal volume. Observations of humans with metabolic alkalosis owing to diuretic use, vomiting, or gastric suction yielded a mean $\Delta Paco_2/\Delta[HCO_3^-]$ slope of 0.7 mmHg per mEq/L; expected $Paco_2 = 40 + [(\text{current } HCO_3 - 24) \times 0.7]$.[23,26] Contrary to early views, neither hypoxemia nor potassium depletion prevents expression of this response. The requisite time for development of the secondary hypercapnia remains uncertain. Although studies indicate that full expression of the hypoventilatory response requires 24 to 36 hours, such a lag might not occur in patients who develop metabolic alkalosis at a slow pace.

CAVEATS

In assessing the appropriateness of the secondary response to an acid-base disorder, there are several caveats.

Time Course

As noted, considerable uncertainty exists regarding the time course for completion and eradication of the secondary responses in humans. A mixed acid-base disorder might be diagnosed incorrectly because insufficient time has elapsed for the secondary response to a single primary disorder to develop or resolve.[3]

Confidence Intervals

Empirical data have been used to construct confidence intervals that define the limits of the secondary response to each acid-base disorder. In clinical practice, these limits can be taken as ±3 mEq/L for plasma $[HCO_3^-]$ and ±5 mmHg for $Paco_2$ from the values calculated from the mean, steady-state slopes (Table 1).[3] Values falling outside these limits denote the presence of a mixed acid-base disorder. Importantly, values falling within the limits of the secondary response can be interpreted as consistent with but not diagnostic of a particular disorder. In fact, a given set of acid-base values is never diagnostic of a specific acid-base disorder; clinical correlation is always required to establish the correct diagnosis. Interpretation of acid-base data of patients undergoing ventilator support must consider that this procedure sets the $Paco_2$ level and thus has the potential of altering preexisting acid-base status, whether normal or abnormal.[1]

Impact of Preexisting Acid-Base Disorders

Clinicians tend to apply equally the slopes depicted in Table 1 to patients presumed to have a single acid-base disorder and those with mixed disorders. This practice assumes preexisting acid-base disorders do not influence the secondary response to superimposed disorders. Extensive studies of the dog demonstrate this supposition is largely erroneous. The $\Delta[HCO_3^-]/\Delta Paco_2$ response to acute hypercapnia in dogs with background metabolic acidosis or chronic respiratory alkalosis is larger than that in normal animals, whereas this response is smaller than normal in dogs with preexisting metabolic alkalosis or chronic respiratory acidosis.[27,28] Similarly, the $\Delta[HCO_3^-]/\Delta Paco_2$ response to chronic respiratory acidosis is larger in dogs with underlying metabolic acidosis and smaller in those with background metabolic alkalosis than in normal dogs.[29,30] Normal dogs and dogs with background metabolic acidosis have an identical secondary response to chronic hypocapnia, but this response is much larger in dogs with underlying metabolic alkalosis.[13,31,32] It is highly probable but still unknown whether humans exhibit a similar response to that demonstrated in dogs. Consequently, the direct applicability of the slopes depicted in Table 1 to patients with mixed acid-base disorders is uncertain.

Hybrid Nature of Plasma $[HCO_3^-]$ in Metabolic Disorders

It is generally assumed that changes in $Paco_2$ that attend metabolic disorders have no impact on plasma $[HCO_3^-]$ other than the small change occurring as a consequence of buffering; however, this formulation assumes that the kidney has a way to discriminate between primary and secondary changes in $Paco_2$, mounting a vigorous acidification response to the former, as reflected in the $\Delta[HCO_3^-]/\Delta Paco_2$ slopes of chronic respiratory alkalosis and chronic respiratory acidosis (Table 1) but remaining indifferent to the latter. This formulation proves fallacious in studies of dogs with metabolic acidosis or metabolic alkalosis, in which the kidney elicits major acidification responses to the prevailing

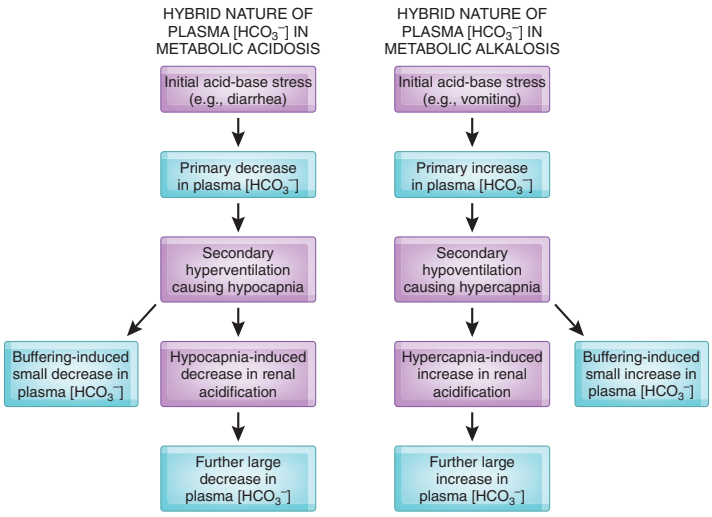

Figure 1. Pathophysiologic basis of the change in plasma $[HCO_3^-]$ in metabolic acidosis (left) and metabolic alkalosis (right) in the dog. Only a part of the change in plasma $[HCO_3^-]$ is attributed to the primary metabolic process. The remainder, approximately 40% of the overall change, is due to adjustments in renal acidification engendered by the associated secondary hypocapnia or hypercapnia. These renal responses are maladaptive because they undermine the salutary effect on blood pH afforded by the ventilatory responses acutely. Based on data from Madias and colleagues.[30,33]

secondary hypocapnia or hypercapnia. Indeed, fully 40% of the overall change in plasma [HCO_3^-] in metabolic disorders results not from the metabolic processes themselves, particularly the acid load in metabolic acidosis or volume and Cl^- deficits in metabolic alkalosis, but from the indiscriminant responses of the kidney to secondary changes in Pa_{CO_2} (Figure 1).[30,33] These renal responses are maladaptive because they undermine the salutary effect on blood pH afforded by the ventilatory responses acutely. Indeed, under certain conditions, this maladaptation nullifies a beneficial impact or even yields a more abnormal pH than would occur in the complete absence of a ventilatory response. The similarity of the acidification processes between dogs and humans suggests strongly that these observations are also applicable to humans; however, until the requisite studies are carried out, such extrapolations must remain conjectural.

DISCLOSURES

None.

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