A REVIEW

Ventilatory and Metabolic Compensation in Dogs With Acid-Base Disturbances

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Summary

Ventilatory and metabolic compensation to acid-base disturbances is reviewed. The mechanisms for compensation as well as the values obtained from several studies using normal dogs and dogs with experimentally induced diseases are provided. Compensation is not the same in dogs and human beings. Dogs have a better ability to adapt to most respiratory disorders, and human beings adapt better to metabolic acidosis. In metabolic alkalosis and chronic respiratory acidosis there is no difference in compensation between these species. Ventilatory compensation for metabolic disorders in dogs is the same whether they have metabolic acidosis or metabolic alkalosis, whereas metabolic compensation in respiratory disturbances is less effective in acidosis. Values for the expected changes in PCO_2 in dogs with metabolic acidosis and metabolic alkalosis, and for bicarbonate concentration (HCO_3–) in dogs with acute and chronic respiratory alkalosis and acidosis are presented.

Key Words: dogs, respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis

Introduction

According to one hypothesis of acid-base regulation, the body maintains acid-base balance by inducing changes in strong ion difference (SID) and carbon dioxide pressure (PCO_2).[1-3] Strong ions are substances that are completely dissociated at body pH. The most important strong ions in plasma are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, lactate, β-hydroxybutyrate, acetoacetate, and SO_42-. The influence of strong ions on pH and the HCO_3– concentration (HCO_3–) can always be expressed in terms of the difference between strong cations and strong anions.[1-3] Strong ion difference can be estimated clinically by: $Na^+ + K^+ - Cl^-$. The principal ions involved in acid-base physiology are expressed in this equation. Organic strong anions, however, are not included in this formula, and therefore, it has been called the inorganic SID (SID_i).[2]

Three independent variables exist in acid base physiology. Independent variables in any system are those that can be directly altered from outside the system, without affecting one another. In arterial blood plasma, PCO_2 can be independently changed from outside the system by changes in alveolar ventilation.[4] The SID also can be changed independently from outside the system (by reabsorption of Cl^- in the renal tubules). The third independent variable in plasma is the total concentration of nonvolatile weak acids, the sum of

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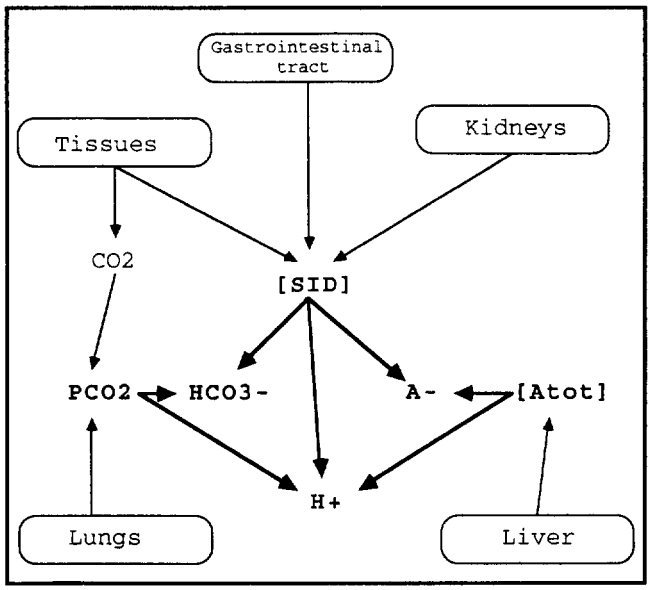

FIG. 1 – Determinants of SID, PCO_2, and A_{TOT}, and the dependent variables H^+, HCO_3–, and A^-.

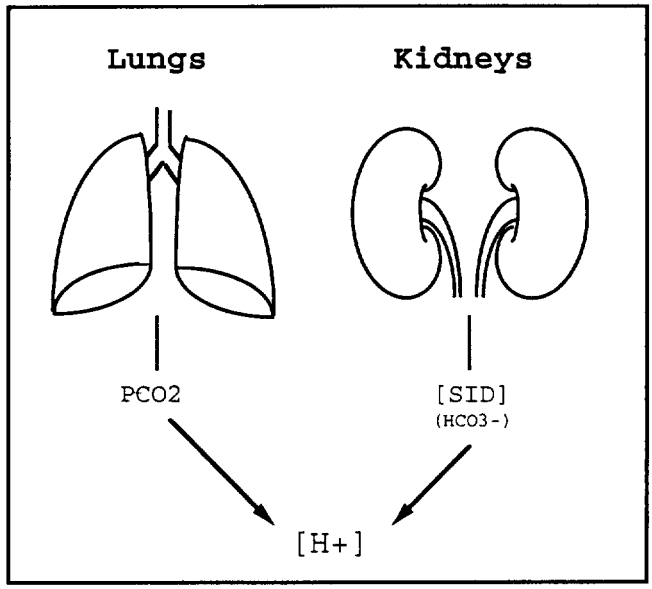

FIG. 2 – Principal organs involved in long-term regulation of acid-base status. Kidneys regulate SID whereas lungs regulate PCO_2.

the dissociated and nondissociated forms (A_{TOT} = A^- + HA). The main components of A_{TOT} in plasma are plasma proteins (> 95% of A_{TOT}) and inorganic phosphate (Pi_{TOT} = PO_32- + HPO_42- + H_2PO_4- + H_3PO_4). All other variables, H^+, pH, HCO_3–, and total concentration of nonvolatile weak acids in a dissociated form (A^-), are dependent variables and can only change when one or more of the independent variables change. The principal determinants of the independent variables are presented in Figure 1.

Each primary acid-base disturbance is accompanied by a secondary change in the opposing component of the system and this change returns the pH toward normal. This compensation is due to changes in alveolar ventilation (and consequently PCO_2) in metabolic acid-base disturbances, and by transmembrane changes in strong ions in erythrocytes and renal tubular cells changing plasma SID (and consequently HCO_3–) during respiratory acid-base disturbances (Fig. 2). The anticipated compensation in primary acid-base disorders is presented in Table 1. The lungs control PCO_2 by alveolar ventilation and by changing PCO_2 may alter H^+ within minutes to prevent potentially detrimental pH changes in metabolic acidosis. The kidneys control SID by epithelial transport of strong ions, primarily Na^+ and Cl^-. The response of the kidneys is relatively slow compared to that of the lungs, requiring 2 to 5 days for maximal effect. The gastrointestinal (GI) tract also may alter plasma SID both in physiologic and pathologic states. Gastrointestinal alterations in SID, however, are a consequence of primary GI functions or disease states and are not directly concerned with acid-base regulation.

TABLE 1
Primary and Secondary Changes in Simple Acid-Base Disorders

Primary Disorder	Compensatory Response
Metabolic Acidosis ⇓ HCO_3–	Respiratory Alkalosis ⇓ PCO_2
Metabolic Alkalosis ⇑ HCO_3–	Respiratory Acidosis ⇑ PCO_2
Respiratory Acidosis ⇑ PCO_2	Metabolic Alkalosis ⇑ HCO_3–
Respiratory Alkalosis ⇓ PCO_2	Metabolic Acidosis ⇓ HCO_3–

Knowledge of the normal compensatory response is important in clinical assessment of patients with acid-base disorders. In many situations, the distinction between a simple and mixed acid-base disorder cannot be made without this knowledge, and important complications of the primary disease process can be overlooked. Unfortunately, compensatory responses in dogs with respiratory and metabolic acid-base disorders often are predicted based on values used clinically in human medicine and based on the assumption that the "response curves of man and dogs are sim-

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ilar."[5] Recently, an expected range of compensation for dogs with acid-base disorders was proposed based on review of a limited number of reports.[6] The purpose of this review is to further evaluate the expected range of compensation for acid-base disorders in normal dogs with experimentally induced acid-base disturbances.

Metabolic Disorders

METABOLIC ACIDOSIS

The kidneys increase net acid excretion (primarily by enhanced $NH_4 + Cl^-$ excretion) in metabolic acidosis, beginning on Day 1 of the disturbance and reaching a maximal response after 5 to 6 days.[7] An increase in Cl^- excretion without an increase in Na^+ excretion increases plasma SID and returns HCO_3- and H^+ toward normal. A compensatory decrease in PCO_2 will occur because the resulting increase in H^+ will stimulate the respiratory centers in the central nervous system to increase ventilation. The initial response is mediated by peripheral chemoreceptors, whereas the complete response must await an increase in H^+ in the cerebrospinal fluid (CSF) (H^+_{CSF}).[8] Complete respiratory compensation will not occur until Cl^- is exchanged across the blood brain barrier, thus altering SID in the CSF.[9] This exchange is not complete before 14 to 17 hours.[9]

Metabolic acidosis has been produced experimentally in dogs by supplementation of the diet with strong anions (e.g., NH_4Cl, HCl, H_2SO_4) or administration of acetazolamide, which causes Cl^- retention.

HCl and NH_4Cl Models. Addition of HCl to the diet is a well-recognized method of promoting metabolic acidosis in dogs. Despite a wide range of dosages, the results are very consistent. The amount of HCl added to the diet has varied from 2.0 mEq/kg[10,11] to 10.0 mEq/kg[12] daily. The most commonly used dose has been 7.0 mEq/kg,[13-21] with some studies using more than one dose.[10,11,14]

Metabolic acidosis also has been produced experimentally by administering NH_4Cl at a dosage of 10 mEq/kg daily[22-24] or 186 mEq daily (an average of 6.6 mEq/kg).[25] Apparently, no difference exists between the degree of metabolic acidosis obtained using NH_4Cl or HCl in human beings,[26] and results obtained using NH_4Cl can be compared with those obtained using HCl.

Chronic studies in dogs fed a diet containing HCl suggest a variable decrease in PCO_2 for each 1 mEq/L fall in HCO_3-. The decrement in PCO_2 ranged from 0.5[11] to 1.1,[14] with most authors reporting values between 0.6 and 0.8.[10,13-21,27-29] When NH_4Cl was used to produce metabolic acidosis instead of HCl, PCO_2 decreased 0.5[30] to 0.6[24] mm Hg for each mEq/L decrease in HCO_3-.[24] Based on this data, the expected decrease in PCO_2 in dogs with metabolic acidosis may be estimated as 0.7 mm Hg for each 1 mEq/L decrease in HCO_3-.

The H^+ increased 1.25 to 2.2 nEq/L for each mEq/L decrease in HCO_3- in dogs with metabolic acidosis produced by HCl[10,13-21,27-29] or NH_4Cl.[24,30] The change in H^+ fell outside of this range in only one study in which HCl was used.[11]

Other Models. Chronic hyperchloremic acidosis has been induced in dogs using acetazolamide.[31,32] The PCO_2 decreased 0.9 mm Hg for each 1 mEq/L decrease in HCO_3- when acetazolamide was given intramuscularly every 8 hours to dogs at a dosage of 10 mg/kg,[32] but decreased 0.6 mm Hg when acetazolamide was given orally at a dosage of 7.1 mg/kg every 8 hours.[31] The H^+ increased 1.6[32] to 2.0[31] nEq/L for each 1 mEq/L decrease in HCO_3-.

Metabolic acidosis induced by chronic administration of amiloride in nonadrenalectomized dogs and in adrenalectomized dogs supplemented with glucocorticoids and mineralocorticoids has been studied.[33] The administration of 2 mg/kg of amiloride for 9 days in nonadrenalectomized dogs caused hyperchloremic acidosis. The compensatory response in this setting was characterized by a 0.8 mm Hg decrease in PCO_2 for each 1 mEq/L decrease in HCO_3-.[33] The H^+ increased 1.4 nEq/L for each 1 mEq/L decrease in HCO_3-.[33]

Both HNO_3[14,21] and H_2SO_4[14,29] have been used to produce metabolic acidosis in dogs. Hydrogen ion concentration and HCO_3- did not change significantly when HNO_3 was used at 7.0 mEq/kg/day in dogs.[14] Renal net acid excretion, however, was increased.[14] In a subsequent study, however, HNO_3 caused a significant decrease in HCO_3- and H^+ 3 hours after feeding. These parameters gradually returned to baseline within 24 hours.[21] Experimental metabolic acidosis induced by feeding 5 to 7 mEq/kg/day of H_2SO_4 caused a decrease in PCO_2 of 1.8 mm Hg for each 1 mEq/L decrease in HCO_3- in one study[29] and no change in PCO_2 in another study where dogs also were fed a NaCl-deficient diet.[14]

Metabolic acidosis also has been induced in adrenalectomized dogs supplemented with glucocorticoids, but not with mineralocorticoids.[34,35] In both studies, PCO_2 decreased 0.7 mm Hg and the H^+ increased 1.3 nEq/L for each 1 mEq/L decrease in HCO_3-.

METABOLIC ALKALOSIS

The normal response of the body is to decrease SID and increase PCO_2 during metabolic alkalosis.[8] The

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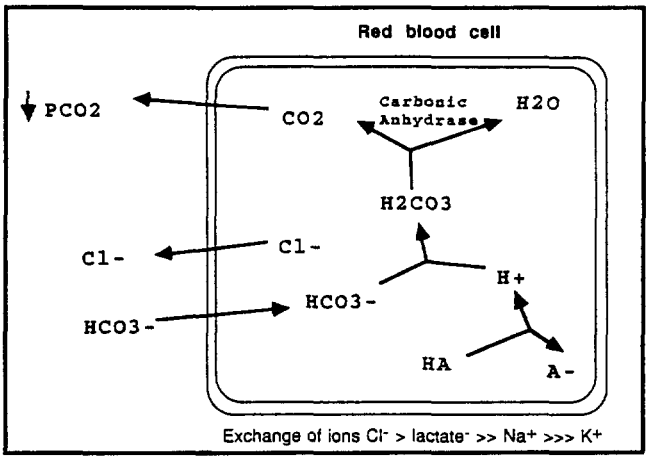

FIG. 3 – Compensation for acute respiratory alkalosis.

cellular response is limited because intracellular Cl^- is low.[8] A decrease in ventilation is observed in patients with hypochloremic alkalosis and is believed to result from an adjustment in the ionic composition of CSF with a consequent decrease in H^+_{CSF}.[4,8,9] The time course for the development of respiratory compensation in plasma following the onset of hypochloremic alkalosis and the time course of its disappearance after correction corresponds to the turnover rate of cerebral fluids.[4,9]

The most commonly used methods for creating metabolic alkalosis in dogs are induction of Cl^- depletion (increase in SID) by administering a low Cl^- diet, loop[10,11,19,30,36-39] or thiazide diuretics,[19] or by gastric drainage.[19,27,40,41] Chloride ion depletion caused by isovolumetric hemofiltration also has been attempted.[42] Alternatively, SID can be increased by increasing Na^+ following the administration of desoxycorticosterone acetate (DOCA).[19,43]

Diuretic-induced metabolic alkalosis causes an increase in PCO_2 of 0.5 to 0.9 mm Hg for each 1 mEq/L increase in HCO_3–,[10,11,19,30,36-39] whereas gastric drainage[19,27,40,41] and DOCA administration cause compensatory increase in PCO_2 of 0.55 to 1.3 mm Hg and 0.8 to 1.1 mm Hg, respectively, for each 1 mEq/L increase in HCO_3–. In a study comparing several methods for inducing metabolic alkalosis in dogs,[19] no significant difference was found between PCO_2 values, and it was concluded that an increase in PCO_2 of 0.7 mm Hg occurred for each 1 mEq/L increase in HCO_3–. Interestingly, this also was the midpoint for the respiratory compensation in the diuretic-induced alkalosis studies.

Hydrogen ion concentration decreased 0.54 to 0.8 nEq/L for each 1 mEq/L increase in HCO_3– in the majority of these studies.[10,11,19,27,36-40] When chlorothiazide was used to induce metabolic alkalosis and in one study with gastric-drainage-induced alkalosis,[41] H^+ decreased below the 0.54 nEq/L limit,[19] whereas in one study with furosemide[30] and one with DOCA,[19] H^+ increased above the 0.8 nEq/L limit.

Respiratory Disorders

Changes in PCO_2 will cause secondary changes in SID. In acute respiratory disturbances, SID will be changed by strong ion shifts across cell membranes (particularly erythrocytes), whereas in chronic disturbances SID will be changed mainly by differential reabsorption of Na^+ and Cl^- in the kidneys.

ACUTE RESPIRATORY ALKALOSIS

A decrease in PCO_2 occurs, as well as a consequent decrease in dissolved CO_2 concentration inside cells in acute respiratory alkalosis. This decrease in CO_2 will cause dehydration of H_2CO_3 in the erythrocyte. This reaction is accelerated by the enzyme carbonic anhydrase during normal gas exchange in the lungs.[44] Chloride ions leave red blood cells in exchange for HCO_3–, increasing intracellular SID and decreasing plasma SID (Fig. 3). Although usually ignored, Na^+ and K^+ also move in this setting.[2,45] Lactate, another strong ion in blood, also has been shown to increase during acute respiratory alkalosis[46-48] but returns to baseline within 6 to 8 hours.[46,47] In one study using nephrectomized dogs with acute respiratory alkalosis induced by hyperventilation, the extracellular buffer decrease was 90% due to HCO_3– and 10% due to $HPO_4=$.[45] The changes in HCO_3– were caused by changes in SID and can be broken down as follows:

- 37% due to an increase in Cl^-;
- 35% due to an increase in lactate;
- 16% due to a decrease in Na^+; and
- 4% due to a decrease in K^+ (total = 92%).

Acute respiratory alkalosis has been induced by increasing the respiratory rate in anesthetized dogs[46,48-51] or by exposing awake dogs to barometric chambers in which the inspired pressure of O_2 (P_IO_2) was decreased by a decrease in barometric pressure.[47,52] Compensation for acute respiratory alkalosis in anesthetized dogs is characterized by a decrease in plasma HCO_3– of approximately 0.14 to 0.36 mEq/L for each 1 mm Hg decrease in PCO_2.[46,48-51] Hydrogen ion concentration decreases 0.5 to 1.0 nEq/L for each 1 mm Hg decrease in PCO_2.[46,48-51] Changing the fraction of inspired O_2 (F_IO_2) to 40% from 10% did not change these results.[49] Bicarbonate concentration decreased 0.2 to 0.3 mEq/L for each 1 mm Hg decrease in PCO_2 in conscious dogs exposed to low barometric pres-

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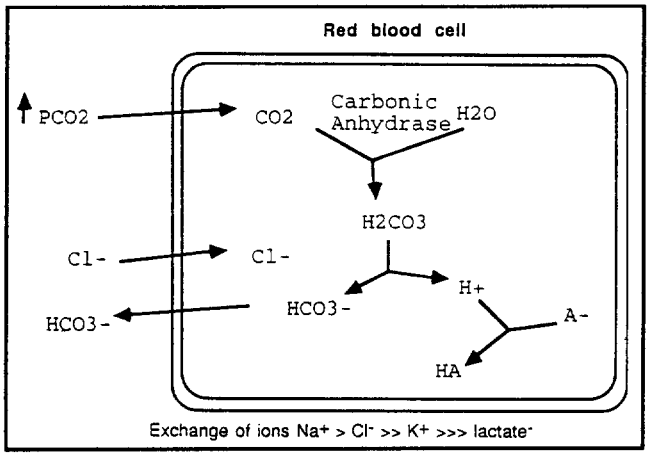

FIG. 4 — Compensation for acute respiratory acidosis.

sure.[47,52] The H^+ decreased 0.7 nEq/L for each 1 mm Hg decrease in PCO_2.[47,52]

The acute response to superimposed hypocapnia is a decrease of 0.11 to 0.18 mEq/L of HCO_3– for each 1 mm Hg decrease in PCO_2 in dogs chronically fed HCl and maintained eucapnic (PCO_2 = 36 mm Hg).[18] The response to a superimposed respiratory alkalosis is a decrease of 0.47 mEq/L in HCO_3– for each 1 mm Hg decrease in PCO_2 in eucapnic dogs with chronic metabolic alkalosis.[16,37] Based on these data, a 0.25 mEq/L decrease in HCO_3– for each 1 mm Hg decrease in PCO_2 has been proposed for dogs.[53,54]

ACUTE RESPIRATORY ACIDOSIS

An increase in PCO_2 causes CO_2 to diffuse into cells during acute respiratory acidosis. Carbonic anhydrase will catalyse the formation of H_2CO_3, which in turn will dissociate into H^+ and HCO_3– within red blood cells and renal tubular cells. The increase in H^+ within cells is buffered by intracellular buffers and the exchange of strong ions (mainly Cl^-, but also Na^+ and K^+) will cause plasma HCO_3– to increase (Fig. 4). A classic study by Giebisch and colleagues in nephrectomized dogs showed that during acute respiratory acidosis, 86% of the increase in the extracellular buffer is due to an increase in HCO_3–, and 14% is due to an increase in $HPO_4=$.[45] The changes in HCO_3– were caused by changes in SID and can be broken down as follows:

- 37% due to an increase in Na^+;
- 29% due to a decrease in Cl^-;
- 14% due to an increase in K^+; and
- 6% due to a decrease in lactate$^-$ (total = 86%).

Acute respiratory acidosis has been produced by increasing the fraction of inspired CO_2 (F_ICO_2), with[49,55] or without[46,50,56-62] hypoxemia. In one study F_IO_2 also was increased.[49] Although an attempt has been made to produce hypocapnia in awake dogs by exposure to heat, this method is not effective.[60] Bicarbonate concentration increased 0.04 to 0.19 mEq/L for each mm Hg increase in PCO_2 in anesthetized nonhypoxic dogs.[46,50,57] In one study, however, a lower degree of compensation was achieved.[56] Hydrogen ion concentration increases 0.53 to 1.1 nEq/L for each mm Hg increase in PCO_2 in anesthetized nonhypoxic dogs.[46,50,56,57] An increase in F_IO_2 to 40% or a decrease to 10% did not change these responses.[49]

Bicarbonate concentration increased 0.12 to 0.20 mEq/L for each mm Hg increase in PCO_2 in conscious dogs exposed to up to 11% F_ICO_2.[58-62] Hydrogen ion concentration increased 0.68 to 0.93 nEq/L for each mm Hg increase in PCO_2.[58-63] Bicarbonate concentration increased only 0.9 mEq/L and H+ increased 0.96 nEq/L for each mm Hg increase in PCO_2 in dogs also made hypoxemic.[55] An expected compensation of 0.15 mEq/L increase in the HCO_3– for each mm Hg increase in PCO_2 has been proposed for dogs.[6,53,54]

CHRONIC RESPIRATORY ALKALOSIS

Renal H^+ excretion is decreased during chronic hypocapnia, probably mediated by a decrease in intracellular H^+.[7] The amount of NH_4+Cl^- excreted in the urine decreases and renal Cl^- reabsorption increases. The increase in Cl^- reabsorption decreases SID (and consequently HCO_3–), and is responsible for the hyperchloremia observed in human patients with chronic respiratory alkalosis[64] and in dogs with experimental chronic hypocapnia.[65]

Chronic respiratory alkalosis has been induced in dogs by exposure to a low P_IO_2 caused either by decreasing F_IO_2[11,65,66] or decreasing barometric pressure.[52] Significant hypoxemia occurred in both models.[52,65] A gradual decrease in F_IO_2 to 9% during a 4-day period of time caused chronic respiratory alkalosis. During the steady state, HCO_3– decreased 0.53 to 0.56 mEq/L for each 1 mm Hg decrease in PCO_2.[11,65] Dogs on electrolyte-restricted diets developed a compensatory decrease in HCO_3– of 0.43 to 0.51 mEq/L for each 1 mm Hg decrease in PCO_2.[66] Hydrogen ion concentration decreased 0.15 to 0.17 nEq/L for each 1 mm Hg decrease in PCO_2 in dogs on a normal diet,[11,65] and 0.21 to 0.36 nEq/L in dogs receiving an electrolyte-restricted diet.[66]

Long-term monitoring of dogs in hypobaric chambers exposed to a barometric pressure of 490 mm Hg has been carried out.[52] The decrease in HCO_3– for each 1 mm Hg decrease in PCO_2 was 0.67 and 0.76 mEq/L after 2 and 4 weeks, respectively, of exposure to the low barometric pressure. The H^+ decreased

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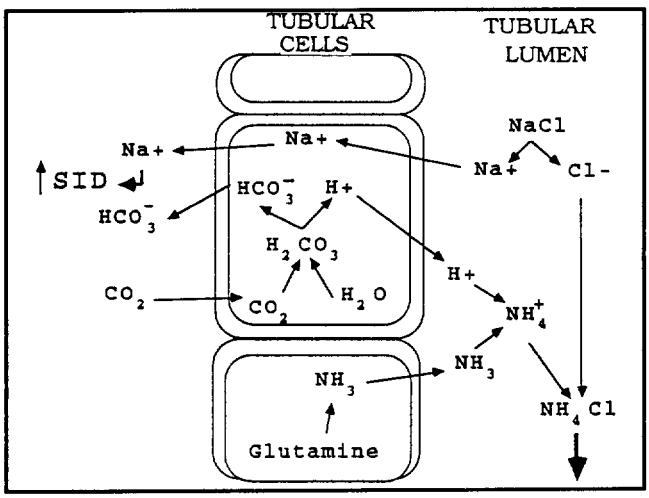

FIG. 5 – Renal compensation for chronic respiratory acidosis.

0.34 to 0.39 nEq/L for each 1 mm Hg decrease in PCO_2.[52] The degree of adaptation using this model was greater than that obtained by decreasing F_IO_2 to 9%. A potential explanation for these results may be the observation that dogs at a barometric pressure of 490 mm Hg had a higher PaO_2 (PaO_2 = 52 mm Hg)[52] than those exposed to an F_IO_2 of 9% (PaO_2 = 40 mm Hg).[65] Results similar to those obtained in hypobaric chambers have been observed in dogs with experimentally induced hyperchloremic acidosis exposed to a F_IO_2 of 16%.[13] Although the PaO_2 was not reported in this study, dogs were exposed to three different levels of F_IO_2 (9%, 11.5%, and 16%), and the degree of compensation was higher with higher levels of F_IO_2.[13]

The superimposition of hypocapnia on eucapnic metabolic acidosis causes a decrease in HCO_3– of 0.5 mEq/L for each 1 mm Hg decrease in PCO_2.[18] Similar results have been obtained with superimposition of chronic respiratory alkalosis in dogs with experimentally induced hyperchloremic acidosis.[13] Induction of chronic respiratory alkalosis in dogs with experimentally induced metabolic alkalosis, however, results in a decrease in HCO_3– of 0.7 mEq/L for each 1 mm Hg decrease in PCO_2.[37] Although the compensatory response in respiratory alkalosis may depend on the degree of hypoxemia present, a 0.55 mEq/L decrease in HCO_3– for each 1 mm Hg decrease in PCO_2 has been suggested for use in dogs.[6,53,54]

CHRONIC RESPIRATORY ACIDOSIS

The increase in PCO_2 during chronic respiratory acidosis causes intracellular H^+ to increase in renal tubular cells, increasing net acid excretion (primarily as $NH_4 + Cl^-$).[7] The Cl^- lost in the urine is not accompanied by Na^+ and will decrease urine SID, while increasing plasma SID and HCO_3– (Fig. 5). Hypochloremia is a common finding in human patients with chronic respiratory acidosis[84] and in dogs with experimentally induced chronic hypercapnia.[20,57,58,67-69] Net acid excretion returns to normal in dogs with respiratory acidosis after the initial phase of adaptation but not in dogs with metabolic acidosis.[70] The decrease in net acid excretion is due to a decrease in titratable acidity and to persistent bicarbonaturia. Renal ammoniagenesis, however, remains enhanced during chronic acidosis in dogs.[70]

Chronic respiratory acidosis has been induced in dogs by increasing F_ICO_2 without changing F_IO_2. Values for F_ICO_2 of 5%,[63,71,72] 6%,[20] 7%,[68] 8.5 to 8.8%,[27,62] 10%,[58,70] 11%,[11,68] and 12%[57,67,69] have been studied. The HCO_3– increased 0.29 to 0.39 mEq/L for each 1 mm Hg increase in PCO_2.[11,20,27,57,58,68,70,72] Hydrogen ion concentration increased 0.23 to 0.5 nEq/L for each 1 mm Hg increase in PCO_2.[11,20,27,57,58,62,68,70,72,73] Although a 0.37 mEq/L increase in HCO_3– for each 1 mm Hg increase in PCO_2 has been suggested as the expected compensation for dogs,[6] analysis of a larger number of reports suggests that (as in human beings) the midpoint may be 0.35. Dogs with experimentally induced hyperchloremic acidosis (H^+ = 55 nEq/L, HCO_3– = 14.7 mEq/L, and PCO_2 = 32 mm Hg) when exposed to a F_ICO_2 of 6% showed an increase in the HCO_3– of 0.43 mEq/L for each 1 mm Hg increase in PCO_2.[20]

Discussion

Compensation for acid-base disorders in dogs differs from that observed in human beings.[6] A summary of the compensatory responses expected in dogs for the various acid-base disorders is presented in Table 2; however, the time course of the illness must be considered when using the table. Sufficient time must have elapsed for full compensation to occur. Otherwise, compensatory values cannot be used to estimate the magnitude of expected compensation. Twelve to 24 hours are required to reach maximal respiratory compensation in humans with metabolic acidosis.[74] Renal adaptation for chronic respiratory disorders may take 2 to 5 days to reach a chronic steady state in dogs.[65,67,68] A steady state in dogs with experimentally induced chronic respiratory alkalosis was not reached until 4 weeks in at least one special situation, a high altitude adaptation.[52]

It is interesting to note that in metabolic disturbances, the expected compensation is approximately the same whether metabolic alkalosis or metabolic acidosis is considered. This observation also has been made ex-

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TABLE 2
Compensatory Response in Simple Acid-Base Disturbances in Dogs

Disturbance	Clinical Guide for Compensation	
Metabolic acidosis	Each 1 mEq/L ⇓ HCO_3^-	PCO_2 ⇓ by 0.7 mm Hg H^+ ⇑ 1.25 to 2.1 nEq/L
Metabolic alkalosis	Each 1 mEq/L ⇑ HCO_3^-	PCO_2 ⇑ by 0.7 mm Hg H^+ ⇓ 0.55 to 0.80 nEq/L
Respiratory acidosis		
acute	Each 1 mm Hg ⇑ PCO_2	HCO_3^- ⇑ by 0.15 mEq/L H^+ ⇑ 0.53 to 1.1 nEq/L
chronic	Each 1 mm Hg ⇑ PCO_2	HCO_3^- ⇑ by 0.35 mEq/L H^+ ⇑ 0.23 to 0.47 nEq/L
Respiratory alkalosis		
acute	Each 1 mm Hg ⇓ PCO_2	HCO_3^- ⇓ by 0.25 mEq/L H^+ ⇓ 0.5 to 1 nEq/L
chronic	Each 1 mm Hg ⇓ PCO_2	HCO_3^- ⇓ by 0.55 mEq/L H^+ ⇓ 0.15 to 0.39 nEq/L

perimentally in dogs.[19] On the other hand, normal compensation for respiratory disorders of acid-base balance is more effective during alkalosis than acidosis. Compensation for respiratory acidosis in dogs is only 60% of that achieved with respiratory alkalosis in either acute or chronic disorders. Chronic respiratory alkalosis is the only primary disturbance in which compensation is so effective that the compensated pH usually falls within the normal range for dogs.[54]

The dependence of normal plasma HCO_3^- on $PaCO_2$ has been studied in dogs.[75] The observed plasma HCO_3^- is highly dependent on the prevailing $PaCO_2$. Approximately 50% of the normal variation in plasma HCO_3^- can be explained simply by variation in PCO_2. The relationship is such that a 1 mm Hg change in PCO_2 will change HCO_3^- by 0.35 mEq/L.[75] This value coincides with that found for dogs with chronic respiratory acidosis.

Although changes in the total concentration of nonvolatile weak acids can cause metabolic acid-base disorders such as hypoproteinemic alkalosis, hyperproteinemic acidosis, and hyperphosphatemic acidosis,[1-4,8,76] no data are available in dogs regarding compensation for these disturbances. If there is a respiratory compensation in human patients with hypoproteinemic alkalosis, it is not well documented.[77,78] Compensatory changes in inorganic SID in response to acute and chronic respiratory acidosis and compensatory changes in PCO_2 during primary disturbances of SID in dogs have been reviewed elsewhere.[76]

The respiratory response in human patients with metabolic alkalosis is not as predictable as that observed in metabolic acidosis. Many patients with stable chronic metabolic alkalosis demonstrate a variable increment in PCO_2.[64] The PCO_2 increases by 0.5 to 1.0 mm Hg for each 1 mEq/L increase in HCO_3^-.[79] As a result of this variation, some authors do not use specific formulas for calculation of the respiratory compensation, but rather suggest that one would expect "some increase in PCO_2" in patients with metabolic alkalosis.[64] A PCO_2 less than normal would indicate concomitant respiratory alkalosis (i.e., a mixed disorder). A normal or slightly increased PCO_2 in a patient with a substantial increase in serum HCO_3^- also suggests a less than expected compensation. A careful search for potential causes of respiratory alkalosis is warranted in both situations.[64] On the other hand, it is unusual for human patients to have PCO_2 values greater than 55 mm Hg without primary respiratory acidosis, even in the presence of severe metabolic alkalosis.[80] This issue was not addressed in clinical reviews of dogs with metabolic alkalosis,[81,82] and it is not known whether dogs show the same clinical variation suggested to occur in human beings.

It has been suggested that patients with lactic acidosis may hyperventilate to a greater extent than patients with other forms of metabolic acidosis, leading to suspicion of a mixed disorder.[64] Unfortunately, no systematic observations on the magnitude of the ventilatory adaptation to lactic acidosis are available.[83]

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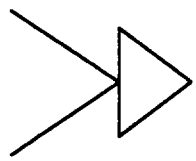
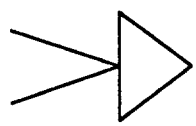
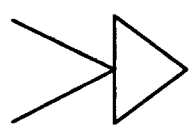
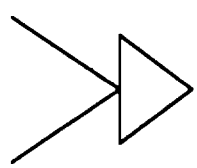
TABLE 3
Common Causes of Acid-Base Disturbances and the Expected Compensatory Response

Uremia Diabetic ketoacidosis Shock Hypoadrenocorticism Diarrhea Ethylene glycol toxicity		Metabolic acidosis with compensatory respiratory alkalosis
Gastric-origin vomiting Diuretic administration $NaHCO_3$ treatment		Metabolic alkalosis with compensatory respiratory acidosis
Neuromuscular diseases Severe pulmonary edema Drug-induced respiratory depression Airway obstruction Advanced pulmonary disease		Respiratory acidosis with compensatory metabolic alkalosis
Hypoxemia Anemia Pulmonary edema Corticosteroid administration Sepsis/fever Pulmonary disease Primary central nervous system diseases		Respiratory alkalosis with compensatory metabolic acidosis

Since lactic acidosis usually is associated with other processes that can stimulate ventilation (e.g., hypoxemia, hypotension, sepsis, pulmonary disease, hepatic failure, and exercise), PCO_2 can be expected to be lower in these settings than in other forms of metabolic acidosis.

No cases of mixed respiratory alkalosis and metabolic alkalosis were identified in a retrospective study in dogs with alkalemia.[82] Induction of chronic respiratory alkalosis in dogs with experimentally induced metabolic alkalosis has been shown to cause a decrease in HCO_3- that not only prevents development of significant alkalemia but also entirely offsets the effect of hypocapnia on plasma H^+.[37]

Little clinical data exist on normal compensation for acid-base disorders in dogs, but some data are available for dogs with experimentally induced diseases. Metabolic acidosis resulting from hypokalemia has been studied in dogs.[84-86] Dietary potassium restriction was associated with a decrease of PCO_2 of 0.76 mm Hg and an increase in H^+ of 1.2 nEq/L for each 1 mEq/L decrease in HCO_3-.[88] Distal renal tubular acidosis induced by amiloride administration in dogs caused a respiratory compensation[33] similar to that found in other forms of experimental hyperchloremic acidosis.

Acid-base disturbances associated with some experimentally induced endocrine disorders also have been studied in dogs. Despite some reports of metabolic alkalosis associated with hypoparathyroidism in human patients, no acid-base disturbances have been found in dogs with experimentally induced hypoparathyroidism.[87] An experimental model that simulated hypoadrenocorticism has been studied in dogs.[34,35] Metabolic acidosis was observed, and the respiratory compensation was the same as that observed in hyperchloremic models of metabolic acidosis. Although the Cl^- decreased in these dogs, Na^+ decreased to a greater extent and caused a decrease in SID that paralleled the observed change in HCO_3-.[34,35] The respiratory compensation for metabolic acidosis and metabolic alkalosis in alloxan-induced diabetes in dogs was different from that observed in normal dogs.[30] Diabetic dogs compensated better for diuretic-induced metabolic alkalosis. The PCO_2 increased 0.5 mm Hg in normal dogs, and 0.9 mm Hg in diabetic

Continued

TABLE 4
Examples of Causes of Mixed Respiratory and Metabolic Acid-Base Disturbances

Disease	Metabolic Disturbance (Cause)	Respiratory Disturbance (Cause)
Cardiopulmonary arrest	Metabolic acidosis (lactic acidosis)	Respiratory acidosis (pulmonary arrest)
Severe pulmonary edema	Metabolic acidosis (lactic acidosis) Metabolic alkalosis (diuretic administration)	Respiratory alkalosis (hyperventilation) Respiratory acidosis (ventilation/perfusion mismatch)
Heart failure	Metabolic acidosis (lactic acidosis) Metabolic alkalosis (diuretic administration)	Respiratory alkalosis (pulmonary edema) Respiratory acidosis (ventilation/perfusion mismatch)
Septic shock	Metabolic acidosis (lactic acidosis)	Respiratory alkalosis (sepsis-caused hyperventilation) Respiratory acidosis (ventilation/perfusion mismatch)
Gastric dilation volvulus	Metabolic acidosis (lactic acidosis) Metabolic alkalosis (sequestration of gastric fluid)	Respiratory acidosis (compression of diaphragm) Respiratory alkalosis (pain/sepsis)
Acute tumor lysis syndrome	Metabolic acidosis (lactic acidosis)	Respiratory alkalosis (pulmonary disease) Respiratory acidosis (severe pulmonary disease)
Liver disease	Metabolic acidosis (Type-B lactic acidosis, renal tubular acidosis) Metabolic alkalosis (vomiting)	Respiratory alkalosis (multifactorial)

dogs for each 1 mEq/L increase in HCO_3^-.[30] The opposite occurred during NH_4Cl-induced metabolic acidosis. The PCO_2 decreased 0.66 mm Hg for each 1 mEq/L decrease in HCO_3^- in normal dogs, whereas diabetic dogs had a decrease of only 0.47 mm Hg for each 1 mEq/L decrease in HCO_3^-.[30] Both normal dogs and diabetic dogs had similar blood gas values before induction of metabolic acid-base disturbance.[30] No explanation was given for the different compensation in dogs with alloxan-induced diabetes and normal dogs.

The common causes of simple acid-base disorders in dogs and their expected compensation are presented in Table 3. In many situations, however, more than one primary acid-base disturbance may occur at the same time, and these disorders are called mixed acid-base disorders. Mixed acid-base disturbances should be suspected whenever the calculated expected compensation (using the values in Table 2) is at least 2 to 3 mm Hg or 2 mEq/L greater or less than the predicted value. Any time the PCO_2 and HCO_3^- are outside of the normal range, and changing in opposite directions, a mixed acid-base disturbance must be present. Some examples of mixed-acid base disorders in dogs are listed in Table 4.

Despite a lack of clinical data describing metabolic and respiratory compensation in dogs with acid-base disturbances, evaluation of experimental data from normal dogs suggests that the compensatory rules of thumb used in human medicine may not be applicable to dogs. The compensatory response is the same in both species during chronic respiratory acidosis and metabolic alkalosis, whereas dogs compensate better than human beings in the acute respiratory acid-base

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disturbances and chronic respiratory alkalosis, and human beings compensate better than dogs during metabolic acidosis. The expected compensatory values proposed here should be considered clinical guidelines and be assessed together with complete history, physical examination, and accompanying laboratory work. ■

REFERENCES

1. Stewart PA: Independent and Dependent Variables of Acid-Base Control. Resp Physiol 33:9-28, 1978.
2. Stewart PA: How to Understand Acid-Base. New York, Elsevier, 1981, p 186.
3. Stewart PA: Modern Quantitative Acid-Base Chemistry. Can J Physiol Pharmacol 61:1444-1461, 1983.
4. Fencl V, Rossing TH: Acid-Base Disorders in Critical Care Medicine. Ann Rev Med 40:17, 1989.
5. Haskins SC: An Overview of Acid-Base Physiology. JAVMA 170(4):423-428, 1977.
6. Adams LG, Polzin DJ: Mixed Acid-Base Disorders. Vet Clin N Amer Small Anim Pract 19(2):307-326, 1989.
7. Rose BD: Clinical Physiology of Acid-Base and Electrolyte Disorders, ed 3. New York, McGraw-Hill, 1989, p 853.
8. Jones NL: Blood Gases and Acid Base Physiology, ed 2. New York, Thieme Medical Publishers, 1987, p 224.
9. Fencl V: Acid-Base Balance in Cerebral Fluids. In: Handbook of Physiology: Respiratory System. Ed by American Physiological Society. Bethesda, MD, American Physiological Society, 1986, pp 115-140.
10. Adrogué HJ, Brensilver J, Madias NE: Changes in Plasma Anion Gap During Chronic Metabolic Acid-Base Disturbances. Am J Physiol 235:F291-F297, 1978.
11. Adrogué JH, Brensilver J, Cohen JJ, Madias N: Influence of Steady-State Alterations in Acid-Base Equilibrium on the Fate of Administered Bicarbonate in the Dog. J Clin Invest 71:867-883, 1983.
12. Fine A: The Effects of Chronic Metabolic Acidosis on Liver and Muscle Glutamine Metabolism in the Dog in vivo. Biochem J 202:271-273, 1982.
13. Cohen JJ, Madias NE, Wolf CJ, Schwartz WB: Regulation of Acid-Base Equilibrium in Chronic Hypocapnia: Evidence That the Response of the Kidney is not Gerated to the Defense of Extracellular H^+. J Clin Invest 57:1483-1489, 1976.
14. DeSousa RC, Harrington JT, Ricanati ES, et al: Renal Regulation of Acid-Base Equilibrium During Chronic Administration of Mineral Acid. J Clin Invest 53:465-476, 1974.
15. Harrington JT, Hulter HN, Cohen JJ, Madias NE: Mineralocorticoid-Stimulated Renal Acidification: The Critical Role of Dietary Sodium. Kidney Int 30:43-48, 1986.
16. Honer WG, Jennings DB: PCO_2 Modulation of Ventilation and HCO_3- Buffer During Chronic Metabolic Acidosis. Resp Physiol 54:241-258, 1983.
17. Lowance DC, Garfinkel HB, Mattern WD, Schwartz WB: The Effect of Chronic Hypotonic Volume Expansion on the Renal Regulation of Acid Base Equilibrium. J Clin Invest 51:2928-2940, 1972.
18. Madias NE, Schwartz WB, Cohen JJ: The Maladaptive Renal Response to Secondary Hypocapnia During Chronic HCl Acidosis in the Dog. J Clin Invest 60:1393-1401, 1977.
19. Madias NE, Bossert WH, Adrogué HJ: Ventilatory Response to Chronic Metabolic Acidosis and Alkalosis in the Dog. J Appl Physiol 56:1640-1646, 1984.
20. Madias NE, Wolf CJ, Cohen JJ: Regulation of Acid-Base Equilibrium in Chronic Hypercapnia. Kidney Int 27:538-543, 1985.
21. Madias NE, Zelman SJ: The Renal Response to Chronic Mineral Acid-Feeding: A Re-examination of the Role of Systemic pH. Kidney Int 29:667-674, 1986.
22. Halperin ML, Vinay P, Gougoux A, et al: Regulation on the Maximum Rate of Renal Ammoniagenesis in the Acidotic Dog. Am J Physiol 248:F607-F615, 1985.
23. Halperin ML, Bun-Chen C: Influence of Acute Hyponatremia on Renal Ammoniagenesis in Dogs With Chronic Metabolic Acidosis. Am J Physiol 258:F328-F332, 1990.
24. Magner PO, Robinson L, Halperin RM, et al: The Plasma Potassium Concentration in Metabolic Acidosis: A Re-evaluation. Am J Kidney Dis 11(3):220-224, 1988.
25. Gougoux A, Vinay P, Zizian L, et al: Effect of Acetazolamide on Renal Metabolism and Ammoniagenesis in the Dog. Kidney Int 31:1279-1290, 1987.
26. Fine A, Carlyle JE, Bourke E: The Effects of Administration of HCl, NH4Cl and NH_4HCO_3 on the Excretion of Urea and Ammonium in Man. Europ J Clin Invest 7:587-589, 1977.
27. Chazan JA, Appleton FM, London AM, Schwartz WB: Effects of Chronic Metabolic Acid-Base Disturbances on the Composition of Cerebrospinal Fluid in the Dog. Clin Sci 36:345-358, 1969.
28. Clark DD, Chang BS, Garella SG, et al: Secondary Hypocapnia Fails to Protect "Whole-Blood" Intracellular pH During Chronic HCl-Acidosis in the Dog. Kidney Int 23:336-341, 1983.
29. Hulter HN, Toto RD, Sebastian A, et al: Effect of Extracellular Fluid Volume Depletion on Renal Regulation of Acid-Base and Potassium Equilibrium During Prolonged Mineral Acid Administration. J Lab Clin Med 103:854-868, 1984.
30. Hetenyi G Jr, Paradis H, Kucharczyk J: Glucose and Lactate Turnover and Gluconeogenesis in Chronic Metabolic Acidosis and Alkalosis in Normal and Diabetic Dogs. Can J Physiol Pharmacol 66:140-145, 1988.
31. Haskins SC, Munger RJ, Helphrey MG, et al: Effects of Acetazolamide on Blood Acid-Base and Electrolyte Values in Dogs. JAVMA 179(8):792-796, 1981.
32. Rose RJ, Carter J: Some Physiological and Biochemical Effects of Acetazolamide in the Dog. J Vet Pharmacol Therap 2:215-221, 1979.
33. Hulter HN, Licht JH, Glynn RD, Sebastian A: Pathophysiology of Chronic Renal Tubular Acidosis Induced by Administration of Amiloride. J Lab Clin Med 95:637-653, 1980.
34. Hulter H, Ilnicki L, Harbottle J, Sebastian A: Impaired Renal H^+ Secretion and NH_3 Production in Mineralocorticoid-Deficient Glucocorticoid-Repleted Dogs. Am J Physiol 232(2):F136-F146, 1977.
35. Hulter HN, Licht JH, Glynn RD, Sebastian A: Renal Acidosis in Mineralocorticoid Deficiency is not Dependent on NaCl Depletion or Hyperkalemia. Am J Physiol 236(3):F283-F294, 1979.
36. Cohen JJ, Ellis JH: Correction of Metabolic Alkalosis by the Kidney After Isometric Expansion of Extracellular Fluid. J Clin Invest 47:1181-1192, 1968.
37. Madias NE, Cohen JJ, Adrogué HJ: Influence of Acute and Chronic Respiratory Alkalosis on Pre-existing Chronic Metabolic Alkalosis. Am J Physiol 258:F479-F485, 1990.
38. Penman RW, Luke RF, Jarboe TM: Respiratory Effects of Hypochloremic Alkalosis and Potassium Depletion in the Dog. J Appl Physiol 33:170-174, 1972.
39. Peterson LN, Sztorc D, Jamshaid A, et al: Plasma AVP and Renal Concentration Defect in Chloride Depletion Metabolic Alkalosis. Am J Physiol 254:F15-F24, 1988.
40. Marone CC, Wong NLM, Sutton RLA, Dirks JH: Effects of Metabolic Alkalosis on Calcium Excretion in the Conscious Dog. J Lab Clin Med 101(2):264-273, 1983.
41. Needle MA, Kaloyanides GJ, Schwartz WB: The Effects of Selective Depletion of Hydrochloric Acid on Acid-Base and Electrolyte Equilibrium. J Clin Invest 43:1836-1846, 1964.
42. Borkan S, Northrup T, Cohen J, Garella S: Renal Response to Metabolic Alkalosis Induced by Isovolemic Hemofiltration in the Dog. Kidney Int 32:322-328, 1987.
43. Atkins EL, Schwartz WB: Factors Governing Correction of the Alkalosis Associated With Potassium Deficiency; the Critical Role of Chloride in the Recovery Process. J Clin Invest 41:218-229, 1962.
44. Klocke RA: Carbon Dioxide Transport. In: Handbook of Physiology: Respiratory System. Ed by American Physiological Society. Bethesda, MD, American Physiological Society, 1987, pp 173-197.
45. Giebisch G, Berger L, Pitts R, et al: The Extrarenal Response to Acute Acid-Base Disturbances of Respiratory Origin. J Clin Invest 34:231-245, 1955.
46. Kazemi H, Valence LM, Shannon DC: Brain and Cerebrospinal Fluid Lactate Concentration in Respiratory Acidosis and Alkalosis. Resp Physiol 6:178-186, 1969.
47. Cain SM, Dunn JE II: Transient Arterial Lactic Acid Changes in Unanesthetized Dogs at 21,000 Feet. Am J Physiol 206(6):1437-1440, 1964.
48. Brice AG, Welch HG: Effect of Respiratory Alkalosis on Skeletal Muscle Metabolism in the Dog. J Appl Physiol 58(2):658-664, 1985.
49. Brimioulle S, Lejeune P, Vachiery J-L, et al: Effects of Acidosis and Alkalosis on Hypoxic Vasoconstriction in Dogs. Am J Physiol 258:H347-H353, 1990.
50. Kazemi H, Shannon DC, Carvallo-Gil E: Brain CO_2 Buffering Capacity in Respiratory Acidosis and Alkalosis. J Appl Physiol 22(2):241-246, 1967.
51. Muir WW III, Wagner AE, Buchanan C: Effects of Acute Hyperventilation on Serum Potassium in the Dog. Vet Surg 19(1):83-87, 1990.
52. Bureau M, Bouverot P: Blood and CSF Acid-Base Changes, and Rate of Ventilatory Acclimatization of Awake Dogs to 3,550 M. Resp Physiol 24:203-216, 1975.
53. DiBartola SP, De Morais HSA: Respiratory Acid-Base Disorders. In: Fluid Therapy in Small Animal Practice. Ed by SP DiBartola. Philadelphia, WB Saunders, 1992.
54. De Morais HSA: Mixed Acid-Base Disorders. In: Fluid Therapy in Small Animal Practice. Ed by SP DiBartola. Philadelphia, WB Saunders, 1992.
55. Rose CE Jr, Dougherty MJ, Brashers VL, et al: Effect of α-Adrenergic Blockade on the Cardiovascular Responses to Hypoxemia and Hypercapnia Acidosis in Conscious Dogs (42843). Proc Soc Exper Bio Med 190:155-162, 1989.
56. Adrogué HJ, Stinebaugh BJ, Gougoux A, et al: Decreased Distal Acidification in Acute Hypercapnia in the Dog. Am J Physiol 244:F19-F27, 1983.
57. Bleich HL, Berkman PM, Schwartz WB: The Response of Cerebrospinal Fluid Composition to Sustained Hypercapnia. J Clin Invest 43:11-16, 1964.
58. Canzanello VJ, Bodvardsson M, Kraut JA, et al: Effect of Chronic Respiratory Acidosis on Urinary Calcium Excretion in the Dog. Kidney Int 38:409-416, 1990.
59. Cohen JJ, Brackett NC, Schwartz WB: The Nature of the Carbon Dioxide Titration Curve in the Normal Dog. J Clin Invest 43:777-786, 1964.
60. Maskrey M, Jennings DB: Ventilation and Acid-Base Balance in Awake Dogs Exposed to Heat and CO_2. J Appl Physiol 58(2):549-557, 1985.
61. Rose CE Jr, Anderson RJ, Carey RM: Acute Hypercapnic Acidosis Diminishes Renal Water Excretion in Conscious Dogs. Mineral Electrolyte Metab 11:131-136, 1985.
62. Rose CE Jr, Van Benthuysen K, Jackson JT, et al: Right Ventricular Performance During Increased Afterload Impaired by Hypercapnic Acidosis in Conscious Dogs. Circ Res 52:76-84, 1983.
63. Jennings DB, Chen CC: Ventilation in Conscious Dog During Acute and Chronic Hypercapnia. J Appl Physiol 41(6):839-847, 1976.
64. Narins RG, Emmett M: Simple and Mixed Acid-Base Disorders: A Practical Approach. Medicine 59(3):161-187, 1980.
65. Gennari FJ, Goldstein MB, Schwartz W: The Nature of the Renal Adaptation to Chronic Hypocapnia. J Clin Invest 51:1722-1730, 1972.
66. Gougoux A, Kaehny WD, Cohen JJ: Renal Adaptation to Chronic Hypocapnia: Dietary Constraints in Achieving H^+ Retention. Am J Physiol 229(5):1330-1337, 1975.
67. Polak A, Haynie GD, Hays RM, et al: Effects of Chronic Hypercapnia on Electrolyte and Acid-Base Equilibrium. I. Adaptation. J Clin Invest 40:1223-1237, 1961.
68. Schwartz WB, Brackett NC, Cohen JJ: The Response of Extracellular Hydrogen Ion Concentration to Graded Degrees of Chronic Hypercapnia: The Physiologic Limits of Defense of pH. J Clin Invest 44(2):291-301, 1965.
69. Van Ypersele de Strihou C, Gulyassy PF, Schwartz WB: Effects of Chronic Hypercapnia on Electrolyte and Acid-Base Equilibrium. III. Characteristics of the Adaptive and Recovery Process as Evaluated by Provision of Alkali. J Clin Invest 41:2246-2253, 1962.

Continued

70. Adrogué HJ, Madias NE: Renal Acidification During Chronic Hypercapnia in the Conscious Dog. Pflürges Arch. 406:520-528, 1986.

71. Jennings DB: Body Temperature and Ventilatory Response to CO_2 During Chronic Respiratory Acidosis. J Appl Physiol 46(3):491-497, 1979.

72. Jennings DB, Davidson JSD: Acid-Base and Ventilatory Adaptation in Conscious Dogs During Chronic Hypercapnia. Resp Physiol 58:377-393, 1984.

73. Goldstein MB, Gennari FJ, Schwartz WB: The Influence of Graded Degrees of Chronic Hypercapnia on the Acute Carbon Dioxide Titration Curve. J Clin Invest 50:208-216, 1971.

74. Pierce NF, Fedson DS, Brigham KL, et al: The Ventilatory Response to Acute Base Deficit in Humans. Time Course During Development and Correction of Metabolic Acidosis. Ann Intern Med (72):833-845, 1970.

75. Madias NE, Adrogué HJ, Cohen JJ, Schwartz WB: Effect of Natural Variations in $PaCO_2$ on Plasma [HCO^-_3] in Dogs: A Redefinition of Normal. Am J Physiol 236(1):F30-F35, 1979.

76. De Morais HSA: A Nontraditional Approach to Acid-Base Disorders. In: Fluid Therapy in Small Animal Practice. Ed by SP DiBartola. Philadelphia, WB Saunders, 1992.

77. McAuliffe JJ, Lind LJ, Leith DE, Fencl V: Hypoproteinemic Alkalosis. Am J Med 81-90:86, 1986.

78. Rossing TH, Boixeda D, Maffeo N, Fencl V: Hyperventilation With Hypoproteinemia. J Lab Clin Med 112:553, 1988.

79. Bia M, Thier SO: Mixed Acid-Base Disturbances: A Clinical Approach. Med Clin N Amer 65(2):347-361, 1981.

80. Elkinton JR: Clinical Disorders of Acid-Base Regulation. A Survey of Seventeen Years' Diagnostic Experience. Med Clin N Amer 50:1352-1363, 1966.

81. Cornelius LM, Rawlings CA: Arterial Blood Gas and Acid-Base Values in Dogs With Various Diseases and Signs of Disease. JAVMA 178(9):982-985, 1981.

82. Robinson EP, Hardy RM: Clinical Signs, Diagnosis, and Treatment of Alkalemia in Dogs: 20 Cases (1982-1984). JAVMA 7(I):943-949, 1988.

83. Madias NE: Lactic Acidosis. Kidney Int 29:752-774, 1986.

84. Burnell JM, Dawbron JK: Acid Base Parameters in Potassium Depletion in the Dog. Am J Physiol 218:1583-1589, 1970.

85. Burnell JM, Teubner EJ, Simpsom DP: Metabolic Acidosis Accompanying Potassium Deprivation. Am J Physiol 227:329-333, 1974.

86. Hulter HN, Sebastian A, Sigala JF, et al: Pathogenesis of Renal Hyperchloremic Acidosis Resulting From Dietary Potassium Restriction in the Dog: Role of Aldosterone. Am J Physiol 238:F79-F91, 1980.

87. Hulter HN, Toto RD, Bonner EL, et al: Renal and Systemic Acid-Base Effects of Chronic Hypoparathyroidism in Dogs. Am J Physiol 241:F495-F501, 1981.