Minireview

nephron
Physiology

Nephron Physiol 2003;93:p61–p66
DOI: 10.1159/000069557

Cross-Talk between Two Organs: How the Kidney Responds to Disruption of Acid-Base Balance by the Lung

Nicolaos E. Madias Horacio J. Adrogué

Department of Medicine, Tufts University School of Medicine, and the Division of Nephrology and the Tupper Research Institute, Tufts-New England Medical Center, Boston, Mass., and Department of Medicine, Baylor College of Medicine, and Renal Section, Veterans Affairs Medical Center, Houston, Tex., USA

Key Words
Respiratory acidosis · Hypercapnia · Respiratory alkalosis · Hypocapnia

Abstract
Hypoventilation increases $PaCO_2$ (hypercapnia) and initiates the acid-base disorder known as respiratory acidosis. Hyperventilation decreases $PaCO_2$ (hypocapnia) and initiates the acid-base disorder known as respiratory alkalosis. The impact on acidity of these primary changes in $PaCO_2$ is ameliorated by secondary, directional changes in plasma bicarbonate concentration that occur in two stages. Acutely, modest changes in plasma bicarbonate originate from titration of the body's nonbicarbonate buffers. In chronic hypercapnia and hypocapnia, larger changes in plasma bicarbonate occur that reflect adjustments in renal acidification mechanisms. As a result, the amelioration of systemic acidity is more pronounced in the chronic forms of the respiratory acid-base disorders.

Introduction

Clinical acid-base disorders are conventionally defined from the vantage point of their impact on the carbonic acid-bicarbonate buffer system. Hence, changes in systemic acidity can occur through changes in the values of the two determinants of this buffer system, the carbon dioxide tension and the plasma bicarbonate concentration. Respiratory acid-base disorders are those abnormalities in acid-base equilibrium initiated by a change in the arterial carbon dioxide tension ($PaCO_2$). Increases and decreases in $PaCO_2$ are denoted by the terms hypercapnia and hypocapnia, respectively. Hypercapnia acidifies body fluids and initiates the acid-base disturbance known as respiratory acidosis. Hypocapnia alkalinizes body fluids and initiates the acid-base disturbance known as respiratory alkalosis.

Respiratory acidosis and alkalosis activate physiological responses that lead to directional changes in the level of plasma bicarbonate concentration; hypercapnia elicits a secondary increase in plasma bicarbonate and hypocapnia causes a secondary decrease in plasma bicarbonate. The secondary adjustments in plasma bicarbonate level serve to ameliorate the impact on acidity of the primary changes in $PaCO_2$; they should be viewed as integral parts of the respiratory disorders. Adaptation to acute hyper-

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1660–2137/03/0933–0061$19.50/0

Accessible online at:
www.karger.com/nep

Nicolaos E. Madias, MD
Tufts University School of Medicine
136 Harrison Avenue, Sackler 828
Boston, MA 02111 (USA)
Tel. +1 617 636 6800, Fax +1 617 636 0375, E-Mail nicolaos.madias@tufts.edu

capnia or hypocapnia emanates exclusively from titration of the body's nonbicarbonate buffers. By contrast, adaptation to chronic hypercapnia or hypocapnia originates from the kidneys and entails adjustments in renal acidification mechanisms. In this article, we will focus on the renal acidification response to respiratory acid-base disorders.

Renal Response to Respiratory Acidosis

Adaptation to acute hypercapnia elicits an immediate increment in plasma HCO_3^- concentration that is attributed to titration of non-HCO_3^- body buffers; such buffers generate HCO_3^- by combining with H^+ derived from the dissociation of carbonic acid. This adaptation is completed within 5–10 min from the rise in $PaCO_2$, and assuming a stable level of hypercapnia, no further changes in blood acid-base equilibrium are detectable for a few hours (i.e. 'acute steady state') [1, 2]. Empirical observations indicate that the overall limit of adaptation of plasma HCO_3^- is quite small. Moderate hypoxemia does not alter the adaptive response to acute respiratory acidosis. However, pre-existing hypobicarbonatemia (whether caused by metabolic acidosis or chronic respiratory alkalosis) enhances the magnitude of the HCO_3^- response to acute hypercapnia; by contrast, this response is diminished in hyperbicarbonatemic states (whether caused by metabolic alkalosis or chronic respiratory acidosis).

If hypercapnia persists, the plasma bicarbonate increases further due to renal responses entailing augmentation of tubular hydrogen ion secretion. Thus, net acid excretion (largely as ammonium) transiently exceeds endogenous acid production, leading to negative hydrogen ion balance and the generation of new bicarbonate ions [3]. Conservation of these new ions is ensured by an augmented rate of bicarbonate reabsorption, itself a reflection of the hypercapnia-induced persistent increment in hydrogen ion secretion. Observations during the provision of exogenous alkali indicate that this adaptive increase in renal bicarbonate reabsorption occurs roughly in parallel with the spontaneous rise in plasma bicarbonate concentration [2]. A new, chronic steady state emerges when the augmented filtered load of bicarbonate is precisely balanced by the accelerated rate of bicarbonate reabsorption and when net acid excretion returns to the level required to offset daily endogenous acid production. This adaptation requires 3–5 days for completion. Notably, the return of net acid excretion to baseline during the chronic steady state reflects continued increase in ammonium excretion that is balanced by increased bicarbonate excretion and suppressed titratable acidity [4]. As bicarbonate stores are gradually being augmented by the transient increase in net acid excretion, chloride stores are correspondingly depleted by a transient rise in renal chloride excretion. Chloruresis appears to outstrip acid excretion during the first 1 or 2 days of adaptation; the difference is accounted for by an increase in the excretion of sodium and potassium. Thus, some degree of sodium and potassium depletion typically accompanies adaptation to chronic hypercapnia. The resultant hypochloremia is sustained by a persistently depressed renal chloride reabsorption rate that accompanies chronic respiratory acidosis [2, 3].

The specific nephronal segments responsible for the response to chronic hypercapnia have not been characterized fully. Micropuncture observations in the rat proximal tubule indicate that, whereas absolute bicarbonate reabsorption is increased only mildly in acute hypercapnia, a substantial increase is observed during chronic hypercapnia [5]. Total CO_2 absorption was unchanged in microperfused cortical collecting tubules obtained from rabbits exposed to hypercapnia for 3–6 h, but it was substantially increased in tubules derived from animals that had been exposed to hypercapia for a 24-hour period [6]. Parallel increases in the rates of luminal Na^+/H^+ exchanger (presumably the NHE-3) and the basolateral $Na^+/3HCO_3^-$ cotransporter in the proximal tubule have been identified reflecting an increase in the V_{max} of each transporter but no change in the K_m for sodium [7, 8]. However, the finding of a stimulated Na^+/H^+ exchanger during chronic hypercapnia has not been reproduced by other workers [9, 10]. In addition, acute or chronic hypercapnia induces exocytotic insertion of H^+-ATPase-containing subapical vesicles to the luminal membrane of both proximal tubule cells and type A intercalated cells of cortical and medullary collecting ducts [11–14]. Such a redistribution of H^+-ATPase pumps during hypercapnia is not associated with a detectable increase in their quantity in either cortex or medulla [12]. Rat tubule microdissection studies showed that by 24 h of hypercapnia the activity of the H^+-ATPase along the entire nephron and that of H^+-K^+-ATPase in the cortical and medullary collecting tubules were increased [15]. Similar increases in the activities of these transporters during hypercapnia were observed in adrenalectomized rats replaced with physiological doses of aldosterone [15]. Further, chronic hypercapnia increases the steady-state abundance of mRNA coding for the basolateral Cl^-/HCO_3^- exchanger (band 3 protein) of type A intercalated cells in the renal cortex and medulla

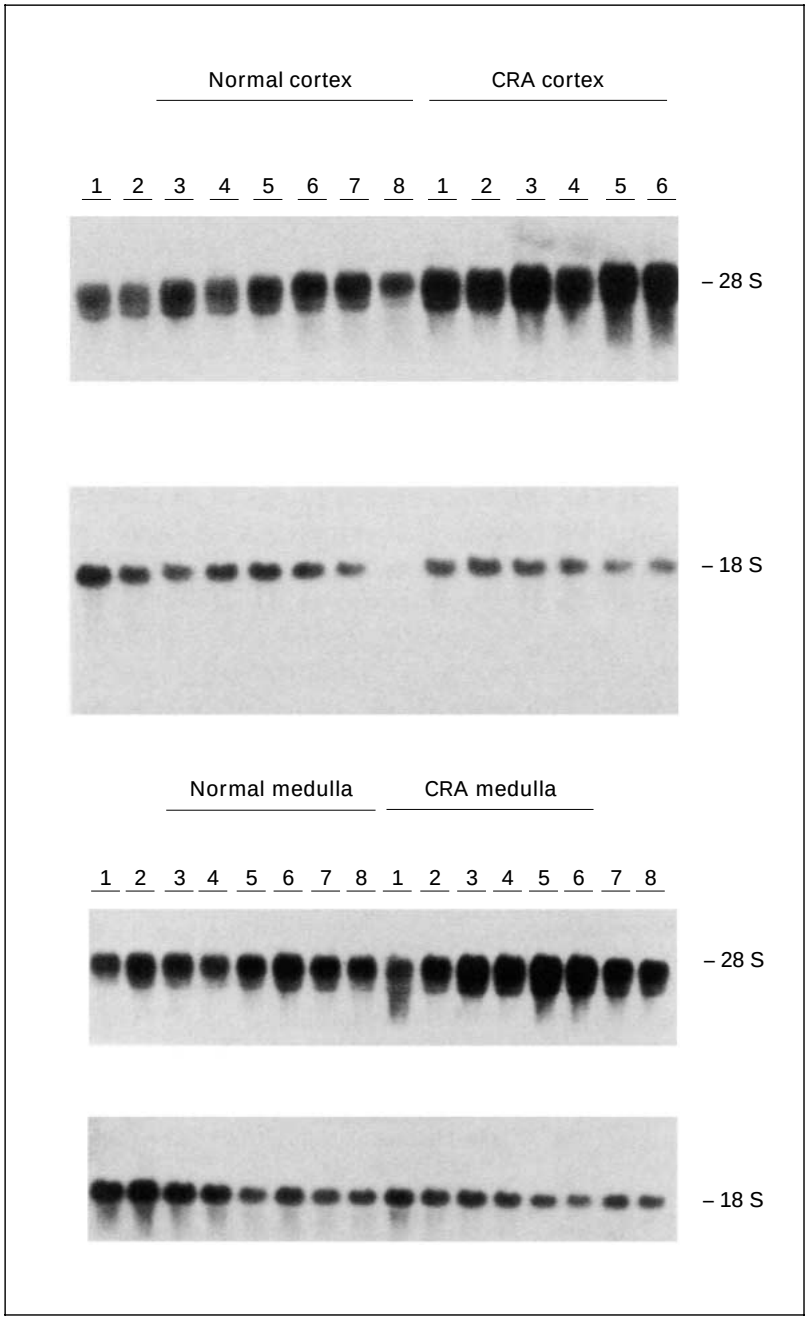

Fig. 1. Northern analysis of kidney band 3 (basolateral Cl^-/HCO_3^- exchanger) mRNA in renal cortex (upper panel) or renal medulla (lower panel) using a 3′ cDNA probe. Total RNA was obtained from rats exposed to hypercapnia for 5 days and normal controls. Forty micrograms were used in each lane. Densitometric readings disclosed increase of 2.8-fold (renal cortex) or 2.3-fold (renal medulla) in animals with chronic respiratory acidosis after normalization for β-actin signals (18S marker). Band 3 message is at the level of 28S marker. Autoradiograms were exposed as follows: band 3, 48 h; β-actin, 4 h. From Teixeira Da Silva et al. [16].

[16] (fig. 1). The signal that triggers the renal adaptation to hypercapnia remains undefined, but present evidence favors the increase in $PaCO_2$ itself rather than the decrease in systemic pH [17].

Studies in dogs indicate that a highly predictable relationship exists between the degree of chronic hypercapnia and the level at which plasma bicarbonate and hydrogen ion concentration stabilize following full physiological adaptation [2, 3]. Over the range of $PaCO_2$ values between 40–90 mm Hg, which would encompass most values encountered clinically, each mm Hg chronic increment in $PaCO_2$ is associated, on average, with a 0.3 mEq/l increment in steady-state plasma bicarbonate and a 0.3 nEq/l increment in blood hydrogen ion concentration. Systematic observations in patients with chronic, stable respiratory acidosis, appear to confirm the presence of

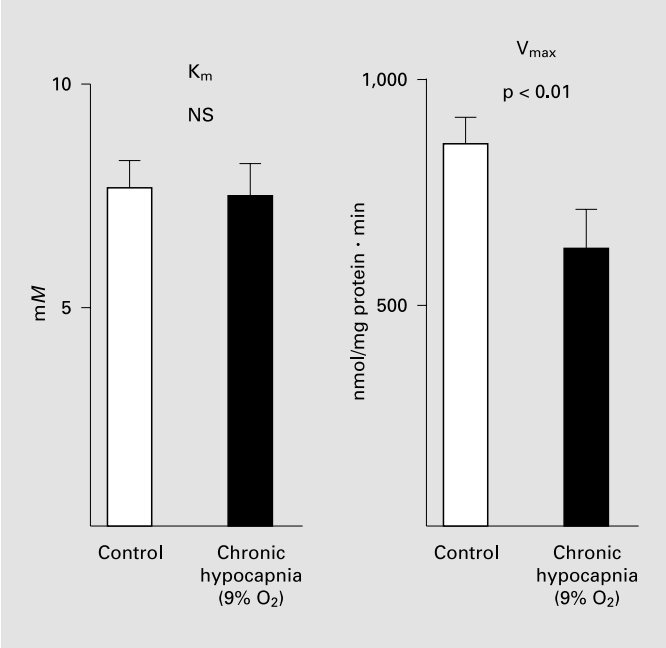

Fig. 2. Kinetic characteristics of rabbit renal cortical brush-border membrane vesicle Na^+-H^+ exchanger in animals adapted to chronic hypocapnia (9% O_2) (shaded bars) or in paired, contemporaneous controls (open bars). Data on K_m for sodium are depicted on the left, and those on V_{max} are shown on the right. Data represent means ± SE for seven paired sets of rabbits. Chronic hypocapnia resulted in a significant decrease in the V_{max} of the exchanger, whereas the K_m for sodium remained unaltered. From Hilden et al. [29].

similar quantitative relationships when no complicating acid-base disturbances are present [2, 18, 19].

The renal response to chronic hypercapnia is not altered appreciably by moderate hypoxemia (PaO_2 of 45–55 mm Hg), dietary sodium or chloride restriction, moderate potassium depletion, alkali loading, or adrenalectomy [2, 15]. However, recovery from chronic hypercapnia is crippled by a chloride-deficient diet. In this circumstance, despite normalization of the level of $PaCO_2$, plasma bicarbonate remains elevated as long as the state of chloride deprivation persists, thus creating the entity of 'posthypercapnic metabolic alkalosis' [2, 20]. Moderate potassium depletion does not interfere with full repair of acid-base equilibrium following return to eucapnia [2].

It is currently unknown to what extent renal insufficiency of variable severity limits the renal response to respiratory acidosis. Obviously, patients with end-stage renal disease cannot mount a renal response to chronic hypercapnia and, thus, they are more subject to severe acidemia. The degree of acidemia is more pronounced in patients receiving hemodialysis rather than peritoneal dialysis because the former treatment maintains, on average, a lower plasma bicarbonate concentration.

Renal Response to Respiratory Alkalosis

An immediate decrement in plasma bicarbonate occurs in response to hypocapnia. This adaptation is accounted for exclusively by alkaline titration of the body's nonbicarbonate buffers and is complete within 5–10 min from the onset of hypocapnia; no further detectable changes in blood acid-base equilibrium occur for a period of several hours establishing an operational 'acute steady state' [21, 22].

If hypocapnia persists, plasma bicarbonate falls further due to renal responses entailing dampening of tubular hydrogen ion secretion. As a result, a transient suppression of net acid excretion occurs, largely manifested by a fall in ammonium excretion and, early on, by an increase in bicarbonate excretion. Transient bicarbonaturia and a rise in urinary pH occur when hypocapnia develops abruptly but not in response to gradually evolving hypocapnia. These changes in net acid excretion, in turn, lead to positive hydrogen ion balance and a reduction in the body's bicarbonate stores. Maintenance of the resulting hypobicarbonatemia is ensured by the gradual suppression in renal bicarbonate reabsorption, itself a reflection of the hypocapnia-induced decrease in tubular hydrogen ion secretion [22, 24]. A new, chronic steady state emerges when the reduced filtered bicarbonate load is precisely balanced by the dampened bicarbonate reabsorption and when net acid excretion returns to the level required to offset daily endogenous acid production [22–24].

Micropuncture and microperfusion studies have documented suppressed proximal and distal acidification during acute hypocapnia, including decreased proximal bicarbonate reabsorption, and depressed formation and delivery of ammonium and titratable acid [25–27]; reduced proximal bicarbonate reabsorption was also demonstrated by micropuncture in chronic hypocapnia [28] but distal acidification has not been examined with these techniques in chronic hypocapnia. A reduction in systemic PCO_2 also leads to a disproportional reduction in renal cortical PCO_2 and augmentation of proximal chloride reabsorption.

Parallel decreases in the rates of the luminal Na^+/H^+ exchanger (presumably the NHE-3) (fig. 2) and the basolateral $Na^+/3HCO_3^-$ cotransporter in the proximal tubule have been found in chronic hypocapnia reflecting a de-

crease in the V_{max} of each transporter but no change in the K_m for sodium [8, 29]. Moreover, hypocapnia induces endocytotic retrieval of H^+-ATPase pumps from the luminal membrane of the proximal tubule cells as well as type A intercalated cells of cortical and medullary collecting tubules [11]. In rat tubule microdissection studies, the activity of the H^+-ATPase along the entire nephron and that of the H^+-K^+-ATPase in the cortical and medullary collecting tubules were decreased by 6 h of hypocapnia and thereafter [15]. The inhibitory effect of hypocapnia on the renal proton ATPases appears to be independent of potassium and aldosterone [15].

The adaptive retention of acid during sustained hypocapnia is normally accompanied by a loss of sodium into the urine [22–24, 30, 31]; the resultant extracellular fluid loss has been proposed as being responsible for the characteristic hyperchloremia. When a new steady state emerges, hypobicarbonatemia and hyperchloremia are maintained by a reduced bicarbonate reabsorption and an enhanced chloride reabsorption, respectively. In the presence of dietary sodium restriction, acid retention is achieved in the company of increased potassium rather than increased sodium excretion. If both sodium and potassium are restricted, phosphate retention rather than cation loss accompanies the renal acid retention during adaptation to hypocapnia [24, 30]. There is no appreciable change in plasma lactate during chronic hypocapnia even in the presence of moderate hypoxemia [22–24, 31].

Evidence suggests that the renal response to persistent hypocapnia is likely mediated not by changes in blood or 'whole-body' intracellular pH but by some direct effect of reduced $PaCO_2$ itself [32–34]. Thus, animals in which plasma bicarbonate had been substantially reduced prior to adaptation to sustained hypocapnia (by means of the chronic administration of a large HCl load) evidenced the same renal response to a primary reduction in $PaCO_2$ as normal animals, even though the net effect of such adaptation was an overt fall in blood pH [32].

Approximately 2–3 days are required for completion of the renal response to hypocapnia. These mechanisms produce and maintain the reduction in plasma bicarbonate characteristic of the new, chronic steady state and result in a highly predictable relationship between the degree of chronic hypocapnia and the level at which plasma bicarbonate stabilizes; in the dog, each mm Hg chronic reduction in $PaCO_2$ is associated with a fall in plasma bicarbonate averaging 0.4–0.5 mEq/l [22, 24, 32, 33]. Limited data in humans (patients subjected to chronic hypocapnia, high-altitude dwellers, volunteers studied at high altitude or at simulated altitude) have indicated that plasma bicarbonate decreases, on average, by approximately 0.4 mEq/l for each mm Hg chronic decrease in $PaCO_2$ [22, 31, 35]. Despite the similarity in the magnitude of the secondary response of plasma bicarbonate to chronic hypocapnia between dogs and humans, the resultant impact on blood hydrogen ion concentration is substantially disparate: Whereas in the dog blood hydrogen ion concentration falls by only 0.17 nEq/l for each mm Hg chronic reduction in $PaCO_2$ [24], the corresponding decrease in humans is in the order of 0.4 nEq/l [31]. The main reason for this discrepancy is the higher baseline level of plasma bicarbonate in humans (24–25 vs. 21 mEq/l in the dog).

Patients with end-stage renal disease are obviously at risk of developing severe alkalemia in response to chronic hypocapnia because they cannot mount a renal response. Such a risk is higher in patients receiving peritoneal dialysis rather than hemodialysis because the former treatment maintains, on average, a higher plasma bicarbonate concentration.

Conclusion

Adaptation to chronic hypercapnia or hypocapnia elicits adjustments in renal acidification mechanisms that generate and maintain directional changes in plasma bicarbonate concentration. These changes in plasma bicarbonate pursue a characteristic time course and tend to ameliorate the impact on acidity of the primary changes in $PaCO_2$. It is currently unknown to what extent graded degrees of chronic renal insufficiency might influence the renal response to respiratory acid-base disorders.

References

1 Brackett NC Jr, Cohen JJ, Schwartz WB: Carbon dioxide titration curve of normal man: effect of increasing degrees of acute hypercapnia on acid-base equilibrium. N Engl J Med 1965;272:6–12.

2 Madias NE, Adrogué HJ: Respiratory alkalosis and acidosis; in Seldin DW, Giebisch G (eds): The Kidney: Physiology and Pathophysiology, ed 3. Philadelphia, Lippincott/Williams & Wilkins, 2000, pp 2131–2166.

3 Schwartz WB, Brackett NC Jr, 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 1965;44:291–301.

4 Adrogué HJ, Madias NE: Renal acidification during chronic hypercapnia in the conscious dog. Pflügers Arch 1986;406:520–528.

5 Cogan MG: Chronic hypercapnia stimulates proximal bicarbonate reabsorption in the rat. J Clin Invest 1984;74:1942–1947.

6 Laski ME, Kurtzman NA: Collecting tubule adaptation to respiratory acidosis induced in vivo. Am J Physiol 1990;258:F15–F20.

7 Krapf R: Mechanisms of adaptation of chronic respiratory acidosis in the rabbit proximal tubule. J Clin Invest 1989;83:890–896.

8 Ruiz OS, Arruda JAL, Talor Z: Na-HCO_3^- cotransport and Na-H antiporter in chronic respiratory acidosis and alkalosis. Am J Physiol 1989:256:F414–F420.

9 Northrup TE, Garella S, Perticucci E, Cohen JJ: Acidemia alone does not stimulate rat renal Na^+-H^+ antiporter activity. Am J Physiol 1988; 255:F237–F243.

10 Zeidel ML, Seifter JL: Regulation of Na/H exchange in renal microvillus vesicles in chronic hypercapnia. Kidney Int 1988;34:60–66.

11 Al-Awqati Q: The cellular renal response to respiratory acid-base disorders. Kidney Int 1985;28:845–855.

12 Bastani B, Gluck S, Hilden S, Johns C, Yang L, Madias NE: Adaptation if renal vascuolar H^+-ATPase to acute or chronic respiratory acidosis in the rat (abstract). J Am Soc Nephrol 1993;4: 831.

13 Madsen KM, Tischer CC: Cellular response to acute respiratory acidosis in rat medullary collecting duct. Am J Physiol 1983;245:F670–F679.

14 Verlander JW, Madsen KM, Tischer CC: Effect of acute respiratory acidosis on two populations of intercalated cells in rat cortical collecting duct. Am J Physiol 1987;253:F1142–F1156.

15 Eiam-Ong S, Laski ME, Kurtzman NA, Sabatini S: Effect of respiratory acidosis and respiratory alkalosis on renal transport enzymes. Am J Physiol 1994;267:F390–F399.

16 Teixeira Da Silva JC Jr, Perrone RD, Johns CA, Madias NE: Rat kidney band 3 mRNA modulation in chronic respiratory acidosis. Am J Physiol 1991;260:F204–F209.

17 Madias NE, Wolf CJ, Cohen JJ: Regulation of acid-base equilibrium in chronic hypercapnia. Kidney Int 1985;27:538–543.

18 Brackett NC Jr, Wingo CF, Muren O, Solano JT: Acid-base response to chronic hypercapnia in man. N Engl J Med 1969;280:124–130.

19 Van Ypersele de Strihou C, Brasseur L, De Goninck J: The 'carbon dioxide response curve' for chronic hypercapnia in man. N Engl J Med 1966;275:117–122.

20 Adrogué HJ, Madias NE: Management of life-threatening acid-base disorders. N Engl J Med 1998;338:26–34, 107–111.

21 Arbus GS, Hebert LA, Levesque PR, Etsten BE, Schwartz WB: Characterization and clinical application of the 'significance band' for acute respiratory alkalosis. N Engl J Med 1969; 280:117–123.

22 Gennari FJ, Kassirer JP: Respiratory alkalosis; in Cohen JJ, Kassirer JP (eds): Acid-Base. Boston, Little, Brown, 1982, pp 349–376.

23 Gledhill N, Beirne GJ, Dempsey JA: Renal response to short-term hypocapnia in man. Kidney Int 1975;8:376–386.

24 Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia. J Clin Invest 1972;51:I722–I730.

25 Jacobson HR: Effects of CO_2 and acetazolamide on bicarbonate and fluid transport in rabbit proximal tubules. Am J Physiol 1981; 240:F54–F62.

26 Cogan M: Effects of acute alterations in PCO_2 on proximal HCO_3^-, Cl^-, and H_2O reabsorption. Am J Physiol 1984;246:F21–F26.

27 Bengele HH, McNamara ER, Schwartz JH, Alexander EA: Acidification adaptation along the inner medullary collecting duct. Am J Physiol 1988;255:F1155–F1159.

28 Santella RN, Maddox DA, Gennari FJ: Delivery dependence of early proximal bicarbonate reabsorption in the rat in respiratory acidosis and alkalosis. J Clin Invest 1991;87:631–638.

29 Hilden SA, Johns CA, Madias NE: Adaptation of rabbit renal cortical Na^+-H^+-exchange activity in chronic hypocapnia. Am J Physiol 1989; 257:F615–F622.

30 Gougoux A, Kaehny WD, Cohen JJ: Renal adaptation to chronic hypocapnia: Dietary constraints in achieving H^+ retention. Am J Physiol 1975;229:1330–1337.

31 Krapf R, Beeler I, Hertner D, Hulter HN: Chronic respiratory alkalosis: The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 1991;324: 1394–1401.

32 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 geared to the defense of extracellular $[H^+]$. J Clin Invest 1976;57:1483–1489.

33 Madias NE, Schwartz WB, Cohen JJ: The maladaptive renal response to secondary hypocapnia during chronic HCl acidosis in the dog. J Clin Invest 1977;60:1393–1401.

34 Clark DD, Chang BS, Garella SG, Cohen JJ, Madias NE: Secondary hypocapnia fails to protect 'whole body' intracellular pH during chronic HCl-acidosis in the dog. Kidney Int 1983;23:336–341.

35 Gennari FJ, Kaehny WD, Levesque PR, Cohen JJ: Acid-base response to chronic hypocapnia in man (abstract). Clin Res 1980;28:533A.