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Chronic respiratory alkalosis induces renal PTH-resistance, hyperphosphatemia and hypocalcemia in humans

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Chronic respiratory alkalosis induces renal hyperphosphatemia and hypocalcemia in humans. The effects of chronic respiratory alkalosis on divalent ion homeostasis have not been reported in any species. We studied four normal male subjects during a four-day control period (residence at 500 m), during six days of chronic respiratory alkalosis induced by hypobaric hypoxia (residence at 3450 m), followed by a six-day eucapnic recovery period (500 m) under metabolic balance conditions. Chronic respiratory alkalosis ($\Delta PaCO_2$, −8.4 mm Hg, $\Delta[H^+]$ −3.2 nmol/liter) resulted in a sustained decrement in plasma ionized calcium concentration ($\Delta[IoCa^{++}]_p$, −0.10 mmol/liter, $P < 0.05$) and a sustained increment in plasma phosphate concentration ($\Delta[PO_4]_p$, +0.14 mmol/liter, $P < 0.005$) associated with increased fractional excretion of Ca^{++} (+0.5%, $P < 0.005$), decreased phosphate clearance (−6.1 ml/min, $P < 0.025$) and decreased excretion of nephrogenous cAMP (−1.5 nmol/100 ml GFR, $P < 0.0025$). Urinary phosphate excretion decreased by 15.4 mmol/24 hr on day 1 of chronic respiratory alkalosis ($P < 0.0025$), but returned to control values by day 6 despite hyperphosphatemia. Serum intact [PTH] did not change. Sustained hypomagnesuria (−0.8 mmol/24 hr, $P < 0.05$) occurred during chronic respiratory alkalosis and was accounted for, at least in part, by decreased fractional excretion of Mg^{++} (−0.7%, $P < 0.05$) in the absence of change in plasma magnesium concentration. Serum $1,25(OH)_2D$ levels were unchanged by chronic respiratory alkalosis. In conclusion, the decrease in nephrogenous cAMP generation despite unchanged serum intact PTH concentration suggests that chronic respiratory alkalosis results in impaired renal responsiveness to PTH as manifested by alterations in PTH-dependent renal calcium and phosphate transport. Hypomagnesuria in chronic respiratory alkalosis may be due, at least in part, to hypocalcemia-induced enhancement of renal magnesium reabsorption. The failure of [PTH] to increase during hypocalcemia may reflect defective PTH secretion.

Chronic respiratory alkalosis is the commonly encountered acid-base disorder initiated and sustained by a primary reduction in arterial carbon dioxide tension (hypocapnia), which, in turn, results in secondary hypobicarbonatemia due to hypocapnia-induced suppression of renal acid excretion [1, 2]. Frequent clinical settings for chronic respiratory alkalosis include tissue hypoxia, malignancy, neurologic disorders, pregnancy, and hepatic failure. Since diverse alterations in divalent ion metabolism also occur in these settings [3–6], a precise characterization of the potential independent role of chronic hypocapnia in producing disorders of mineral metabolism is of substantial clinical importance.

Calcium and phosphorus homeostasis has been characterized incompletely in chronic respiratory acid-base disorders. In chronic hypercapnia produced in dogs by exposure to a 10% CO_2 atmosphere, sustained hypercalciuria occurs despite no changes in filtered Ca^{++} load, total plasma calcium concentration, blood ionized Ca^{++} concentration, serum PTH, and $1,25(OH)_2D$ concentration [7]. These results suggest that impaired renal tubular calcium reabsorption is responsible, at least in part, for the observed increase in fractional Ca^{++} excretion. A preliminary report in rats has also documented hypercalciuria during sustained hypercapnia [8].

No data are currently available in any species which characterize the plasma or urinary calcium response to chronic hypocapnia. Acute hypocapnia induced by voluntary hyperventilation in human volunteers results in no significant change in plasma total calcium concentration [9, 10]. However, small but statistically significant reductions in plasma ionized $[Ca^{++}]$ have been reported in both rats and humans [11, 12], which average about −0.4 mmol/liter per pH unit. The magnitude of this acute decrease in plasma ionized $[Ca^{++}]$ is similar to that observed in vitro as the net result of counter-balancing pH-induced changes in albumin-Ca^{++} binding and HCO_3^--Ca^{++} complex dissolution [11–16]. There are no reports evaluating urinary calcium excretion during acute hypocapnia in humans. A single report in dogs suggested no change in urinary calcium excretion [17]. The reported effects of chronic chloride deficiency-induced metabolic alkalosis on calcium and PTH homeostasis might be of value in predicting the results of studies of chronic respiratory alkalosis [18]. These studies demonstrated that an alkalosis of metabolic origin resulted in chronic hypocalcemia with a secondary increase in plasma PTH concentration accompanied by hypocalciuria and increased tubular reabsorption of Ca^{++}, possibly PTH-driven. The etiology of hypocalcemia, however, was not determined.

Reported measurements of the plasma and urinary phosphorus responses to chronic hypocapnia are limited to studies in dogs which showed reversible hyperphosphatemia, but did not provide values for daily phosphorus excretion nor estimates of GFR to permit assessment of the role of the kidney in altered phosphorus homeostasis [19–21]. No data have been reported

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Table 1. Effect of chronic hypocapnia on steady-state mineral metabolism

Period	$PaCO_2$	Ca^{++}	PO_4	Mg	Intact PTH	$1,25(OH)_2$ D
	mm Hg	*mmol/liter*			*pg/ml*	
Control	39.1 ± 0.6	1.17 ± 0.02	1.03 ± 0.04	0.82 ± 0.03	23.0 ± 3.2	26.3 ± 3.8
Hypocapnia	30.7 ± 0.4[a]	1.07 ± 0.02[a]	1.17 ± 0.05[b]	0.85 ± 0.02	26.2 ± 4.8	24.8 ± 4.2
Recovery	38.3 ± 0.9[a]	1.14 ± 0.01[a]	1.08 ± 0.05[b]	0.83 ± 0.03	28.2 ± 4.2	24.2 ± 4.1

Plus-minus values are means ± SE. Abbreviations are: $PaCO_2$, arterial carbon dioxide tension; Ca^{++}, ionized calcium; PO_4, phosphate; Mg, magnesium; PTH, intact parathyroid hormone; $1,25(OH)_2D$, 1,25-dihydroxycholecalciferol. For definition of study periods see **Methods** section. To convert mm Hg into kilopascals, multiply by 0.1333. Steady state values are means of values from the last three days of each period.

[a] $P < 0.001$ for the comparison with the previous steady-state period (control or hypocapnia)

[b] $P < 0.005$ for the comparison with the previous steady-state period (control or hypocapnia)

describing the plasma and urinary magnesium response to chronic hypocapnia in any species. Acute hypocapnia resulted in no change in plasma magnesium concentration in dogs [17]. No data have been reported describing the responses of PTH or vitamin D metabolites to chronic hypocapnia in any species.

Accordingly, the present studies were undertaken to examine the impact of chronic hypocapnia in humans on divalent cation, phosphorus, parathyroid hormone and $1,25(OH)_2D$ metabolism.

Methods

The protocol was designed to determine the effects of chronic hypocapnia on divalent cation, phosphate, PTH, and $1,25(OH)_2D$ metabolism in normal subjects. Four normal male volunteers [mean age (± SD) 26.3 ± 3.7 years; weight, 71.9 ± 6.4 kg] were studied during a four-day control period [residence at 500 m, partial pressure of oxygen 150 mm Hg, (20 kPa)], during six days of chronic hypocapnia induced by hypobaric hypoxia [residence at the High Alpine Research Station, Jungfraujoch, Swiss Alps, altitude 3450 m, partial pressure of oxygen 104 mm Hg (13.9 kPa)], followed by a six-day eucapnic recovery period (residence at 500 m) under metabolic balance conditions. All subjects were medical students who volunteered for the study, were paid for participation, and gave informed consent. None were smokers or were taking any drugs before or during the study. Transfer to and from the High Alpine Research Station was performed by train in less than four hours.

The subjects ingested a constant metabolic diet for at least six days before the study (prestudy phase) and during all three study periods (control, hypocapnia, and recovery). The diet provided the following for every kilogram of body weight per day: sodium 1.75 mmol, potassium 1.53 mmol, calcium 0.395 mmol (15.8 mg), phosphate 0.51 mmol (15.8 mg), nitrogen 15.7 mmol (0.22 g), water 40.7 ml, and 35 kCal.

Daily fasting, arterialized venous blood samples were obtained in a heparin-coated syringe from a heated hand or forearm vein [22]. Blood samples were accepted only if the partial pressure of oxygen was greater than 70 mm Hg (9.3 kPa). Weight and oral temperature were measured at the time of blood sampling; 24-hour urine samples were collected in plastic bottles containing mineral oil and thymol-chloroform preservative. Exercise was limited to minimal ambulation throughout the study. During each study period, a subject was considered to be in a steady state when plasma values obtained on three consecutive days varied by no more than 1.5 mmol/per liter for bicarbonate and by no more than 3 mm Hg (0.4 kPa) for $PaCO_2$.

Analytical procedures

All determinations were performed in duplicate. Acid-base and electrolyte values in blood and urine were determined as described previously [2]. Ionized calcium was measured with an ion-selective electrode (Ciba-Corning, Model 634). Phosphate was determined by the method of Fiske and Subbarow [23]. Serum intact parathyroid hormone [24] and $1,25(OH)_2D$ concentration [25] were measured with specific radioimmunoassay/radioreceptor assay kits (Nichols Institute, San Juan Capistrano, California, USA). cAMP in plasma and urine was determined by radioimmunoassay kit (Amersham, Arlington Heights, Illinois, USA). Nephrogenous cAMP was calculated according to the method of Broadus et al [26]. Results are reported as means ± standard error of the mean (SE) unless stated otherwise. Statistical significance was determined by two-tailed *t*-test for paired data.

The study protocol was approved by the ethics committee of the University of Berne School of Medicine.

The steady state plasma and urinary acid-base composition, creatinine clearance, and plasma albumin levels of these subjects have been the subject of a previous report [2].

Results

Chronic exposure to hypobaric hypoxia resulted in significant hypocapnia with a decrease in $PaCO_2$ from 39.1 ± 0.6 to 30.7 ± 0.4 mm Hg ($P < 0.001$, Table 1). In response to hypocapnia, blood hydrogen ion concentration decreased from 36.9 ± 0.3 to 33.7 ± 0.3 nmol/liter ($P < 0.001$), while plasma bicarbonate concentration decreased from 25.2 ± 0.4 to 21.7 ± 0.5 mmol/liter ($P < 0.001$). Chronic hypocapnia resulted in a small increase in plasma albumin concentration from 44.0 ± 1.1 to 45.8 ± 1.1 g/liter ($P < 0.05$), but did not result in significant changes in creatinine clearance (Table 2), body weight and hematocrit (data not shown).

The effects of chronic respiratory alkalosis on steady-state blood ionized calcium, plasma phosphate, magnesium, serum intact parathyroid hormone and $1,25(OH)_2D$ concentrations are depicted in Table 1. Table 2 shows the effect of chronic hypocapnia on urinary net acid, electrolyte, calcium, phosphate, magnesium and nephrogenous cAMP (ncAMP) excretion as well as its effects on the fractional excretions (FE) of calcium and magnesium. The natriuretic response to hypocapnia was most prominent on day 1 and was absent by day 6 (mean day 6 urinary sodium excretion 120.1 mmol/24 hr).

Table 2. Effect of chronic hypocapnia on urinary net acid, electrolyte, mineral and ncAMP excretion

	Net acid	Na^+	K^+	Cl^-	Ca^{++}	PO_4	Mg	FE_{ca}	FE_{Mg}	PO_4 clearance	ncAMP *nmol/ 100 ml GFR*	Creatinine clearance
	mmol/24 hr							*%*		*ml/min*		*ml/sec*
Control	44.4	114.5	91.4	123.3	5.87	28.9	6.1	1.88	3.73	19.5	1.77	2.33
	±3.5	±5.9	±3.1	±6.4	±0.45	±1.7	±0.15	±0.26	±0.24	±1.6	±0.31	±0.10
Hypocapnia												
Day 1	5.0[a]	158.0[a]	72.1[a]	128.6	5.90	10.9[a]	4.8	2.60[a]	3.10[c]	10.0[b]	0.55[a]	
	±0.5	±14.0	±2.8	±8.0	±0.6	±1.7	±0.2	±0.30	±0.25	±1.5	±0.15	
Days 4–6	41.9[b]	130.5[b]	85.9	124.1	5.4	23.7	5.0	2.48[b]	3.24[d]	13.8[b]	0.55[a]	2.15
	±3.0	±10.5	±4.0	±8.9	±0.75	±1.1	±0.1	±0.32	±0.21	±1.4	±0.21	±0.18
ΣΔ (Day 6)	−88[e]	+153[e]	−69[e]	+27	−2.42	−65[f]	−8.1[f]	—	—	—	−7.10[f]	
Recovery												
Day 1	47.5[b]	139.9	96.0[b]	133.6	5.21	25.8[a]	6.7	1.65[b]	3.95[b]	14.2	1.25[b]	
	±3.2	±5.3	±10.0	±8.0	±0.81	±1.8	±0.2	±0.31	±0.20	±1.1	±0.25	
Days 4–6	51.5[d]	105.9[d]	94.8	119.7	5.03	35.0[c]	6.4	1.87[b]	3.88[b]	22.3[b]	1.72[a]	2.28
	±3.8	±5.6	±4.2	±6.3	±0.90	±2.8	±0.2	±0.29	±0.18	±1.8	±0.34	±0.10
ΣΔ (Day 6)	+69[e]	−139[e]	+55[e]	+6	−2.0	+31[f]	+9.8[f]	—	—	—	+6.4[f]	

Plus-minus values are means ± SE. ΣΔ denotes the cumulative change in excretion, calculated as the accumulated sum of the daily differences from the mean value of the previous steady-state period.

[a] $P < 0.001$
[b] $P < 0.005$
[c] $P < 0.025$
[d] $P < 0.05$
} vs. the previous steady-state period

[e] $P < 0.001$
[f] $P < 0.05$
} significantly different from zero

Chronic respiratory alkalosis resulted in a significant and sustained decrease in renal phosphate clearance (Table 2, Fig. 1) as well as in significant steady-state hyperphosphatemia (Table 1, Fig. 1). During eucapnic recovery, both phosphate clearance and plasma phosphate concentration returned to control values (Tables 1 and 2, Fig. 1). Urinary phosphate excretion decreased by 15.4 mmol/24 hr on day 1 of chronic respiratory alkalosis ($P < 0.0025$), but returned to control values by day 6 despite hyperphosphatemia. Chronic hypocapnia induced a significant decrease in blood ionized calcium concentration that occurred in association with a significant and persistent increase in the fractional excretion of calcium (FE_{Ca}, Tables 1 and 2, Fig. 1). FE_{Ca} and blood ionized calcium concentration returned to control values during eucapnic recovery. Importantly, these changes occurred without significant alterations in the cumulative change in urinary calcium excretion (sum of the daily changes in urinary calcium excretion from the previous steady-state mean value, Table 2).

Chronic respiratory alkalosis also resulted in a large and reversible decrease in ncAMP excretion of −1.5 ± 0.14 nmol/ 100 ml GFR ($P < 0.0025$, Table 2, Fig. 2). Despite steady-state ionized hypocalcemia and hyperphosphatemia, there were no significant changes in the serum concentrations of either intact PTH or $1,25(OH)_2D$ (Table 1, Fig. 2). Sustained hypomagnesuria was observed during chronic respiratory alkalosis (−0.8 mmol/24 hr, $P < 0.05$) and was accounted for in part, by decreased FE_{Mg} (−0.7%, $P < 0.05$) despite no change in plasma magnesium concentration (Table 2, Fig. 3).

Discussion

The present study is the first to examine the effects of chronic respiratory alkalosis on divalent ion, PTH and $1,25(OH)_2D$ metabolism in humans. The key findings summarized in Figure 4 are: (1) chronic respiratory alkalosis results in sustained hyperphosphatemia and hypocalcemia; (2) renal phosphate clearance decreases while fractional excretion of calcium increases despite hyperphosphatemia and hypocalcemia, respectively; (3) nephrogenous cAMP excretion decreases; and (4) there are no significant changes in serum intact PTH and $1,25(OH)_2D$ concentrations.

The findings of persistent hypocalcemia during sustained hypocapnia in humans was unexpected. Whereas it is well known that acute hypocapnia in both humans and rats can result in hypocalcemia [approximately −0.4 mmol/L (Ca^{++}) per pH unit], the magnitude of alkalemia in the present studies can account for only a small fraction (13%) of the observed hypocalcemia [11–16]. Moreover, even if acute acid-base-induced alterations in albumin-Ca^{++} binding and/or HCO_3^--Ca^{++} complexation did operate to produce sudden hypocalcemia of small magnitude, there is no precedent for such changes to be sustained inasmuch as numerous potent counter-regulatory mechanisms defend against prolonged changes in ionized calcium concentration [such as PTH and $1,25(OH)_2D$]. PTH hypersecretion in response to hypocalcemia has been detected with a minimum sensitivity of 0.025 mmol/liter ionized Ca^{++} [27, 28]. Although acute hyperphosphatemia can reduce plasma ionized calcium concentration in humans and experimental animals [29] by virtue of $CaHPO_4$ complexation, this explanation is insufficient to account for our results in chronic hypocapnia, since the magnitude of this effect accounts for less than 3% of the observed hypocalcemia.

The present study demonstrates that chronic hypocapnia does not result in significant changes in urinary calcium excretion in normal subjects. However, since creatinine clearance was unchanged by hypocapnia, sustained hypocalcemia during hypocapnia indicates a sustained reduction in the filtered load

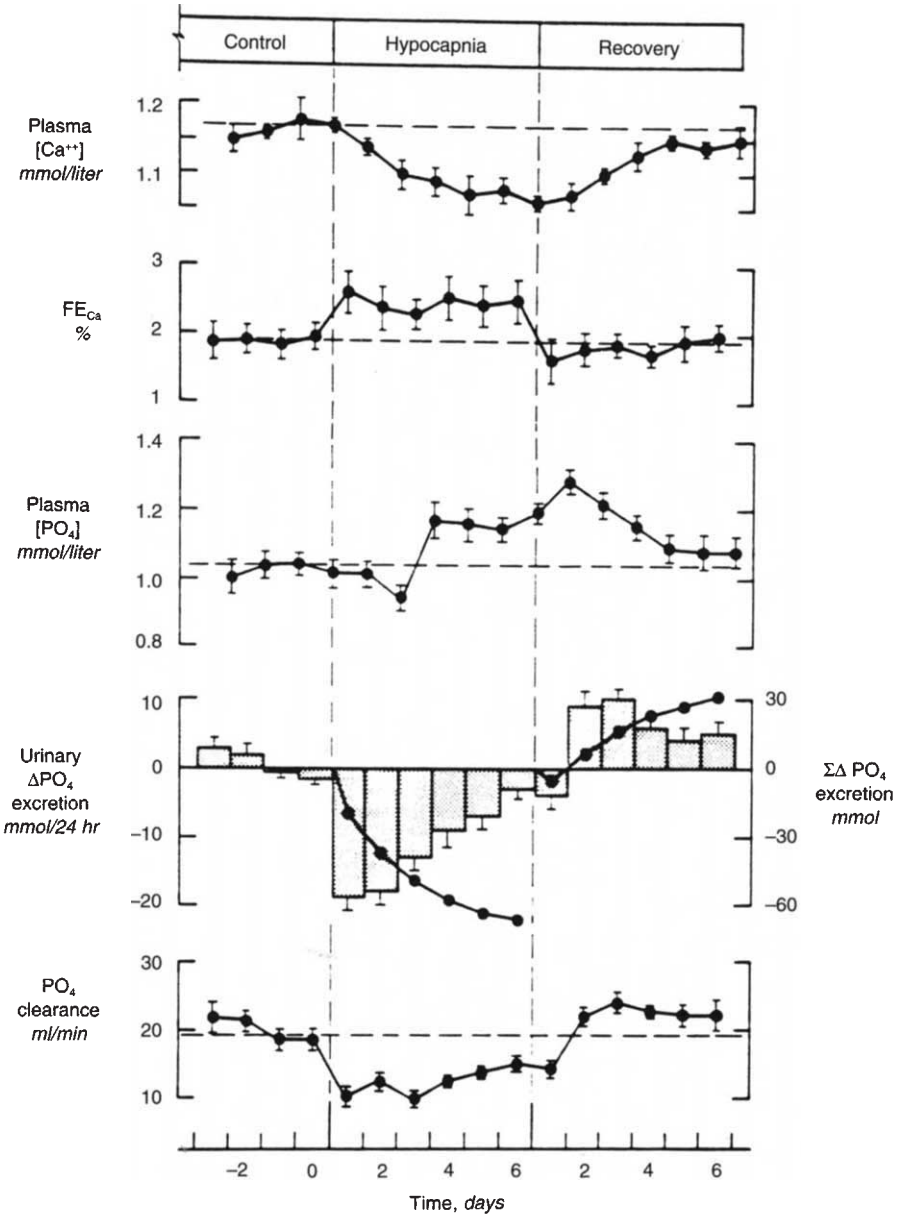

Fig. 1. *Effects of chronic hypocapnia on plasma ionized [Ca^{++}] and plasma phosphate (PO_4) concentration, fractional excretion of calcium (FE_{Ca}), urinary phosphate excretion and phosphate clearance.* Urinary ΔPO_4 excretion denotes the daily changes in phosphate excretion in comparison to the previous steady-state period (that is, control and hypocapnia, respectively). $\Sigma\Delta PO_4$ excretion (●——●) denotes the sum of the daily changes in urinary phosphate excretion from the previous steady-state period mean excretion value.

of calcium. As depicted in Figures 1 and 4, this constellation of findings indicates that sustained hypocapnia results in both an early (24 hr) and sustained increase in the fractional excretion of calcium. This observation indicates that, however generated, a sustained impairment in renal calcium reabsorption is responsible, at least in part, for the maintenance of chronic hypocalcemia. Moreover, the finding that steady-state urinary calcium excretion during hypocapnia was unchanged from control values excludes the possibility that decreased gastrointestinal calcium absorption was responsible, even in part, for the steady state of hypocalcemia observed in the present studies. That is, a putative hypocapnia-induced decrease in steady-state (days 4 to 6) net gut calcium absorption would obligate a decrease in steady-state urinary calcium excretion (in the presence of a constant dietary calcium intake) which was not observed. Only a hypocapnia-induced steady-state increase in bone calcium efflux could account for an unchanged urinary calcium excretion rate in the presence of decreased gut absorption. Since acidosis (not alkalosis) is reported to increase bone calcium efflux, a role for the gastrointestinal tract in hypocapnia-induced hypocalcemia is excluded [30].

Our data demonstrate that chronic hypocapnia induces "relative" hypoparathyroidism, that is, no change in PTH concentration despite significant hypocalcemia. Consequently, the coexistence of impaired renal calcium reabsorption and hypocalcemia observed during chronic hypocapnia might be interpreted to result from hypoparathyroidism. However, both animal and human studies [31–35] have demonstrated that, under ordinary dietary conditions, renal calcium reabsorption is tonically stimulated by *normal* concentrations of PTH. Thus, the possibility requires consideration that an additional defect in the renal action of PTH exists, explaining the increased

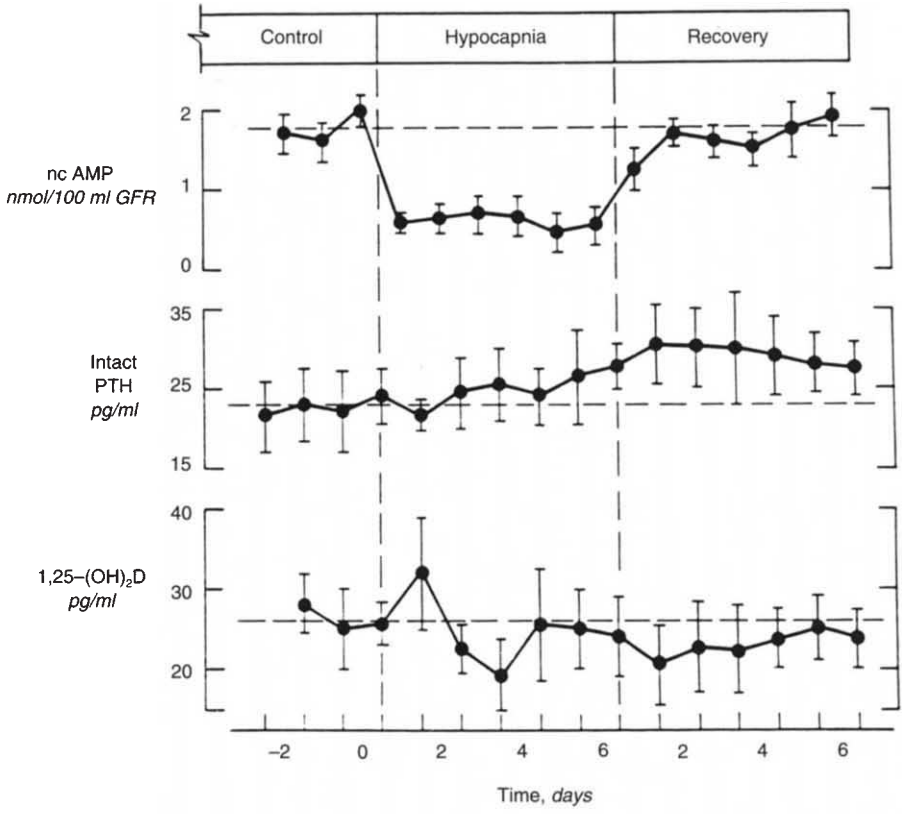

Fig. 2. *Effects of chronic hypocapnia on the urinary excretion of nephrogenous cyclic AMP (ncAMP) and serum intact parathyroid hormone (PTH) and 1,25(OH)$_2$D levels.*

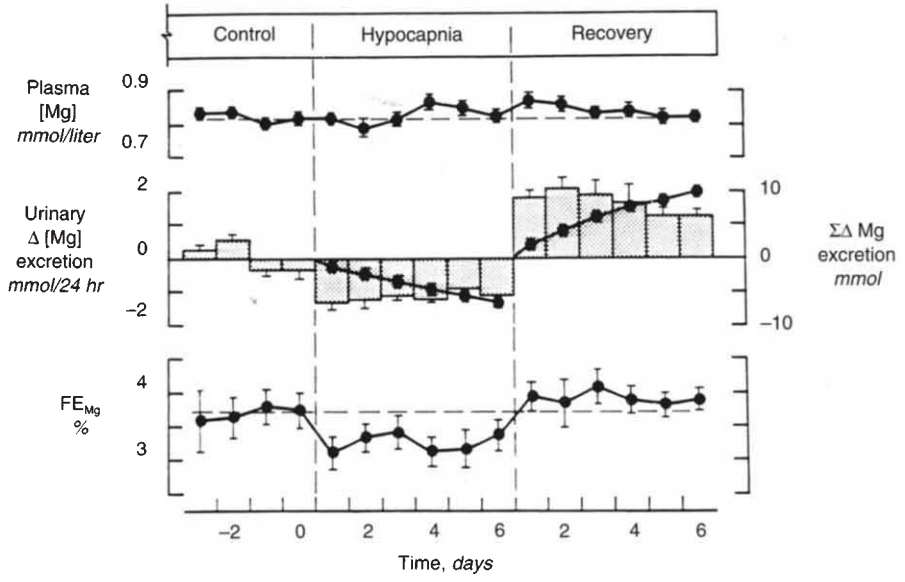

Fig. 3. *Effects of chronic hypocapnia on plasma and urinary magnesium (Mg) homeostasis.* Urinary Δ Mg excretion denotes the daily changes in urinary magnesium excretion as compared with the previous steady-state period mean excretion value (control and hypocapnia, respectively). ΣΔ Mg excretion (●——●) denotes the cumulative changes in urinary Mg excretion from the previous steady-state period. FE_{Mg} denotes fractional urinary excretion of magnesium.

fractional excretion of calcium despite hypocalcemia and suppressed phosphate clearance in the setting of hyperphosphatemia. Our findings of a large decrease in nephrogenous cyclic AMP excretion in response to chronic hypocapnia without change in serum intact PTH concentration provides strong evidence for this hypothesis. Thus, chronic hypocapnia induced a state of renal tubular resistance to the cellular action of PTH, that is functional pseudohypoparathyroidism, type I [36]. Therefore, the present results demonstrate that chronic hypocapnia interferes at two sites of PTH metabolism: The acid-base disorder inhibits both PTH secretion[1] and renal responsiveness

[1] Whereas it is recognized that the steady-state plasma concentration of a hormone is co-determined by its metabolic clearance rate as well as its secretion rate, both acute and steady state alterations in the plasma concentration of PTH in non-uremic subjects and animals have been attributed largely to altered secretion in a wide variety of physiologic and pathophysiologic states [37, 38].

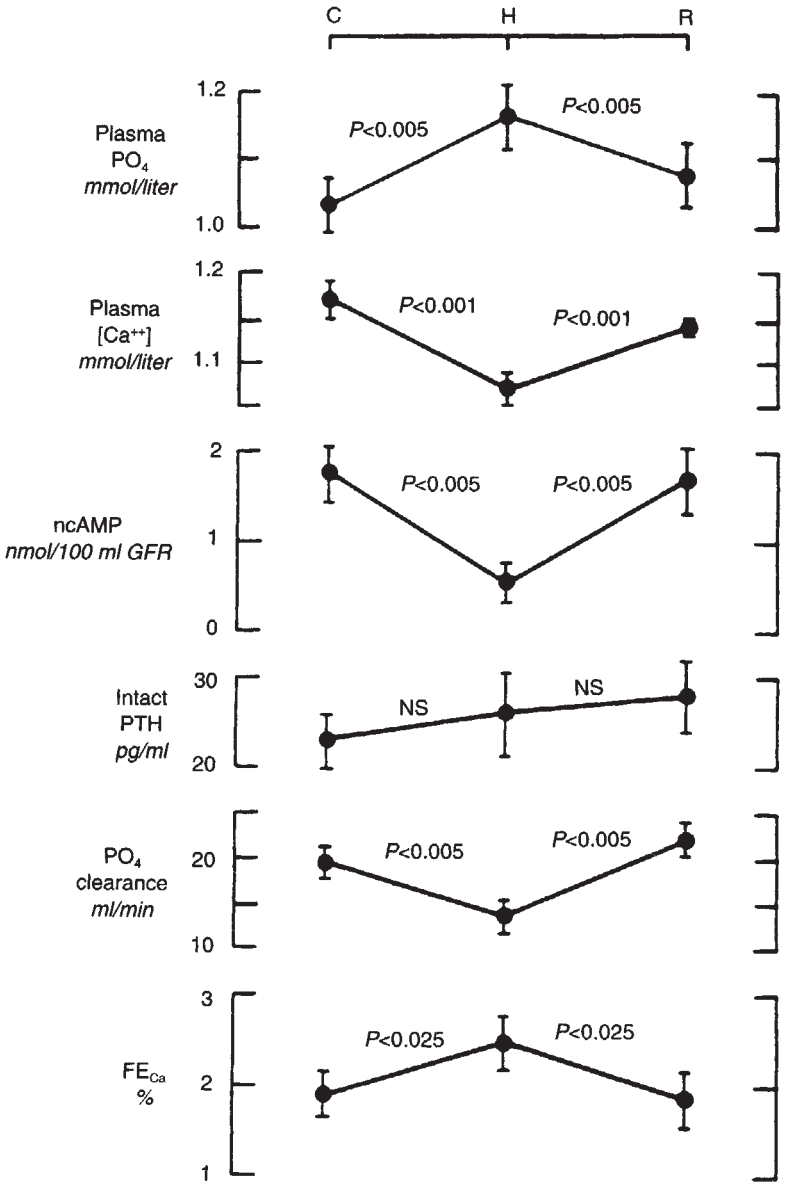

Fig. 4. *Summary of the effects of chronic hypocapnia on steady-state divalent ion metabolism.* C, H, R denote control, hypocapnia and recovery periods, respectively.

to PTH. The mechanism of hypocapnia-induced renal resistance to PTH action remains to be investigated, but might involve a decreased number of renal cellular PTH receptors, an alteration in receptor affinity for PTH, or post-receptor abnormalities (cyclic AMP production and/or degradation rate).

In addition to the hypocapnia-induced changes in PTH metabolism, the chronic hypocalcemia observed in these studies might also result from some consequence of deranged plasma acid-base composition, *per se*, for example decreased blood hydrogen ion or plasma bicarbonate concentration, or decreased $PaCO_2$. Precedent for alkalemia-induced chronic hypocalcemia is the finding of sustained hypocalcemia in a model of chronic metabolic alkalosis in rats [18]. In contrast to the present observations in humans, however, alkalemia was associated with a physiological increase in PTH concentration in response to hypocalcemia in the rat model. Based on both clearance studies in dogs [39–41] and proximal tubule microperfusion studies in rats [42], we cannot, however, exclude the possibility that hypocapnia-induced hypobicarbonatemia (and/or decreased filtered load of HCO_3^-) might impair renal calcium reabsorption, and thereby result in hypocalcemia. Possible effects of alterations in $PaCO_2$ on renal and systemic calcium homeostasis independent of pH and HCO_3^- have not been reported to date.

The present study also demonstrates transient hypophosphaturia and a concomitant tendency to hypophosphatemia in the first 48 hours of sustained hypocapnia, a finding consistent with previous studies of acute hypocapnia in humans [9, 43]. The hypophosphatemia of acute hypocapnia has been attributed to sequestration of extracellular phosphorus in muscle cells in the form of phosphate, adenine nucleotides and glucose-6-phosphate, owing to cell alkalinity-induced stimulation of glycolysis [44]. By the final day of hypocapnia in our subjects (Fig. 1), however, sustained hyperphosphatemia was observed in the

presence of a return of urinary phosphate excretion to control values and suppressed PO_4 clearance, a constellation of findings indicating sustained renal hyperabsorption of phosphate. During recovery, hyperphosphatemia diminished and was accompanied by phosphaturia. Our results are consistent with studies in dogs which documented reversible hyperphosphatemia associated with a cumulative decrease in renal phosphate excretion in response to chronic hypocapnia [19–21]. However, these reports precluded assessment of the role of the kidney in the maintenance of hyperphosphatemia because data for daily phosphate excretion and estimates of glomerular filtration rate were not provided.

Finally, the present study demonstrates sustained hypomagnesuria in response to chronic hypocapnia without change in the filtered load of magnesium. Enhancement of tubular magnesium reabsorption in response to acute metabolic alkalosis is well known [39, 45]. Whether alkalemia of respiratory origin can stimulate renal magnesium transport remains to be determined. However, hypocalcemia, *per se*, has been demonstrated to cause enhanced tubular magnesium reabsorption in thyroparathyroidectomized dogs [46]. The present results do not permit the distinction between a putative alkalemic versus hypocalcemic effect of chronic hypocapnia to augment tubular magnesium reabsorption in humans.

In conclusion, sustained respiratory alkalosis in humans induces hyperphosphatemia and hypocalcemia, at least in part of renal origin. The decreased excretion rate of nephrogenous cAMP which accompanied the alterations in renal calcium and phosphate transport despite unchanged serum PTH concentrations, suggests that chronic hypocapnia induces renal resistance to PTH, that is, functional pseudohypoparathyroidism, Type I. In addition, the observed failure of PTH concentration to increase in response to sustained hypocalcemia reflects a hypocapnia-induced defect in PTH secretion, that is, relative hypoparathyroidism.

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References

1. Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia. *J Clin Invest* 51:1722–1730, 1972
2. 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* 324:1394–1401, 1991
3. Kumar R, Nagubandi S, Mattox VR, Londowski JM: Enterohepatic physiology of 1,25-dihydroxyvitamin D_3. *J Clin Invest* 65:277–284, 1980
4. Kumar R, Cohen WR, Silva P, Epstein FH: Elevated 1,25-dihydroxyvitamin D plasma levels in normal human pregnancy and lactation. *J Clin Invest* 63:342–344, 1979
5. Bergstrom WH: Hypercalciuria and hypocalcemia complicating immobilization. *Am J Dis Child* 132:553–554, 1978
6. Walser M: The separate effects of hyperparathyroidism, hypocalcemia of malignancy, renal failure, and acidosis on the state of calcium, phosphate, and other ions in plasma. *J Clin Invest* 41:1454–1471, 1962
7. Canzanello VJ, Bodvarsson M, Kraut JA, Johns CA, Slatopolsky E, Madias NE: Effect of chronic respiratory acidosis on urinary calcium excretion in the dog. *Kidney Int* 38:409–416, 1990
8. Canzanello VJ, Kraut JA, Johns C, Madias NE: Effect of chronic respiratory acidosis on calcium metabolism in the rat. (abstract) *Clin Res* 36:515A, 1988
9. Mostellar ME, Tuttle EP Jr: Effects of alkalosis on plasma concentration and urinary excretion of inorganic phosphate in man. *J Clin Invest* 43:138–149, 1964
10. Okel BB, Hurst JW: Prolonged hyperventilation in man. *Arch Int Med* 108:157–162, 1961
11. Oberleithner H, Greger R, Lang F: The effect of respiratory and metabolic acid-base changes on ionized calcium concentration: In vivo and in vitro experiments in man and rat. *Eur J Clin Invest* 12:451–455, 1982
12. Seamonds B, Towfighi J, Arvan DA: Determination of ionized calcium in serum by use of an ion-selective electrode. I. Determination of normal values under physiologic conditions, with comments on the effects of food ingestion and hyperventilation. *Clin Chem* 18:155–160, 1972
13. Moore EW: Ionized calcium in normal serum, ultrafiltrates, and whole blood determined by ion exchange electrode. *J Clin Invest* 49:318–334, 1970
14. Pedersen KO: The effect of bicarbonate, PCO_2, and pH on serum calcium fractions. *Scand J Clin Lab Invest* 27:145–150, 1971
15. Schwartz HD, McConville BC, Christopherson EF: Serum ionized calcium by specific ion electrode. *Clin Chim Acta* 31:97–107, 1971
16. Wybenga DR, Ibott FA, Cannon DC: Determination of ionized calcium in serum that has been exposed to air. *Clin Chem* 22:1009–1011, 1976
17. Siggaard Anderson O: Acute experimental acid-base disturbances in dogs. An investigation of the acid-base and electrolyte content of blood and urine. *Scand J Clin Lab Invest* (Suppl. 1) 14:1–20, 1962
18. Bushinsky DA, Kittaka MK, Weisinger JR, Langman CB, Favus MJ: Effects of chronic metabolic alkalosis on Ca^{++}, PTH, and $1,25(OH)_2D_3$ in the rat. *Am J Physiol* 257:E578–E582, 1989
19. Cohen JJ, Madias NE, Wolf CF, Schwartz WB: Regulation of acid-base equilibrium in chronic hypocapnia. *J Clin Invest* 57:1483–1489, 1976
20. 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
21. Gougoux A, Kaehny WD, Cohen JJ: Renal adaptation to chronic hypocapnia: Dietary constraints in achieving H^+ retention. *Am J Physiol* 229:1330–1337, 1975
22. Forster HV, Dempsey JA, Thomson J, Vidruk E, DoPico GA: Estimation of arterial PO_2, PCO_2, pH, and lactate from arterialized venous blood. *J Appl Physiol* 32:134–137, 1972
23. Fiske CH, Subbarow Y: The colorimetric determination of phosphorus. *J Biol Chem* 66:375–400, 1925
24. Nussbaum SR, Zahradivik R, Lavigne JR, Brennan GL, Nozawa-Ung K, Kim LY, Kentman HT, Wang C-A, Potts JT Jr, Segre GV: Highly specific two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypocalcemia. *Clin Chem* 3:1364–1367, 1987
25. Hollis BW: Assay of circulating 1,25-dihydroxyvitamin D involving a single-cartridge extraction and purification procedure. *Clin Chem* 32:2060–2063, 1986
26. Broadus AE, Mahaffey JE, Bartter FC, Neer RM: Nephrogenous cyclic adenosine monophosphate as a parathyroid function test. *J Clin Invest* 60:771–783, 1977
27. Blum JW, Fischer JA, Schwoerer D, Hunziker W, Binswanger U: Acute parathyroid hormone response: Sensitivity, relationship to hypocalcemia, and rapidity. *Endocrinol* 95:753–759, 1974
28. Conlin PR, Fajtova VT, Mortensen RM, LeBoff MS, Brown

EM: Hysteresis in the relationship between serum ionized calcium and intact parathyroid hormone during recovery from induced hyper- and hypocalcemia in normal humans. *J Clin Endocrinol Metab* 69:593–599, 1989
29. ADLER AJ, FERRAN N, BERLYNE G-M: Effect of inorganic phosphate on serum ionized calcium concentration in vitro: A reassessment of the "trade-off hypothesis". *Kidney Int* 28:932–935, 1985
30. BUSHINSKY DA, KRIEGER NS, GEISSER DI, GROSSMAN EB, COE FL: Effects of pH on bone calcium and proton fluxes in vitro. *Am J Physiol* 245:F204–F209, 1983
31. MCELDUFF A, LISSNER D, WILKINSON M, CORNISH C, POSEN S: A 6-hour human parathyroid hormone (1-34) infusion protocol: Studies in normal and hypoparathyroid subjects. *Calcif Tiss Int* 41:267–293, 1987
32. CARNEY S, THOMPSON L: Effect of differing concentrations of parathyroid hormone on rat renal electrolyte excretion. *Am J Physiol* 243:F514–F517, 1982
33. BURNATOWSKA MA, HARRIS CA, SUTTON RAL, DIRKS JH: Effects of PTH and cAMP on renal handling of calcium, magnesium, and phosphate in the hamster. *Am J Physiol* 233:F514–F518, 1977
34. AGUS ZS, CHIU PJS, GOLDBERG M: Regulation of urinary calcium excretion in the rat. *Am J Physiol* 232:F545–F549, 1977
35. AGUS ZS, GARDNER LB, BECK LH, GOLDBERG M: Effects of parathyroid hormone on renal tubular absorption of calcium, sodium, and phosphate. *Am J Physiol* 224:1143–1148, 1973
36. SUTTON RAL, DIRKS JH: Disturbances of calcium and magnesium metabolism, in *The Kidney* (4th ed), edited by BRENNER BM, RECTOR FC JR, Philadelphia, W.B. Saunders, 1991, p. 841
37. FISCHER JA, BLUM JW, BORN W, DAMBACHER MA, DEMPSTER DW: Regulation of parathyroid hormone secretion in vitro and in vivo. *Calcif Tiss Int* 34:313–316, 1982
38. FOX J, OFFORD KP, HEATH H III: Episode secretion of parathyroid hormone in the dog. *Am J Physiol* 241:E171–E177, 1981
39. PERAINO RA, SUKI WN, STINEBAUGH BJ: Renal excretion of calcium and magnesium during correction of metabolic acidosis by bicarbonate infusion in the dog. *Miner Electrol Metab* 3:87–93, 1980
40. PERAINO RA, SUKI WN: Urine HCO_3^- augments renal Ca^{++} absorption independent of systermic acid-base changes. *Am J Physiol* 238:F394–F398, 1980
41. SUTTON RAL, WONG NLM, DIRKS JH: Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. *Kidney Int* 15:520–533, 1979
42. BOMSZTYK K, CALALB MB: Bicarbonate absorption stimulates active calcium absorption in the rat proximal tubule. *J Clin Invest* 82:1455–1461, 1988
43. STANBURY SW, THOMSON AE: The renal response to respiratory alkalosis. *Clin Sci* 11:357–374, 1952
44. BRAUTBAR N, LEIBOVICI H, MASSRY SG: On the mechanism of hypophosphatemia during acute hyperventilation: Evidence for increased muscle glycolysis. *Miner Electrol Metab* 9:45–50, 1983
45. WONG NLM, QUAMME GA, DIRKS JH: Effects of acid-base disturbances on renal handling of magnesium in the dog. *Clin Sci* 70:277–284, 1986
46. COBURN JW, MASSRY SG, KLEEMAN CR: The effects of calcium infusion on renal handling of magnesium with normal and reduced glomerular filtration rate. *Nephron* 7:131–143, 1970