PCO₂ and [K⁺]ₚ in Metabolic Acidosis: Certainty for the First and Uncertainty for the Other

HORACIO J. ADROGUÉ* AND NICOLAOS E. MADIAS†

*Department of Medicine, Renal Section, Baylor College of Medicine, The Methodist Hospital, and Veterans Affairs Medical Center, Houston, Texas; and †Department of Medicine, Tufts University School of Medicine, Division of Nephrology, Caritas St. Elizabeth’s Medical Center, Boston, Massachusetts.

Studies by Schwartz and colleagues at Tufts University School of Medicine in the 1960s described the “whole-body” acid-base response (i.e., secondary changes in plasma [HCO₃⁻] to graded degrees of acute respiratory acidosis and acute respiratory alkalosis in humans (1,2). Corresponding data for acute metabolic acid-base disorders (i.e., secondary changes in PaCO₂) are essentially unavailable: meager observations have been made in acute metabolic alkalosis, and no data exist for acute metabolic acidosis. The report by Wiederseiner et al. (3) in this issue of JASN addresses the secondary physiologic response to acute mineral acid-induced metabolic acidosis in humans.

In a carefully conducted study, the slope of the PCO₂ (artificialized)/[HCO₃⁻] relationship averaged 0.85 mmHg per mmol/L in six healthy male volunteers with acute NH₄Cl-induced metabolic acidosis who had attained an operational steady state (by convention, “acute” corresponds to the interval before any meaningful contribution of changes in renal acidification to plasma [HCO₃⁻]). The range of hypobicarbonatemia achieved in this study was limited (nadir of approximately 19 mmol/L); thus these data serve to define the limits of the ventilatory response to mild, acute metabolic acidosis in humans and enable consideration of the possible coexistence of respiratory acid-base disorders. Whether the same slope applies to more severe degrees of acute metabolic acidosis remains unknown.

The observed slope is substantially less steep than that described for chronic metabolic acidosis in humans, which is on the order of 1.1 to 1.4 mmHg per mmol/L. However, the PaCO₂/[HCO₃⁻] relationship in clinical chronic metabolic acidosis has by necessity been derived by simply correlating the available pathologic values of the two determinants of plasma acidity without regard for their deviation from the control baseline. When we compared the ventilatory response to chronic HCl-induced metabolic acidosis in a large cohort of dogs as obtained by computing the changes in PaCO₂ and plasma [HCO₃⁻] (i.e., experimental minus control values—what we consider as the appropriate methodology) versus only the experimental values, the significantly disparate slopes of 0.86 versus 1.20 mmHg per mmol/L, respectively, were obtained (4). In our opinion, the precise slope of the ventilatory response to chronic metabolic acidosis in humans remains uncertain.

Furthermore, we have previously shown in dogs that acutely the secondary hypocapnia that accompanies metabolic acidosis leaves plasma [HCO₃⁻] undisturbed, thereby providing maximal defense of systemic pH (5). In stark contrast, in the chronic setting, secondary hypocapnia evokes a maladaptive renal response that yields a sizable reduction in plasma [HCO₃⁻] (beyond that attributed to the acid load itself) and diminishes the degree to which plasma acidity is potentially protected by the ventilatory response. Whether these observations are applicable to metabolic acidosis in humans remains to be determined.

In the same protocol, Wiederseiner et al. (3) have also examined the kalemic response to acute NH₄Cl-induced metabolic acidosis. A previous review of the then available studies on the kalemic response to acute mineral acid-induced metabolic acidosis in dogs, rabbits, and cats yielded consistent increases in plasma potassium concentration, albeit of wide variability (6). Observations in 69 patients at 180 min after ingestion of NH₄Cl revealed increases in plasma potassium concentration that correlated with the degree of hypobicarbonatemia (7). In sharp contrast to this background, Wiederseiner et al. found no significant changes in plasma potassium concentration, a finding that they attributed to acidemia-induced stimulation of plasma insulin levels. Consideration of the authors’ protocol in the light of the relevant literature offers alternative insights into the observed absence of a hyperkalemic response to acute mineral acid-induced metabolic acidosis.

Acidemia, whether respiratory or metabolic in origin, causes insulin resistance (8–9). Paired observations in anesthetized dogs showed that moderate to severe acute acidemia of respiratory origin resulted in small but significant increases in fasting glucose concentration accompanied by unchanged arterial insulin levels (8). When control and acidemic dogs received an identical glucose infusion, the acidemic dogs displayed higher plasma glucose and insulin levels. Insulin infusion studies with euglycemic clamp documented that acute acidemia decreases peripheral glucose utilization, insulin-induced suppression of hepatic glucose production, and hepatic extraction of insulin. Furthermore, acidemia was associated
with significant increments in arterial glucagon levels. These derangements in glucoregulation were independent of the activity of the sympathetic nervous system (8). Similar studies were carried out in conscious dogs infused with HCl to discount a confounding effect of pentobarbital anesthesia (10). Acute HCl-induced acidemia caused small and transient but significant increases in plasma glucose levels in hepatic-vein blood but not in arterial blood. Plasma insulin levels measured in arterial, portal, and hepatic samples showed no significant changes during or after the acute HCl infusion. In addition, HCl administration resulted in a progressive increase in plasma glucagon levels that reached statistical significance at several points of observation. Thus, acute respiratory or mineral acidosis-induced insulin resistance (9).

How can these observations be reconciled with the results presented by Wiederseiner et al. (3)? The authors report that acute NH₄Cl-induced metabolic acidosis resulted in increased plasma insulin and decreased glucagon levels. Their data are reminiscent of those observed with acute organic acid-induced acidosis (ketoacid infusion) in conscious dogs (which elicited a hypokalemic response) but not those with mineral acid-induced acidosis (which yielded transient hyperkalemia) (10). Thus it would appear that the intravenous administration of 350 ml/h of 5% glucose during the course of acid infusion to the normal volunteers, and not the mineral-acid load itself, was responsible for the reported increase in plasma insulin and decrease in plasma glucagon levels. In turn, the resulting hyperinsulinemia prevented expression of the anticipated hyperkalemic response.

Two additional comments are in order. First, the degree of acute acidemia observed in the study by Wiederseiner et al. (3) was small, a mere 0.05 decrease in blood pH. Greater degrees of acute acidemia might have lent significance to the trend toward increases in plasma potassium levels despite the complicating hyperinsulinemia. Second, infusion of ammonium salts inhibits insulin release independent of the associated acidosis (11–13). Thus interpretation of the effects of the acute NH₄Cl load on the plasma insulin levels of the normal volunteers studied becomes even more difficult. Definitive characterization of the kalemic response to mineral-acid acidosis in humans will require avoidance of NH₄Cl loading (e.g., use of HCl infusion) and assurance that the endocrine response to acidosis is not perturbed by factors other than the changes in systemic acidity.

References