

Acute Metabolic Acidosis: Characterization and Diagnosis of the Disorder and the Plasma Potassium Response

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Abstract. Despite the high incidence of acute metabolic acidosis, there are no reliable human data to enable physicians to accurately diagnose this disorder. In addition, there is uncertainty about the direction and magnitude of plasma potassium changes in acute metabolic acidosis. The systemic and renal acid-base, electrolyte, and endocrine response to acute acid loads (imposed by three timed NH₄Cl infusions into the duodenum, 0.9 mmol of NH₄Cl per kg of body weight over 30 min each) was characterized in six healthy male subjects in whom a metabolic steady-state had been established. Arterialized blood CO₂ tension decreased by 0.85 mmHg per mmol/L decrease in plasma bicarbonate concentration and blood hydrogen ion concentration increased by 0.45 nmol/L per

mmol/L decrease in plasma bicarbonate concentration. Plasma potassium did not change significantly (+0.02 ± 0.02 mmol/L per mmol decrease in plasma bicarbonate concentration). Plasma insulin increased and plasma glucagon levels decreased in acute metabolic acidosis, while catecholamines and aldosterone were not affected significantly. These data provide the first diagnostic criteria for the diagnosis of acute metabolic acidosis in humans. The finding of a hyperinsulinemic response in acute metabolic acidosis suggests that an insulin response counterregulates any acidemia-induced cellular potassium efflux, resulting in stable plasma potassium concentrations.

Metabolic acidosis is the acid-base disturbance caused by a decrease in plasma bicarbonate concentration followed by secondary hyperventilation (hypocapnia). Metabolic acidosis is defined as acute (AMA) on the basis of the characterization of an early steady-state period in which stable acid-base and electrolyte composition was observed during at least the initial 6 h that follow a brief ion equilibration period (1).

In view of the high incidence of AMA in clinical medicine, there is a surprising paucity of information to enable the physician to reliably diagnose the disorder, *i.e.*, to identify metabolic acidosis as acute and/or to decide whether it is present as a single or mixed disturbance. In addition, there is uncertainty about the direction and magnitude of plasma potassium changes during AMA despite the fact that essentially all modern textbooks state that hyperkalemia results from AMA caused by a mineral (but not organic) acid load.

Several reports have provided acid-base and electrolyte data from venous serum samples in normal human subjects after acute NH₄Cl or CaCl₂ loads (2–9). However, since blood PaCO₂ and pH data required for characterization of human

AMA depend on measurements in arterial or arterialized samples, AMA remains uncharacterized in humans. The two reports of arterial(ized) acid-base data are difficult to interpret due to the methodological (no documented acute steady-state or no serial samples) or technical (exposure of samples to room air) limitations and/or because subjects were not treated similarly (2,10).

In experimental animals, AMA has been well characterized during the equilibration period that follows cessation of an acute IV infusion of mineral acid (HCl) in dogs (1). An acute steady-state AMA period of stable arterial acid-base and electrolyte composition was documented 60 to 120 min after acid infusions and before the anticipated renal acid excretory response that returns plasma bicarbonate concentration toward normal. In dogs, AMA reflects the steady-state consequences of both prior ECF and tissue buffering of an acid load (stable plasma bicarbonate concentration) and an ongoing and stable hyperventilatory (hypocapnic) response attributed to neural chemoreceptors (11,12).

Based largely on studies in anesthetized dogs but supported by an often-cited report of acute HCl and NH₄Cl treatment of preexisting metabolic alkalosis in a single patient (13), it has been widely accepted that human AMA (of mineral acid origin) is characterized by statistically and clinically significant acute hyperkalemia of varying magnitude (14,15) and is even thought to represent a major adverse consequence of the disorder (16).

In dogs, AMA induced a shift of K⁺ from the intracellular space that resulted in moderate to severe acute hyperkalemia

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(1). In human studies reporting venous plasma or serum (2,4,5,17) potassium values after a small acute NH_4Cl load, a tendency to elevated values was observed, with statistical significance in only one study (2), but interpretation was precluded by high variance and modest degrees of acidosis. Importantly, no arterial or arterialized plasma or serum potassium values have been reported in normal human subjects with experimentally induced AMA of any cause. The high variance reported for human venous serum *versus* arterial plasma potassium may have contributed to the failure to discern the significant hyperkalemia observed in dog arterial plasma (18–20) as might the small degree of AMA produced in those normal subjects (venous total $\text{CO}_2 > 20$ mmol/L), owing to the dose limitations attendant to oral NH_4Cl administration. When simultaneous arterial plasma and venous serum potassium values have been reported in humans, the mean venous serum values were always greater and the range of differences was very large (0.1 to 1.1 mmol/L), with differences attributed largely to hemolytic and clotting processes observed in venous serum (19). Given the clinical importance and frequency of the diagnosis and treatment of hyperkalemic states and the concomitant frequency of AMA, it is essential to know the contribution, if any, of AMA to acute hyperkalemia in humans.

Accordingly, the present study was designed to provide the first systematic characterization of AMA and to provide diagnostic criteria for the disorder in normal human subjects using arterialized plasma. An additional aim was to clarify the direction and magnitude of arterialized plasma potassium changes in AMA and to characterize the endocrine alterations that might determine the potassium response.

Materials and Methods

To assess the effects of an acute acid load on acid-base, electrolyte, and endocrine homeostasis, six healthy, male volunteers (age \pm SD, 24 ± 4.5 yr) weighing 72.3 ± 4.5 kg were examined under metabolic balance conditions. None were smokers, and none were taking any drugs before or during the study. They ingested a constant diet for 5 d before the day of study containing (per kg of body weight) the following: 1.8 mmol sodium, 1.1 mmol potassium, 44.4 ml water, 1.28 g protein, and 36 kcal.

To characterize acid-base, electrolyte, and endocrine responses, arterialized blood samples (21) were obtained after heating the forearm in a water bath (43°C). No tourniquet pressure was applied, and the samples were collected in heparin (for all acid-base and electrolyte analyses) or EDTA-coated syringes from a venous catheter placed 2 h before the first blood sample. Blood samples were accepted if the partial pressure of oxygen was >70 mmHg (9.3 kPa). Blood acid-base and plasma electrolyte analysis of freshly separated plasma were performed immediately; for hormonal analysis, samples were kept on ice, cold centrifuged, and separated, and the plasma stored at -30°C until analyzed.

All subjects volunteered for the study, were paid for their participation, and gave written informed consent. The study protocol was approved by the Ethics committees of both Cantons of Basle (Switzerland).

Experimental Design

AMA was induced by infusion of NH_4Cl into the duodenum. The infusion catheter was introduced transnasally and placed into the

distal portion of the duodenum (near the angle of Treitz) under endoscopic guidance. The endoscope was introduced orally after local anesthesia. Two venous catheters (one for blood sampling, the other for infusion) were placed into hand veins of both arms. Placement and insertion of all catheters was completed at least 2 h before baseline blood sampling was initiated.

After an overnight fast, NH_4Cl was administered in three periods (30 min each, 0.9 mmol NH_4Cl per kg of body weight in each period) followed by a 2-h equilibration period after each acid infusion period. To avoid the increased ketoacid production, increased plasma aldosterone concentration, renal K^+ retention, hyperkalemia, natriuresis, decreased sympathetic activity, and renal gluconeogenesis/ NH_3 effects of 24-h fasting, the volunteers received 350 ml/h 5% glucose intravenously. The subjects were in a comfortable sitting position (hemodialysis chair) throughout the study. Blood losses due to sampling were replaced by infusion of equal volumes of 0.9% NaCl. Blood sampling was performed for blood acid-base and plasma electrolyte determination at 10, 20, and 30 min during duodenal NH_4Cl infusion (acid infusion periods 1 to 3, A1 to A3). During the equilibration periods (E1 to E3) after each acid infusion, blood sampling for acid-base, electrolyte, and endocrine analysis was done at 15, 30, 60, 90, and 120 min post-infusion.

Analytical Procedures

Analysis of plasma and urine electrolyte and acid-base composition was performed as described previously (22). Determination of plasma insulin was performed by microparticle immunoassay (Abbot), of cortisol by chemiluminescence immunoassay (Beckman), of adrenocorticotropic hormone (ACTH) and growth hormone by immunoradiometric assay (DSL), and of glucagon and Ghrelin by radioimmunoassays (Linco Research Inc). Norepinephrine and epinephrine were determined by HPLC with electrochemical detection.

Results

Placement of catheters into the duodenum and the NH_4Cl infusions into the duodenum were well tolerated by all subjects. One subject reported slight nausea during the last 15 min of NH_4Cl infusion. No other adverse events were observed.

Acid-Base Response to Duodenal NH_4Cl Infusion

Figure 1 illustrates that each NH_4Cl infusion induced a rapid decrease in $[\text{HCO}_3^-]_p$. Each infusion period was followed by a slight increase in $[\text{HCO}_3^-]_p$ from its nadir value during the infusion. Between 30 and 120 min after infusion, $[\text{HCO}_3^-]_p$ remained “equilibrated” and did not change significantly, thereby defining the acute steady state of metabolic acidosis.

The mean blood and plasma acid-base and electrolyte values for each subject during these three consecutive, acute steady states provide the group mean values shown in Table 1. NH_4Cl infusions resulted in a dose-dependent magnitude of AMA with $[\text{HCO}_3^-]_p$ decreasing in three sequential steps by -3.3 ± 0.4 , -1.7 ± 0.3 , and -0.8 ± 0.4 mmol/L, respectively. The total mean decrease in $[\text{HCO}_3^-]_p$ amounted to -5.8 ± 0.4 mmol/L.

The characterizations of the equilibrated blood acid-base data of Figures 2a and 2b can be used to define diagnostic criteria for AMA. Significant linear correlations obtained for the regression of acute steady state $[\text{HCO}_3^-]_p$ on blood hydrogen ion concentration ($[\text{H}^+]_b$) as well as on arterialized carbon

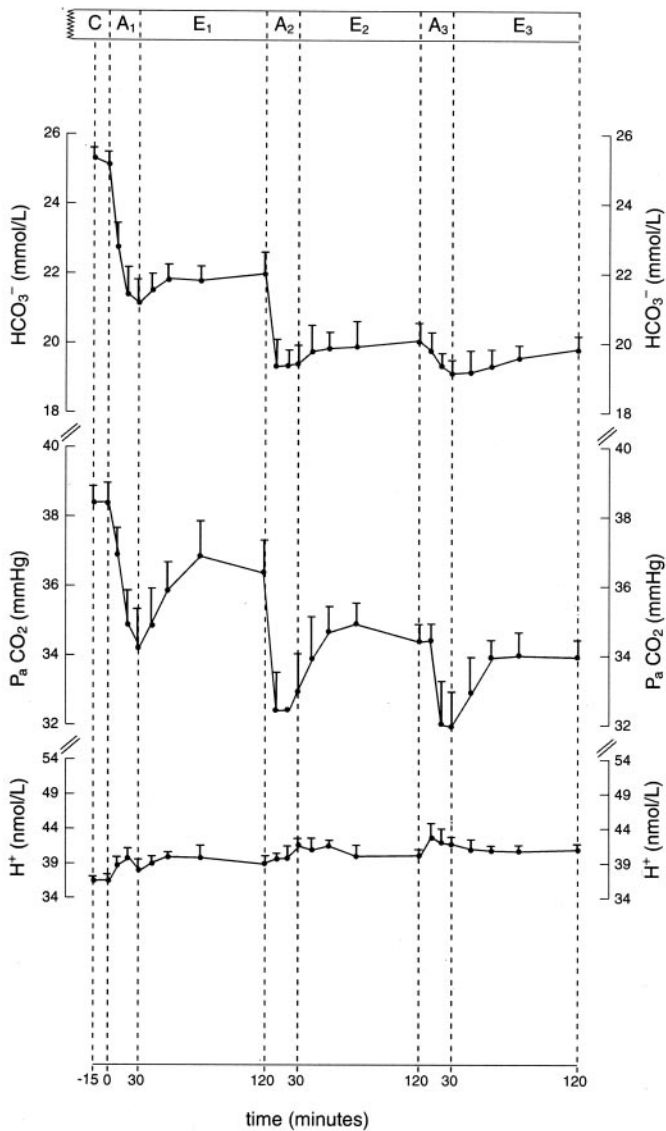


Figure 1. Effect of three consecutive NH₄Cl (A1 through A3) administrations (0.9 mmol/kg of body wt over 30 min) on plasma acid-base composition. Each 30 min infusion was followed by an equilibration (E1 to E3) period lasting 120 min. x denotes *P* < 0.05 in comparison to control and the previous equilibration periods, respectively.

dioxide tension (P_aCO₂). As depicted, AMA is characterized by a 0.45 nmol/L increase of [H⁺]_b per mmol/L decrease in [HCO₃⁻]_p. P_aCO₂ decreases by 0.85 mmHg per mmol/L decrease in [HCO₃⁻]_p. The figures also show the 95% confidence limits for AMA in normal human subjects.

Renal Acid Excretory Response to AMA

The total exogenous acid load imposed during the three NH₄Cl infusion periods amounted to 189 mmol of H⁺ in a 70-kg subject. Table 2 and Figure 1 depict plasma acid-base composition and the renal net acid excretion (NAE), urinary ammonium (NH₄u), and titratable acid (TA) excretion rates (per hour) during control, each acid infusion/equilibration pe-

Table 1. Acute steady-state in acute metabolic acidosis: plasma electrolyte and acid-base composition

Study Period ^a	H ⁺ mmol/L	PaCO ₂ mmHg	HCO ₃ ⁻ mmol/L	Unmeasured Anions mmol/L	Na ⁺ mmol/L	K ⁺ mmol/L	Cl ⁻ mmol/L	Ca ⁺⁺ mmol/L	PO ₄ mmol/L	Mg ⁺⁺ mmol/L
Control	36.5 ± 0.3	38.6 ± 0.5	25.5 ± 0.3	15.6 ± 0.8	140.6 ± 0.5	4.06 ± 0.15	103.6 ± 0.5	1.19 ± 0.03	1.06 ± 0.04	0.91 ± 0.03
E1	39.0 ^b ± 1.0	36.6 ^b ± 0.9	22.2 ^b ± 0.6	15.9 ± 0.9	139.3 ± 0.9	4.15 ± 0.22	105.4 ± 0.7	1.21 ± 0.04	1.02 ± 0.03	0.86 ± 0.04
E2	40.1 ^b ± 1.2	34.5 ^b ± 0.5	20.5 ^b ± 0.5	15.2 ± 0.7	137.8 ± 0.8	4.18 ± 0.16	106.3 ± 0.9	1.21 ± 0.03	1.00 ± 0.06	0.85 ± 0.03
E3	41.1 ^b ± 0.9	34.0 ^b ± 0.5	19.7 ^b ± 0.4	16.1 ± 0.9	138.8 ± 0.7	4.20 ± 0.20	107.2 ± 0.7	1.22 ± 0.02	1.08 ± 0.06	0.84 ± 0.05
42 h	38.5 ± 0.6	38.1 ± 0.5	23.8 ± 0.5	16.9 ± 0.08	140.0 ± 0.6	4.11 ± 0.15	103.4 ± 0.8	1.18 ± 0.04	1.09 ± 0.05	0.90 ± 0.04

^a E1, E2, and E3 denote the acute steady-state (equilibration period) that occurred after each incremental NH₄Cl infusion (see Figure 1). Unmeasured anions in plasma were calculated as (Na⁺ + K⁺) - (Cl⁻ + HCO₃⁻). The data 42 h after the last acid infusion are also given. They can be used in conjunction with Table 2.

^b *P* ≤ 0.05 in comparison to control.

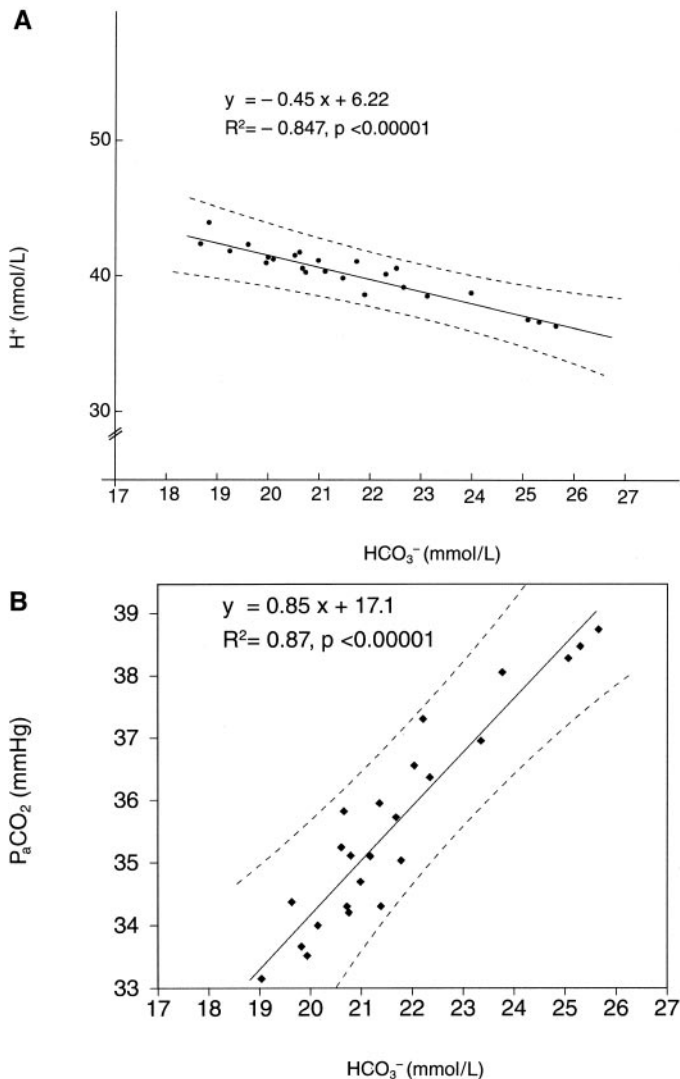


Figure 2. Relationship of blood hydrogen ion (top) and P_aCO_2 (bottom) to plasma bicarbonate concentration. Each data point represents a mean value for an individual subject during the equilibration periods. The solid lines show the regression of hydrogen or P_aCO_2 on plasma bicarbonate concentration. The dashed lines indicate the 95% confidence limits for uncomplicated acute metabolic acidosis in normal subjects. To convert values for P_aCO_2 to kiloPascals, multiply by 0.1333.

riod, and during recovery (up to 42 h after the last NH_4Cl infusion period). Hourly NAE started to increase during the second acid infusion/equilibration period due to small but significant increases in both NH_4u and TA excretion rates. Assuming a constant endogenous acid load (commensurate with the control rate of NAE excretion), only 8.8 ± 2.1 mmol of “additional” NAE were excreted by the end of period E3 in response to the acid load. Overall, 149.8 ± 11.2 mmol of the 189 mmol of “additional” acid were excreted in response to the infused acid by 42 h after the end of the last acid infusion (129.6 ± 10.1 as NH_4u and 20.2 ± 2.7 as TA). We did not measure organic acid excretion, which conceivably might have changed and affected overall acid balance during the study.

Plasma Potassium Response to Acute AMA

Table 1 shows that plasma potassium values were not significantly different from control during all three acute steady states. Figures 3a and 3b depict the correlation between plasma potassium concentration and $[HCO_3^-]_p$ or blood pH, respectively. The change in plasma potassium concentration was $+0.02 \pm 0.02$ mmol/L per mmol/L decrease in $[HCO_3^-]_p$, and $+0.16 \pm 0.09$ mmol/L per 0.1 U decrease in pH. Neither slope was statistically or clinically significant.

The cumulative change in renal potassium excretion averaged only $+10 \pm 3$ mmol by the end of the last equilibration period (E3). Inclusion of pre-equilibration data during an acute acid load also failed to show any significant hyperkalemic response. Furthermore, although it is difficult to interpret, pre-equilibrated plasma potassium values, correlation of plasma potassium concentration with $[HCO_3^-]_p$ limited to the pre-equilibration data obtained during infusion of the acid load, showed that plasma potassium concentration regressed on $[HCO_3^-]_p$ by only 0.03 ± 0.02 mmol/L per mmol/L decrease in $[HCO_3^-]_p$ (NS).

Endocrine Response to AMA

Tables 3 and 4 depict the plasma insulin, glucose, growth hormone, Ghrelin, adrenocorticotrophic hormone (ACTH), cortisol, aldosterone, norepinephrine, and epinephrine responses in the acute steady state (equilibration period) of AMA.

With regard to the mechanism of regulation of the plasma potassium concentration in AMA, this table demonstrates that catecholamines, mineralocorticoid hormone and Ghrelin plasma levels were not affected significantly. Cortisol decreased progressively during the course of the experiment. This is most likely explained by the normal decrease dictated by the diurnal rhythm of cortisol secretion (the experiment started around 8 a.m.). However, insulin levels increased significantly without discernible changes in plasma glucose concentrations. Glucagon levels were slightly, but significantly decreased in all three periods. GH levels did not change significantly.

Discussion

The results of the present study provide the first characterization of AMA in humans. Although the rapid onset of appreciable acute hypocapnia within 20 min of an acid load in a human subject was first reported more than 80 yr ago, the quantitative extent of hypocapnia in human AMA has not been reported making diagnosis of the simple *versus* mixed disorder impossible (23). The degree of secondary hypocapnia exhibited during an equilibrated acute steady state of AMA in humans in the present study was 0.85 mmHg decrease in P_aCO_2 per mmol/L of HCO_3^- reduction (Figure 2) and thus appreciably less than the 1.1 mmHg reduction reported for *chronic* metabolic acidosis in humans (22,24). The lesser slope value of 0.85 mmHg per mmol/L HCO_3^- reduction in AMA might be attributed to the delay in the flux of HCO_3^- across the blood-brain barrier and is consistent with observations in experimental animals (25). A tendency for an attenuated hypocapnic response during the first 22h of acidosis was also reported in humans with acute cholera in comparison with later

Table 2. Rates of renal acid excretion, PO₄ excretion, and urinary pH during control, acid infusion, equilibration, and recovery periods

Period ^a	Control	A1/E1	A2/E2	A3/E3	R + 2 h	R + 4 h	R + 6 h	R + 8 h	R + 24 h	R + 30 h	R + 42 h
NH _{4U} (mmol/h)	1.2 ± 0.2	1.8 ± 0.4	2.8 ± 0.4 ^b	2.5 ± 0.5 ^b	2.3 ± 0.6 ^b	5.3 ± 0.6 ^b	3.9 ± 0.7 ^b	3.9 ± 0.5 ^b	7.5 ± 1.1 ^b	3.6 ± 0.8 ^b	2.9 ± 0.6 ^b
TA (mmol/h)	0.6 ± 0.1	0.7 ± 0.3	0.8 ± 0.2	1.2 ± 0.3 ^b	0.9 ± 0.3 ^b	1.4 ± 0.4 ^b	1.2 ± 0.3 ^b	1.4 ± 0.4 ^b	1.9 ^b ± 0.4	0.5 ± 0.5	0.6 ± 0.5
NAE (mmol/h)	1.8 ± 0.3	2.5 ± 0.5	3.6 ± 0.6 ^b	3.7 ± 0.7 ^b	3.2 ± 0.7 ^b	6.7 ± 0.8 ^b	5.1 ± 0.6 ^b	5.3 ± 0.7 ^b	9.4 ± 1.4 ^b	4.1 ± 0.8 ^b	3.5 ± 0.7 ^b
ΣΔ NAE (mmol)		1.4 ± 0.8	5.0 ± 1.2	8.8 ± 1.4	11.6 ± 2.5	21.4 ± 2.3	28.0 ± 3.5	70.0 ± 6.4	115.6 ± 8.1	129.4 ± 9.8	149.8 ± 11.2
U _{pH}	5.71 ± 0.05	5.42 ± 0.11 ^b	5.44 ± 0.10 ^b	5.46 ± 0.09 ^b	5.40 ± 0.08 ^b	5.30 ± 0.09 ^b	5.26 ± 1.0 ^b	5.32 ± 0.09 ^b	4.92 ± 0.07 ^b	4.91 ± 0.11 ^b	5.11 ± 0.12 ^b
PO _{4U} (mmol/h)	0.90 ± 0.08	0.78 ± 0.09	0.80 ± 0.07	0.88 ± 0.06	0.92 ± 0.09	1.49 ± 0.14 ^b	1.32 ± 0.11 ^b	1.55 ± 0.13 ^b	0.82 ± 0.09	0.77 ± 0.09	0.85 ± 0.08

^a NH_{4U}, TA, and NAE are depicted as excretion rates per hour. A/E denotes acid infusion (A) and the following equilibration periods. The numbers in the suffix relate to the three acid infusion/equilibration periods. R denotes recovery over intervals up to 42 h, with the closing time of urinary collection indicated by the number of hours. ΣΔ NAE is the cumulative change from baseline (control) NAE value. At the end of the experiment, the cumulative increment in NAE (ΣΔ NAE) accounted for ≈150 mmol of protons, or about 80% of the 189 mmol (2.7 mmol/kg in a 70-kg subject) administered.

^b P < 0.05 compared with control.

blood samples (26), but transition blood acid-base data were not reported prospectively and concomitant acid-base disorders were not excluded.

Accordingly, the present data, by not providing the time course for the transition from the acute steady state of AMA to the steady state of CMA do not provide reference data for human acid-base diagnoses in patients with AMA of more than 8-h duration. This same shortcoming is present for the clinical diagnosis of acute respiratory alkalosis, which is similarly well characterized only for the acute steady state (27).

As for the hypocapnic response, the prospectively defined plasma potassium response to AMA in humans has remained essentially unexplored. A comprehensive review of all reported serum or plasma potassium values in experimental acute mineral acid-induced metabolic acidosis in mammalian species (human, cat, rabbit, dog) yielded data from only one human

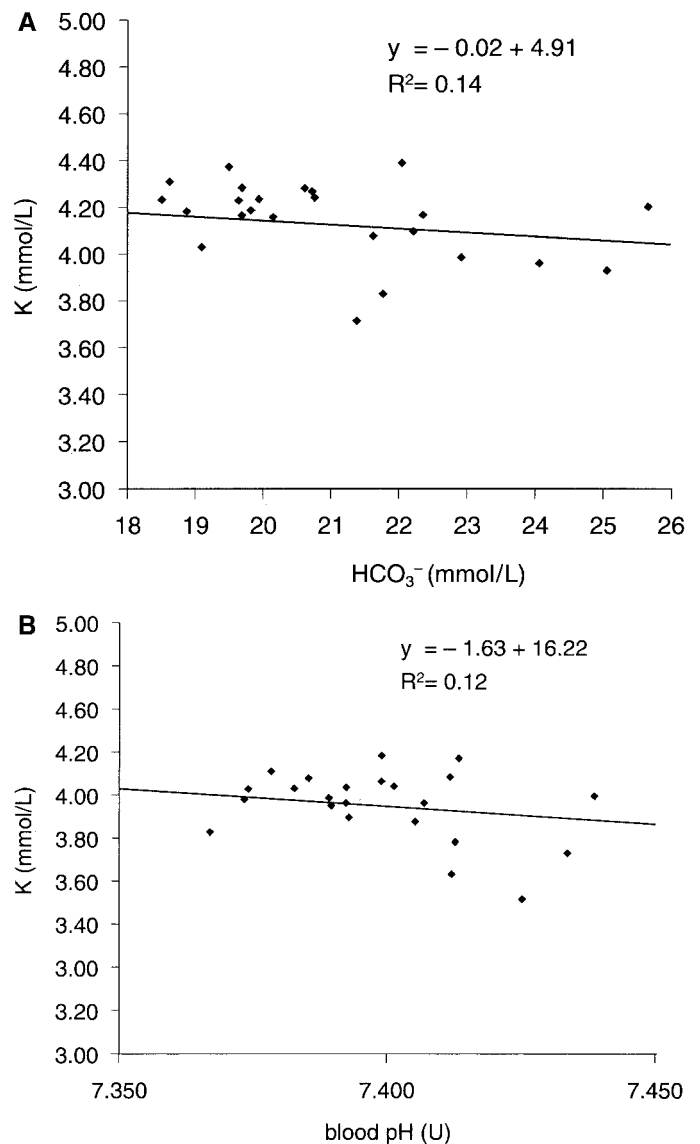


Figure 3. Relationship of plasma potassium concentration to plasma bicarbonate concentration (top) and arterial blood pH (bottom).

patient in a single creditable report (13,14). Thus, based largely on animal data exhibiting an extraordinary variance ($\Delta[K]_p/\Delta pH$ ranged from -2.4 to -16.7), it was concluded that AMA was associated with consistent hyperkalemia, but of uncertain magnitude. However, it is even difficult to interpret the studies in dogs with clarity. Either severe hyperkalemia (1,28) or an unchanged plasma $[K^+]$ (29) were reported during post-IV HCl equilibration periods using arterial plasma samples.

The present study is the first to examine human AMA-induced plasma K^+ changes under carefully controlled conditions or using a clinically meaningful change in plasma bicarbonate concentration. In contrast to prior human reports that described either a tendency to (4,5,17) or a significant increase in $[K]_p$ during AMA (2,13), we found no appreciable change in $[K]_p$. The major methodologic differences between these and the present study are the use of demonstrably arterialized plasma (*versus* venous serum or plasma) and the wider range of plasma bicarbonate values achieved in the present study. It is likely that the reported high variance and *in vitro* artifactual

potassium elevations associated with both venous *versus* arterial and serum *versus* plasma sampling are responsible for the observed differences (18–20). The present study's design with identical treatment of multiple subjects and reporting of the mean of several demonstrably stable control and AMA-induced acute steady state values rather than individual sample values also reduced variance and make the resulting AMA-induced observations more interpretable.

The failure to detect hyperkalemia in AMA does not preclude the existence of acidosis-induced net H^+/K^+ exchange across cell membranes, resulting in K^+ efflux from cells. Such a process could be large in magnitude and hidden by an equal and opposite endocrine response driving K^+ into cells. The observed rise in insulin concentration could have counteracted and neutralized any cellular potassium exit in response to AMA. The small decrease in glucagon concentration may have contributed to limit potassium changes by inhibition of hepatic release of potassium (30). The observed tendency toward hyperglycemia despite significant hyperinsulinemia raises the

Table 3. Response of glucose, glucoregulatory hormones, Ghrelin, and growth hormone during control, acid equilibration, and recovery periods

Period	Glucose (mmol/L)	Insulin (U/L)	Glucagon (pg/ml)	Ghrelin (pg/ml)	Growth Hormone (U/L)
Control	5.7 ± 0.7	7.8 ± 1.9	81.6 ± 5.7	1594 ± 56	1.9 ± 1.7
E1 (30 min)	6.7 ± 0.8	24.7 ^b ± 8.2	69.3 ± 5.1 ^b	1964 ± 225	0.9 ± 0.4
E1 (60 min)	6.2 ± 0.9	11.1 ^b ± 3.9	71.8 ± 4.9 ^b	1962 ± 235	0.5 ± 0.2
E2 (30 min)	7.2 ± 1.3	26.7 ^b ± 9.8	69.2 ± 4.5 ^b	1724 ± 123	0.9 ± 0.4
E2 (60 min)	7.0 ± 0.9	22.5 ^b ± 8.4	65.6 ± 4.8 ^b	1779 ± 122	0.7 ± 0.4
E3 (30 min)	7.0 ± 1.2	26.7 ^b ± 10.4	65.6 ± 3.2 ^b	1682 ± 93	0.9 ± 0.4
E3 (60 min)	5.5 ± 0.8	6.8 ± 1.1	58.9 ± 3.9 ^b	1622 ± 122	2.9 ± 0.8
Recovery (+6 h)	5.3 ± 0.2	8.5 ± 1.0	86.9 ± 7.1	Not done	1.1 ± 0.9
Recovery (+24 h)	5.0 ± 0.2	8.0 ± 2.1	Not done	Not done	0.9 ± 0.3

^a E denotes equilibration period. The suffix number indicates the equilibration that followed the corresponding acid infusion period (A1 to A3). The time that elapsed after stopping acid infusion is indicated in brackets. Numbers are means ± SEM.

^b $P \leq 0.05$.

Table 4. Response of ACTH, cortisol, aldosterone, epinephrine, and norepinephrine during control, acid equilibration, and recovery

Period ^a	ACTH (pmol/L)	Cortisol (mmol/L)	Aldosterone (pmol/L)	Epinephrine (pmol/L)	Norepinephrine (pmol/L)
Control	2.5 ± 0.4	523 ± 62	161 ± 24	432 ± 110	1513 ± 235
E1 (30 min)	1.3 ± 0.4	452 ± 62	175 ± 28	444 ± 102	1179 ± 230
E1 (60 min)	1.4 ± 0.2	406 ± 63	159 ± 21	502 ± 117	1225 ± 300
E2 (30 min)	1.1 ± 0.4	387 ^b ± 52	171 ± 26	458 ± 121	1297 ± 364
E2 (60 min)	1.7 ± 0.4	350 ^b ± 60	155 ± 29	506 ± 109	1220 ± 315
E3 (30 min)	1.9 ± 0.3	259 ^b ± 48	175 ± 24	398 ± 75	1269 ± 360
E3 (60 min)	1.4 ± 0.4	159 ^b ± 41	178 ± 29	297 ± 101	1342 ± 337
Recovery (+6h)	2.3 ± 0.3	516 ± 47	Not done	281 ± 36	Not done
Recovery (+24h)	2.4 ± 0.6	553 ± 69	Not done	Not done	Not done

^a E denotes equilibration period. The suffix number indicates the equilibration that followed the corresponding acid infusion period (A1 to A3). The time that elapsed after stopping acid infusion is indicated in brackets. Numbers are means ± SEM.

^b $P \leq 0.05$.

possibility that the insulin resistance demonstrated in CMA may be an acute effect (31), an issue that will need additional investigation.

Irrespective of the mechanism for normokalemia in the clinically meaningful degree of AMA achieved in the present study, our findings, together with the lack of a discernible hyperkalemic response in albeit difficult models of acute organic acidosis (14), show that hyperkalemia in clinical AMA cannot be attributed to AMA but reflects the presence of a concomitant disorder of potassium metabolism. The current clinical practice of attributing hyperkalemia in patients with AMA to the acid-base disorder will require change (16). If our interpretation of the insulinemic response (counteraction of acidemia-induced K efflux) is correct, our results cannot be applied to patients with insulin deficiency.

The temporal pattern of renal net acid excretion in relation to the acid load is of interest. By the final equilibration period (nadir plasma bicarbonate value) after the final acid load was administered, the kidney had excreted only 8.8 mmol (corrected for a body weight of 70 kg) or less than 5% of the administered acid load, indicating that negligible renal compensation occurs in AMA. Although a modest phosphaturia then ensued, the bulk of the early NAE response was attributable to NH_4^+ excretion. The decrease in urine pH to values below 5.3 was surprisingly delayed to almost 8 h after the final acid load. The delay in reaching a nadir urine pH appeared to be in part related to early rises in NH_4^+ excretion (e.g., from 1.2 to 2.8 mmol/h), which may thus reflect early enhanced renal ammoniogenesis (forcing urine pH to rise by virtue of NH_3 's property as a base) as well as by enhanced trapping of NH_3 in the collecting duct due to a fall in luminal pH (32). The finding of an 8-h delay in reaching pH values of 5.3 suggests that acute acid loading tests in humans should not be considered abnormal on the basis of urine pH criteria unless samples are obtained for at least 8 h after the acid load or nadir plasma bicarbonate value.

In conclusion, the present study has provided novel characterization of the cardinal acid-base disorder AMA in human subjects. The results provide diagnostic criteria for diagnosis of AMA and for discerning its presence or absence in possible mixed disorders. The demonstrable lack of a hyperkalemic response in experimental human AMA will assist clinicians in interpreting the frequent changes in plasma potassium concentration that occur in acutely ill patients with AMA and guide them to seek different explanations for hyperkalemia such as concomitant metabolic, renal, and endocrine disturbances or even problems in the preanalytic handling of the specimens (hemolysis, clotting). Since the rise in plasma insulin may have been responsible for counteracting a possible acidemia-induced potassium efflux in this study, our findings may not be applicable in diabetic patients. The present studies have also not explored the response to acute organic acidosis.

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See related editorial, “PCO₂ and [K⁺]_p in Metabolic Acidosis: Certainty for the First and Uncertainty for the Other,” on pages 1667–1668.

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