Published in final edited form as:

JPEN J Parenter Enteral Nutr. 2007 ; 31(4): 278–283.

Parenteral Amino Acid and Metabolic Acidosis in Premature Infants

Pushkaraj Jadhav, M.D., Prabhu S. Parimi, M.D., and Satish C. Kalhan, M.B.B.S. F.R.C.P.
Schwartz Center for Metabolism and Nutrition, and Department of Pediatrics Case Western Reserve University MetroHealth Medical Center, Cleveland, Ohio

Abstract

OBJECTIVE: Aggressive parenteral nutrition including amino acids is recommended for low birth weight infants to prevent energy and protein deficit. Their impact on acid-base homeostasis has not been examined.

PATIENTS AND METHODS: We investigated the impact of dose and duration of parenteral amino acids, with cysteine, on acid-base parameters in 122 low birth weight infants. Premature infants <32 weeks, <1850g and receiving parenteral amino acids at 1.5g·kg⁻¹·d⁻¹ for an extended period (>24h), or 3g·kg⁻¹·d⁻¹ for a short (5h), extended (24h) or for prolonged (3-5 days) duration were included in the study. Data were obtained at age 0-3 days (n=43) or when clinically stable, age 3-5 days (n=49). Data from thirty infants matched for birth weight, and gestational age and receiving parenteral nutrition during the first five days after birth were also obtained. Acidosis was defined as pH<7.25.

RESULTS: Acidosis was evident in all infants between 2 and 5 days after birth. Infants with large patent ductus arteriosus (PDA) exhibited significantly (p<0.05) lower pH early, had higher blood urea nitrogen levels (26 ± 9 vs. 18±8 mg/dl, p<0.05) and had greater weight loss (~17% of birth weight), when compared with babies without PDA. Gestational age, weight loss and patent ductus arteriosus accounted for 65% of variance in acidosis.

CONCLUSIONS: Low birth weight infants develop metabolic acidosis between 2-5 days after birth irrespective of dose and duration of parenteral amino acid administration.. Careful management of parenteral fluids and co-morbidities may lower the incidence of acidosis and promote protein accretion.

Précis—The association between early parenteral amino acid administration at 1.5 and 3.0g·kg⁻¹·d⁻¹ and blood acid base status was examined in 122 low birth weight infants. The data show that all LBW infants develop metabolic acidosis independent of amino acid dose between 2-5 days after birth, which is exaggerated by associated co-morbidities.

Introduction

Although born appropriate for gestational age, postnatal growth restriction has been consistently observed in low birth weight infants (1-3). Postnatal growth failure in premature infants has been attributed to protein and energy deficits accruing over the duration of hospital stay (4). Therefore greater emphasis has been placed on early aggressive nutritional care of these babies in order to prevent postnatal growth retardation. A number of investigators have suggested that parenteral nutrition should be initiated as early after birth as possible and parenteral amino acids be administered at 3-3.5g·kg⁻¹·d⁻¹ in order to mimic protein accretion during fetal life (5-12). Only few studies have examined the safety of early and aggressive

Corresponding Author: Satish C. Kalhan, M.D. Department of Gastroenterology and Pathobiology Lerner Research Institute The Cleveland Clinic Foundation 9500 Euclid Ave. Cleveland, OH 44195 Tel: 216-444-4225 E-mail: sck@case.edu

These studies were supported by a grant from the National Institute of Child Health and Human Development (RO1-HD042152).

administration of parenteral amino acids to low birth weight infants. A recent publication by Braake *et al* showed that prematurely born infants tolerated parenteral nutrition containing $2.4\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ of amino acids initiated soon after birth, without any significant change in acid base status (11). In their study, the amount of parenteral amino acids provided were lower than the current recommendation (8), and acid base parameters were only monitored once a day. The impact of other factors affecting the acidbase status in premature infants was not explored.

We examined the dose-response relationship between duration, short (5h), extended (24h) and prolonged (3-5 days), and dose 1.5 to $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, of parenteral amino acids on changes in acid-base parameters in premature infants. In addition, we examined the effect of acuity of illness, and clinical morbidities on the above parameters, specifically in relation to age at initiation of parenteral nutrition. Data in the literature (15) had shown that balanced (cation = anion) amino acid mixtures, because they are ionically balanced, do not cause acidosis in-vivo. Therefore, we hypothesized that changes in acid base status in premature infants will be the consequence of associated clinical morbidities, and that early initiation of parenteral amino acids will not impact their acid-base status.

Patients and Methods

The present study was prompted by an anonymous complaint to the Institutional Review Board (IRB) insinuating high incidence of “perceived acidosis” with early parenteral administration of amino acids at $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Prospectively obtained laboratory data from our published (16-18) and unpublished physiological studies of glutamine metabolism and that obtained from chart review of a matched case-control group were examined. The impact of duration (5h, 24h, and 3-5 days) of parenteral amino acids at 1.5 to $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ on acid-base homeostasis was evaluated.

Subjects and study design:

LBW preterm infants ($n=122$) <32 weeks gestation and birth weight $<1850\text{g}$ were included in the study. Babies with congenital anomalies or with birth asphyxia were excluded. All study protocols were approved by the Institutional Review Board. The babies included were (i) all who were part of previously reported kinetic studies ($n=71$, Table 1) (16-18); (ii) another prospective group of infants receiving higher dose ($3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) amino acids between 0-3 days after birth ($n=21$, Table 3), and (iii) a matched for birth weight and gestational age control group ($n=30$, Table 3). The matched control group consisted of infants not participating in any study protocol admitted to the Neonatal Intensive Care Unit within $\pm 48\text{h}$ of the index case (ii) and matched for birth weight and gestational age. The details of the kinetic studies protocols have been reported (16-18). Briefly, preterm infants were randomized to receive parenteral amino acids either at $1.5\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ or $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 24 hours. Thereafter, they received amino acids either at $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ or $1.5\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for short (5h) or extended (24h) duration. Babies were studied between 0-3d or between 3-5 days of age. However, since there was no significant difference in their laboratory parameters, their data have been combined for analysis. An additional group (Table 1) was given amino acids with and without glutamine at $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for a prolonged (3-5d) period. Data in the early high amino acid group were collected between 3-5 days of age (Table 3). Eight infants in this group developed clinical co-morbidities and could not continue the study protocol (withdrawn), while the other 13 completed the study (completed). The control group ($n=30$) was matched with the early high amino acid group and was born within 48 hours of the index cases. Their data were collected from the review of clinical records. They were receiving parenteral amino acids at 1.5 to $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, (2.1 ± 0.4 , mean $\pm$ SD) as per the routine clinical practice of the primary neonatologist.

All decisions regarding clinical management, intravenous fluids, glucose, intralipid, electrolytes, minerals and trace elements in the parenteral nutrition, ventilatory support, use of

vasopressor, etc., were made by the primary physician, irrespective of participation of babies in the study protocols.

Data collection—The data were obtained prospectively, except those from the matched control group which was collected later. Severity of respiratory distress syndrome was graded independently by the pediatric radiologist. The duration of ventilator support (IMV), including the duration of oxygen supplementation, was recorded. Patent ductus arteriosus (PDA) was diagnosed by 2D-ECHO by the pediatric cardiologist, and graded into small, moderate or large PDA based on the ECHO findings. Daily weight was obtained and the percent weight loss during the first 3-4 days after birth was determined. Total intravenous fluids administered, energy intake, glucose load, intralipids, amount of parenteral amino acids, and the amount of cysteine added to the parenteral nutrient mixture were recorded daily for the first five days after birth or for the duration of the study protocol. The chloride/acetate ratio in the parenteral nutrition was obtained. Intravenous fluid (0.45 normal saline with heparin) administered to maintain the patency of the indwelling arterial lines ($\sim 12 \text{ ml}\cdot\text{d}^{-1}$) were not included in the calculation of total intravenous fluids.

The frequency of laboratory tests including the arterial blood gases were decided by the primary physician based upon the clinical status of the infants. Generally, infants had their arterial blood gases monitored every 2-4h. Only arterial blood gas data (pH, PaCO_2 , PaO_2) obtained daily during the first week after birth was collected. Venous and capillary blood gas parameters were not included in the data collection. Serum electrolytes and blood urea nitrogen were obtained daily starting on the second day after birth as per clinical practice. Anion gap $[(\text{Na}+\text{K}) - (\text{Cl} + \text{HCO}_3)]$ was calculated from the data of serum electrolytes. Blood ammonia levels were determined only in study subjects receiving $3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ of parenteral amino acids.

Statistical analysis:

Data are reported as mean $\pm$ SD. All blood gases obtained on a given day were tabulated and data was averaged every 8h to calculate the 24h average of pH, PaO_2 and PaCO_2 for each baby, and for the individual groups. For babies in the “prolonged” study group and those in the control groups, in addition to the daily average, composite averages were determined for each baby and for the entire group. Similarly, averages for each day and composite averages for serum electrolytes were determined. Nominal data was analyzed using sign test and ordinal data using the Wilcoxon signed rank sum test. Analysis of variance was used to compare the data within and between the groups. A stepwise regression model was developed using pH on day 3 and day 4 as a dependent variable and a number of factors (birth weight, gestational age, weight loss during the first five days after birth, total amount of intravenous fluids administered, patent ductus arteriosus, and the amount of cysteine added to TPN) that might affect pH as independent variables. A two-tailed P value $< .05$ was considered statistically significant.

Results

Clinical characteristics of infants enrolled in the previously reported studies (16-18) are summarized in Table 1. Birth weight, gestational age and the score of neonatal acute physiology (SNAP), an indicator of severity of acute illness, were not different among babies recruited in different study protocols. All infants lost approximately 10% of their weight during the first five days after birth.

The impact of amino acid load $1.5\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ vs. $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for a short (5h) extended (24h) and for a prolonged period (3-5d) on acid base parameters is displayed in Table 2. An increase in parenteral amino acids to $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for a shorter or an extended duration had no significant impact on pH. Similarly, infusion of amino acids at $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for a prolonged period had no effect on arterial pH. Arterial PaCO_2 , serum chloride and bicarbonate, anion gap

and blood urea nitrogen were not different between the study groups. The concentration of blood ammonia was within the normal range in babies receiving $3.0\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ amino acids.

We recruited 21 infants between 0-72h after birth to examine the effect of 3-5 days of parenteral amino acids ($3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) with or without supplemental glutamine on glutamine and whole body protein metabolism (unpublished data). Their clinical characteristics along with matched case-controls are shown in Table 3. Birth weight, gestational age, SNAP score, magnitude of weight loss and age when the tracer isotope studies were performed in the “completed” group were similar to our previous studies. Premature infants who were “withdrawn” from the study protocol for clinical reasons had lower birth weight ($p<0.05$), lower gestational age ($p<0.05$) and their weight loss during the first five days after birth was significantly higher ($p<0.05$) compared to those who completed the study. There was no significant difference in birth weight, gestational age and SNAP score between “withdrawn” babies and those in the matched controls.

Babies who were “withdrawn” had greater prevalence of patent ductus arteriosus (70%), had large PDA based on the echocardiography findings, and 5/7 (70%) infants underwent surgical ligation for PDA. In addition, these infants required ventilator support for a prolonged period ($p<0.01$) and had significantly higher weight loss ($p<0.05$) during the first five days after birth. As per the study protocol, babies in the study group received a higher amount of amino acid load and consequently a higher amount of cysteine added to the parenteral amino acid solution (Table 3).

Sequential change in acid base parameters during the first five days after birth in the study group and matched controls are shown in Table 4. Since there were no differences in acid-base parameters among those who completed and those who were withdrawn from the study, the data were combined. Acid-base parameters, obtained *after* the baby was withdrawn from the study, were not included in the analysis. Babies included in the study showed a progressive decline in arterial pH with nadir on day 5 after birth. Infants in the “withdrawn” group also showed a decrease in pH with age; however the lowest pH was evident earlier, i.e. on the third day after birth. Babies matched for birth weight and gestational age (Controls) and receiving lower doses of parenteral amino acids, as ordered by their primary care providers, also demonstrated a similar change in arterial pH with postnatal age. There were no differences in PaCO_2 , serum bicarbonate, serum chloride, and anion gap within and between the groups.

The concentration of blood urea nitrogen on day 5 was higher in babies included in the study ($31 \pm 17\text{ mg}\cdot\text{dl}^{-1}$) compared to controls ($15 \pm 10\text{ mg}\cdot\text{dl}^{-1}$; $p<0.05$). However, blood urea nitrogen levels increased starting day 2 ($p<0.01$) in babies in the “withdrawn” group. There was no change in serum sodium levels with advancing postnatal age. Intravenous fluids were increased in all the groups during the first five days after birth. There were no significant differences in total volume of intravenous fluids administered between the groups..

Since a lower pH was evident at an earlier postnatal age in the “withdrawn” and “control” groups, we examined a number of clinical factors contributing to metabolic acidosis (Table 3). Babies who were “withdrawn” had large PDA, nearly two-thirds of these babies underwent surgical ligation, and had significantly greater weight loss during the first three days after birth ($p<0.05$). Analysis of individual cases revealed that the nadir in pH corresponded to the diagnosis of large PDA, and the use of bicarbonate to treat acidosis.

In order to identify potential factor(s) contributing to metabolic acidosis, we have constructed a model with pH on days 3 and 4 as dependent variable and incorporated all the factors which could potentially cause metabolic acidosis preceding days 3-4 as independent variables. Gestational age, large PDA and weight loss accounted for 65% of variance in pH.

Discussion

We show that all very low birth weight infants developed acidosis ($\text{pH} < 7.25$) between days 3-5 after birth. Infants with moderate to large patent ductus arteriosus developed acidosis earlier. The diagnosis of PDA coincided with higher blood urea nitrogen. A lower pH correlated with gestational age, large patent ductus arteriosus and the magnitude of weight loss during the first 72h after birth. Importantly, the dose or duration of parenteral amino acid and cysteine did not seem to impact arterial pH (acidosis).

Defects in urinary acidification, together with a number of other factors, such as infections, hypotension, inappropriate administration of intravenous fluids, higher insensible water losses and decreased tissue perfusion contribute to metabolic acidosis in premature infants. In such a complex situation, it is difficult to ascertain whether parenteral amino acids worsen metabolic acidosis in premature babies. In this study, we examined the interaction between a number of factors to identify the potential contributors to acidosis, specifically the impact of dose and duration of parenteral amino acids.

Infants included in the present study received crystalline amino acid solution (10% TrophaAmine, Braun Medical Inc, Irvine CA), providing a mixture of essential and non essential amino acids as well as taurine and soluble form of tyrosine, N-Acetyl-L-Tyrosine. Majority were non-salt amino acids except lysine and cysteine which were added respectively as acetate and hydrochloride salt. Although the titratable acidity, the amount of blood buffers consumed in vivo to titrate the infusate ($\text{pH} 5.5$) to a normal blood pH was not determined in babies, Heird and colleagues showed that infants and children receiving amino acid mixtures with high titratable acidity did not become acidotic (15). Their data suggest that metabolism of cationic amino acids and resulting release of excess protons (H^+) may cause hyperchloremic metabolic acidosis, if it is not balanced by an equal proportion of metabolizable anionic amino acids. Thus determination of cationic gap (cationic amino acids-anionic amino acids + acetate) may assist in determining whether there is an imbalance in the amino acid mixture. Trophamine is a balanced amino acid solution containing 156 mmol.L^{-1} of cationic amino acids (Arginine, histidine and lysine) and 155 mmol.L^{-1} of anionic amino acids (glutamic acid and aspartate) plus acetate. Thus the metabolic acidosis observed in the LBW infants could not be attributed to the “balanced” amino acid mixture administered.

Babies in the present study demonstrated a *normal* anion-gap metabolic acidosis with advancing post natal age (nadir on day 4-5). Few limited studies have examined the reasons for such a metabolic acidosis. Sato and colleagues (13) showed that low birth weight infants have a higher urinary pH, higher fractional excretion of bicarbonate, and most importantly lower urinary ammonium excretion rate persisting even on days 4-6 after birth. They suggested that insufficiency of ammonium excretion was the main cause of metabolic acidosis in the early neonatal period (13). The reported pH in their study on day 4-6 (~ 7.32), was significantly higher than that observed in the present study (~ 7.24). Approximately 50% (7/15) of the babies in their study received bicarbonate infusion to treat metabolic acidosis. Exclusion of infants who had been on indomethacin, receiving parenteral nutrition or receiving ionotropic drugs, in their study had led to the selection of babies without common clinical confounders. In contrast, we included all babies, irrespective of clinical co-morbidities.

Metabolic acidosis in the present study occurred independent of the amount and duration of amino acids infusions and the dose of supplemental cysteine, suggesting that factors other than parenteral amino acids contribute to the development of acidosis. A recent study has shown that administration of $2.4 \text{ g.kg}^{-1}.\text{d}^{-1}$ of amino acids was safe and did not result in changes in acid-base parameters (11). Our data are robust in that we determined the dose response relationship, examined sequential changes in blood gas and serum electrolytes in response to

a higher (currently recommended) dose of parenteral amino acid for a prolonged period and examined the impact of cysteine load, and other co-morbidities. We observed that infants with large PDA developed acidosis early (day 3), had significantly lower arterial pH, were given intravenous bicarbonate to treat acidosis, and required inotropic drugs to maintain normal blood pressure (“withdrawn” group: Table 3). Patent ductus arteriosus (PDA) becomes clinically manifest with improvement in pulmonary compliance. The associated “ductal steal” impacts blood flow to vital organs, resulting in hypoperfusion (14). Onset of early acidosis coinciding with the diagnosis of PDA and higher concentration of blood urea nitrogen in the “withdrawn” group suggests renal hypoperfusion. We speculate that in premature infants, renal tubular immaturity, hypoperfusion and hypotension, accompanied by clinical interventions used to treat PDA, may have resulted in a decrease in pH at an earlier postnatal age. Our model confirmed that gestational age, weight loss, possibly as a result of restriction of intravenous fluids, and patent ductus arteriosus accounted for a large majority (~ 66%) of acidosis in premature infants.

The present study underscores the complexities involved in identifying the cause of metabolic acidosis in a rapidly changing clinical situation, i.e. the preterm neonate in the intensive care unit. Since blood pH is a labile parameter influenced by clinical state and confounding complications (PDA, hypovolemia etc), and equally important clinical interventions, it is difficult to identify the cause of change in pH. Infact, the investigating committee appointed by the IRB found it difficult to manage the large amount of clinical and laboratory data obtained in these studies and resolved to identify acidosis based upon administration of bicarbonate by the clinician. They were not able to attribute bicarbonate administration to any identifiable clinical parameters. Only by performing a case-control analysis, we could show that low birth weight babies develop relative metabolic acidosis in the first few days after birth irrespective of the amount of parenteral amino acids administered.

We conclude that non-anion gap metabolic acidosis is common in premature infants. Early recognition and management of PDA, prevention of excess water losses in conjunction with judicious fluid and electrolyte management, balancing cysteine hydrochloride with an equimolar amount of base (acetate) could prevent metabolic acidosis. Such a strategy will result in provision of optimal amount of parenteral amino acids to promote nitrogen accretion in low birth weight infants.

Acknowledgment

The secretarial assistance of Mrs. Joyce Nolan is gratefully appreciated.

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Table 1

Clinical Characteristics

	1.5 g.kg ⁻¹ .d ⁻¹	3.0 g.kg ⁻¹ .d ⁻¹		
	(Extended) ¹	(Short) ¹	(Extended) ¹	(Prolonged) ²
n	(19)	(17)	(15)	(20)
Duration of TPN (h)	24	5	24	72-120
Birth weight (g)	1174 ± 274	1239 ± 312	1117 ± 247	1077 ± 300
Gestational age (wk)	29 ± 2	29 ± 2	29 ± 2	27 ± 2
SNAP [*]	11 (1-18)	12 (5-21)	11 (4-21)	12 (5-16)
Weight loss % (0-5 days)	10 ± 4	10 ± 6	8 ± 3	11 ± 4

Mean ± SD

Infants received parenteral amino acids either at 1.5g.kg⁻¹.d⁻¹ or 3g.kg⁻¹.d⁻¹ for short (5h), extended (24h) or prolonged (3-5 days) duration.

SNAP: Score for Neonatal Acute Physiology (ref. 19)

^{*} Median (25%-75%)

¹ From Ref. 16-17

² From Ref. 18

Table 2

Effect of dose and duration of parenteral amino acids on acid base status

	1.5 g.kg ⁻¹ .d ⁻¹	3.0 g.kg ⁻¹ .d ⁻¹		
	(Extended)	(Short)	(Extended)	(Prolonged)
n	(19)	(17)	(15)	(20)
Duration of TPN (h)	24	5	24	72-120
pH	7.30 ± 0.05	7.32 ± 0.04	7.27 ± 0.02	7.29 ± 0.03
PaCO ₂ (mmHg)	43 ± 6	40 ± 12	44 ± 4	43 ± 5
Chloride (meq.L ⁻¹)	111 ± 6	103 ± 28	114 ± 4	104 ± 3
Bicarbonate (meq.L ⁻¹)	19 ± 3	18 ± 6	20 ± 2	17 ± 3
Anion gap	12 ± 6	12 ± 5	9 ± 3	18 ± 3
Blood urea (mg/dl)	18 ± 7	16 ± 7	17 ± 8	24 ± 5
Ammonia (μm.L ⁻¹)	ND	65 ± 30	76 ± 21	51 ± 7

Infants received parenteral amino acids either at 1.5g.kg⁻¹.d⁻¹ or 3g.kg⁻¹.d⁻¹ for short (5h), extended (24h) or prolonged (3-5 days) duration.

Mean ± SD

Table 3
Clinical Characteristics of Early Amino Acids and Control Groups

<u>Early High Amino Acids</u> *			
	Completed (n=13)	Withdrawn (n=8)	Controls (n=30)
Birth weight (g)	1280 ± 283	1017 ± 250*	1027 ± 393
Gestational age (wk)	30 ± 1	27 ± 2*	27 ± 3
IMV (d)	9 ± 7	30 ± 17**	24 ± 10
Patent ductus arteriosus (n)	3	7	10
Small: large	2:1	1:6	6:4
Age at diagnosis (d)	3 ± 1	5 ± 3	4 ± 2
Indomethacin use (n)	1	2	2
PDA ligation	1	5*	6
Amino acid load (g.kg ⁻¹ .d ⁻¹)	2.7 ± 0.3	2.6 ± 0.3	2.1 ± 0.4
Cysteine (mg.kg ⁻¹ .d ⁻¹)	106 ± 15	105 ± 13	86 ± 20
Fluid Intake (ml.kg ⁻¹ .d ⁻¹)			
Weight loss (%)	12 ± 3	17 ± 5*	10 ± 3

Mean ± SD

Early high amino acids: 3.0 g.kg⁻¹.d⁻¹ administered within 24 hours after birth. Completed: continued on 3.0 g.kg⁻¹.d⁻¹ for 3-5 days. Withdrawn: developed clinical complications and did not continue on this protocol.

*
p<0.05

**
p<0.01

Table 4
Sequential changes in acid base parameters of early high amino acid group and controls

	Day 1	Day 2	Day 3	Day 4	Day 5
Study (n=21)					
Amino acid load (g.kg ⁻¹ .d ⁻¹)	-	2.4 ± 0.7	2.9 ± 0.3	2.8 ± 0.4	2.6 ± 1.3
pH	7.33 ± 0.07	7.30 ± 0.05	7.26 ± 0.06	7.25 ± 0.05	7.23 ± 0.08
P _a CO ₂ (mmHg)	41 ± 8 (20)	41 ± 6 (18)	45 ± 5 (16)	43 ± 7 (14)	46 ± 9 (14)
Bicarbonate (meq.L ⁻¹)	22 ± 2	22 ± 2	20 ± 2	21 ± 3	21 ± 3
Chloride (meq.L ⁻¹)	110 ± 6	112 ± 5	114 ± 4	111 ± 5	109 ± 5
Anion gap	11 ± 4 (8)	12 ± 3 (23)	13 ± 1 (23)	12 ± 2 (23)	12 ± 2 (23)
Controls (n=30)					
Amino acid load (g.kg ⁻¹ .d ⁻¹)	-	1.5 ± 0.7	2.1 ± 0.6	2.5 ± 0.5	2.4 ± 0.8
pH	7.32 ± 0.06	7.30 ± 0.04	7.25 ± 0.05	7.24 ± 0.05	7.24 ± 0.03
P _a CO ₂ (mmHg)	41 ± 6 (30)	43 ± 7 (27)	47 ± 7 (23)	49 ± 6 (22)	48 ± 7 (18)
Bicarbonate (meq.L ⁻¹)	21 ± 6	22 ± 2	22 ± 3	22 ± 3	21 ± 4
Chloride (meq.L ⁻¹)	110 ± 3	112 ± 5	112 ± 6	112 ± 5	110 ± 5
Anion gap	11 ± 2 (21)	12 ± 3(30)	12 ± 3(30)	12 ± 2(30)	12 ± 3(30)
Mean ± SD					