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Acid–base status of critically ill patients with acute renal failure: analysis based on Stewart–Figge methodology

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Abstract

Introduction The aim of the present study is to understand the nature of acid–base disorders in critically ill patients with acute renal failure (ARF) using the biophysical principles described by Stewart and Figge. A retrospective controlled study was carried out in the intensive care unit of a tertiary hospital.

Materials and methods Forty patients with ARF, 40 patients matched for Acute Physiology and Chronic Health Evaluation II score (matched control group), and 60 consecutive critically ill patients without ARF (intensive care unit control group) participated. The study involved the retrieval of biochemical data from computerized records, quantitative biophysical analysis using the Stewart–Figge methodology, and statistical comparison between the three groups. We measured serum sodium, potassium, magnesium, chloride, bicarbonate, phosphate, ionized calcium, albumin, lactate and arterial blood gases.

Results Intensive care unit patients with ARF had a mild acidemia (mean pH 7.30 ± 0.13) secondary to metabolic acidosis with a mean base excess of -7.5 ± 7.2 mEq/l. However, one-half of these patients had a normal anion gap. Quantitative acid–base assessment (Stewart-Figge methodology) revealed unique multiple metabolic acid–base processes compared with controls, which contributed to the overall acidosis. The processes included the acidifying effect of high levels of unmeasured anions (13.4 ± 5.5 mEq/l) and hyperphosphatemia (2.08 ± 0.92 mEq/l), and the alkalinizing effect of hypoalbuminemia (22.6 ± 6.3 g/l).

Conclusions The typical acid–base picture of ARF of critical illness is metabolic acidosis. This acidosis is the result of the balance between the acidifying effect of increased unmeasured anions and hyperphosphatemia and the lesser alkalinizing effect of hypoalbuminemia.

Keywords acid–base disorders, acidosis, acute renal failure, albumin, alkalosis, critical illness, phosphate, unmeasured anions

Introduction

Acute renal failure (ARF) is a common complication of critical illness [1,2]. Patients with ARF and critical illness present with a variety of disorders of acid–base homeostasis, which are poorly understood and have not yet been formally studied. Furthermore, it is difficult to separate the acid–base effects of

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AG = anion gap; APACHE = Acute Physiology and Chronic Health Evaluation; ARF = acute renal failure; ICU = intensive care unit; SIDa = apparent strong ion difference; SIDe = effective strong ion difference.

critical illness *per se* from those of ARF. Understanding the contribution of ARF to acid–base disorders and gaining insight into the nature of such disorders are likely to help clinicians in making the correct physiological diagnosis.

The extent and nature of acid–base disorders in critically ill patients with ARF might be better understood if quantitative biophysical methods are applied to its assessment [3–6] and if control groups are used to appreciate which features might be unique to ARF. Accordingly, we compared a cohort of critically ill patients with ARF with two control groups: a matched control group, an Acute Physiology and Chronic Health Evaluation (APACHE) II-matched cohort without ARF; and an intensive care unit (ICU) control group, a group of consecutive critically ill patients without ARF. We then assessed the acid–base status using quantitative biophysical principles (Stewart–Figge methodology) [7,8].

Materials and methods

The data collection for this type of study is considered an audit by the Institutional Ethics Committee, which waives the need for informed consent.

We retrospectively examined data from 40 consecutive critically ill patients with ARF who subsequently required renal replacement therapy for at least 48 hours. ARF was defined by an acute rise in either urea and/or creatinine concentration to above normal levels (7.7 mmol/l for urea and 110 μmol/l for creatinine) and a urine output <200 ml in the preceding 12 hours, despite fluid resuscitation and furosemide administration.

To define the unique acid–base characteristics of ARF patients, we used two control groups. The matched control group consisted of 40 ICU patients without ARF matched for APACHE II score [9]. The ICU control group consisted of 60 consecutive critically ill patients without ARF.

The data needed for analysis of the ICU patients were originally collected by the ICU staff as part of standard patient care, and are electronically stored and available for computer-based retrieval. We thus retrospectively obtained demographic data (age, sex, APACHE II score, ICU mortality, hospital mortality, and admission diagnosis) and biochemical data from our electronic ICU database. All values for the ARF group were from the latest samples available before initiation of renal replacement therapy. The matched control and the ICU control samples, on the other hand, were routine morning samples (the day after admission) taken from arterial lines in patients requiring intensive care management. No additional sampling was required.

Arterial blood samples were collected in heparinized blood-gas syringes (Rapidlyte; Chiron Diagnostics, East Walpole, MA, USA) and analyzed using the intensive care blood-gas analyzer (Ciba Corning 865; Ciba Corning Diagnostics, Med-

field, MA, USA). The analyzer measured at 37°C. Nursing staff from the ICU who had been taught to use the machine by support staff performed the analysis. Samples were analyzed immediately without storage on ice. We collected data from the output: the pH and partial pressure of carbon dioxide, and the blood levels of lactate, bicarbonate, and ionized calcium. The machine calculated the bicarbonate concentration using the Henderson–Hasselbalch equation. The carbon dioxide solubility coefficient was 0.0307. The apparent overall dissociation constant for carbonic acid was 6.105.

A further arterial sample was simultaneously drawn for each dataset using a vacuum technique with lithium heparin tubes (Vacuette; Greiner Labortechnik, Kremsmunster, Austria). These samples were analyzed by clinical staff at the hospital central laboratory (Hitachi 747; Roche Diagnostics, Sydney, NSW, Australia) for the measurement of multiple biochemical variables including sodium, chloride, potassium, phosphate, total magnesium and albumin, which were used for analysis. Plasma sodium was measured using an ion-selective electrode, plasma potassium using an ion-sensitive electrode with a polyvinylchloride membrane, and plasma chloride using an ion-selective electrode with a chloride-ion exchanger. The plasma magnesium was measured using a xylidyl orange colorimetric technique, plasma phosphate using a phosphomolybdate complex colorimetric technique, and plasma albumin using a bromcresol purple dye binding colorimetric technique. Samples were not stored on ice. All data were stored in computerized records. All data were retrieved from these records for analysis.

Other factors affecting acid–base balance

All patients received resuscitation as clinically indicated and guided by central venous pressure measurements, by clinical assessment, by laboratory measurements, by echocardiography and, in selected cases, by right heart catheterization. Fluid therapy included a combination of crystalloids and gelatine-based colloids. There were no specific changes in this approach during the study period or with regard to patients with ARF. Bicarbonate was not administered to correct acidemia.

Conceptual framework for the interpretation of quantitative acid–base analysis

Quantitative physicochemical analysis of the results was performed using Stewart's [8] quantitative biophysical methods as modified by Figge and colleagues [7] to take into account the effects of plasma proteins. This method first involves calculating the apparent strong ion difference (SIDa) (all concentrations in mEq/l):

$$SIDa = [Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-] - [lactate].$$

This equation, however, does not take into account the role of weak acids (CO_2, albumin and phosphate) in the balance of electrical charges in plasma water. This is expressed through the calculation of the effective strong ion difference (SIDe).

The formula as determined by Figge and colleagues [7] is (pCO$_2$ in mmHg, albumin in g/l and phosphate in mmol/l): SIDe = $1000 \times 2.46 \times 10^{-11} \times$ pCO$_2$/(10^{-pH}) + [Alb] $\times$ (0.12 $\times$ pH $-$ 0.631) + [Phos] $\times$ (0.309 $\times$ pH $-$ 0.469).

The SIDe formula quantitatively accounts for the contribution of weak acids to the electrical charge equilibrium in plasma. Once weak acids are quantitatively taken into account, the SIDa to SIDe difference should equal zero (electrical charge neutrality) unless there are unmeasured charges to explain this 'ion gap'. Such charges are described by the strong ion gap (SIG): SIG = SIDa $-$ SIDe.

A positive value for the SIG must represent unmeasured anions (sulfate, keto acids, citrate, pyruvate, acetate, gluconate, etc.) that must be included to account for the measured pH.

The traditional anion gap (AG) was also calculated (AG = [Na$^+$] + [K$^+$] $-$ [Cl$^-$] $-$ [HCO$_3^-$]) with a reference range of 12–20 mmol/l [10].

Statistical analysis

All statistical analysis was performed using the commercially available Statview statistical program (Abacus Inc, Berkeley, CA, USA). Numerical data were assessed for normal distribution using the Kolmogorov–Smirnov test. When the normal distribution criteria were violated, analysis of variance for nonparametric values (Kruskal–Wallis test) was used for comparison between groups, followed by post-hoc analysis (Mann–Whitney test). When a normal distribution was present, parametric tests were used. As most data were normally distributed, all values are presented as means with standard deviations for consistency. $P < 0.05$ was considered statistically significant.

Results

The demographic features of the three groups are presented in Table 1. There was no difference with respect to age and sex between the three groups. Patients with ARF, the matched control group and the ICU control group had a median APACHE II score of 21 (17, 25), 21 (17, 25), and 19 (15, 23), respectively. The ICU survival rates were 72% for the ARF group, 70% for the matched control group and 82% for the ICU control group. Urea and creatinine concentrations were significantly higher in the ARF group than those in the control groups. Seventeen of the ARF patients had abnormal preadmission creatinine concentrations. An elevated creatinine concentration was present in 19 patients from the ICU control group and in 16 patients from the APACHE II-matched cohort; however, none of these fulfilled the predefined criteria for the diagnosis of ARF.

ARF compared with APACHE II-matched controls

Compared with the APACHE II-matched group, patients with ARF had mild acidemia and a moderate degree of metabolic acidosis (negative base excess and decreased serum bicarbonate) (Table 2). Their mean AG inclusive of potassium was also significantly higher. However, one-half of the ARF patients had an AG within normal limits. Analysis according to the Stewart–Figge methodology revealed that this metabolic acidosis was due to hyperphosphatemia and to the accumulation of additional unmeasured anions (SIG). On average, these two factors contributed an excess of 1.3 mEq and 3.9 mEq/l of acidifying anions, respectively. These effects were only partly attenuated by the 1 mEq/l alkalinizing effect of hypoalbuminemia. The effects of unmeasured anions were particularly strong in some individuals, contributing an excess of >10 mEq/l in 29 patients. The effect of phosphate in other individuals was more marked, contributing >3 mEq/l in six patients. There were no compensatory changes in the SIDa. The lactate was elevated in both groups (Fig. 1).

ARF compared with ICU controls

The same major acid–base differences seen when comparing ARF patients with APACHE II-matched patients were also seen when comparison was made with ICU controls. The effect of hyperphosphatemia and of increased unmeasured anions (SIG) was greater, however, while the effect of albumin was smaller (Table 2). In addition, ARF patients had a smaller SIDa. This was mostly due to significantly higher lactate levels and was contributed to by lower ionized calcium levels (Fig. 1).

Discussion

Acid–base disorders, especially metabolic acidosis, are considered common in patients with ARF [11]. However, we could find no specific studies of such disorders in these patients using electronic reference libraries. The existence and nature of such acidosis is thus only indirectly understood through incidental biochemical details from investigations studying other aspects of ARF [12]. Such studies, however, lack controls and cannot adjust for the effects of the underlying illness or associated physiological disorders. This lack of information has typically led major textbooks to the assumption that the acidosis of ARF is mostly an AG acidosis essentially secondary to the accumulation of unexcreted acids [11]. This simplistic view is unlikely to be correct. This is especially true in the critically ill, where other disorders of acid–base physiology might also be present. This view might lead clinicians to wrong physiological diagnoses and, perhaps, affect their treatment choices. Accordingly, it seems desirable to achieve a better understanding of the nature of the acid–base disorders of ARF in critically ill patients. To achieve this goal, we sought to define and quantify acid–base disorders in these patients by applying the quantitative biophysical principles of acid–base analysis described by Stewart and Figge and colleagues [7,8]. To identify acid–base changes that might be unique to ARF, we studied data from 40 critically ill patients with ARF and compared our findings with those seen in two control groups: 40 APACHE II score-matched patients without ARF, and 60 unmatched critically ill patients also without ARF. Several significant findings emerged from our investigation.

Table 1

Demographic characteristics of the three groups

Characteristic	Acute renal failure group	Matched controls	Intensive care unit controls	*P* value
Age (years)	59.5 ± 16.9	63.4 ± 17.0	61.2 ± 18.8	0.04
Sex (male/female)	26/14	20/20	35/25	Not significant
APACHE II score	21.5 ± 6.3	21.4 ± 6.2	18.4 ± 6.9	< 0.05
Serum urea concentration (mmol/l)	24.6 ± 16.4	8.8 ± 6.0	8.9 ± 5.9	< 0.0001
Serum creatinine concentration (µmol/l)	314.9 ± 250.0	110.6 ± 70.2	128.9 ± 91.0	< 0.0001
Intensive care unit mortality (%)	28	30	18	Not significant
Intensive care unit diagnosis				
Severe sepsis/septic shock (nonpulmonary)	8	8	4	Not significant
Bacterial or viral pneumonia	2	11	6	0.0075
Dissecting/ruptured aorta	1	0	1	Not significant
Cardiogenic shock	3	7	3	Not significant
Open heart surgery	4	0	4	Not significant
Metabolic coma and/or hepatic failure	8	3	4	Not significant
Abdominal aortic aneurysm repair	1	0	1	Not significant
Multitrauma	0	1	5	Not significant
Perforated viscous	2	1	2	Not significant
Infarcted gut	1	0	3	Not significant
Gastrointestinal bleeding	0	4	1	Not significant
Neurological disease	1	3	11	0.03
Liver transplantation	5	0	3	Not significant
Other (chronic obstructive lung disease, drug overdose)	4	2	12	Not significant
Total patient number	40	40	60	

APACHE, Acute Physiology and Chronic Health Evaluation.

First, critically ill patients with ARF are typically more acidemic than control patients. Second, this acidemia appears secondary to metabolic acidosis with a mean base excess of almost −7 mEq/l. Although this acidosis is associated with respiratory compensation, this is insufficient to maintain the pH within normal limits. In these patients, there is also a marked failure to alter the SIDa to achieve a degree of metabolic compensation. ARF patients thus fail to compensate for their hyperphosphatemia and increased SIG. These features differ markedly from those of the control groups. Finally, most of the metabolic acidosis appears secondary to the retention of unmeasured anions. Despite this finding, one-half of the ARF patients had an AG within normal limits. These observations support, in part, the traditional view of the acidosis of ARF [11], but also highlight the previously described serious limitations of the AG approach in the detection of unmeasured anions [13]. Unfortunately, these limitations continue to be ignored in standard textbooks of internal medicine [11].

The mean concentration of unmeasured anions in ARF patients was 13.4 mEq/l, which represents an increase of 3.9–5.7 mEq/l when compared with the control groups. The nature of these unmeasured anions remains unclear both in the control groups and in the ARF group. Possible candidates include sulfate, urate, hydroxypropionate, hippurate, oxalate, and furanpropionate [14]. For example, sulfate has been reported to be elevated from a normal value of 1 mEq/l to a mean value of 3.6 mEq/l in patients with dialysis-dependent renal failure [15]. Other anions such as urate, hydroxypropionate, oxalate, hippurate, and/or furanpropionate might also contribute another 2 or 3 mEq/l. Other anions might also include glutamic and aspartic acid, and, in our patients, the acidifying effect of gelatine, a negatively charged molecule. The clinical effect of these anions in acute renal failure is unknown. In control patients, the SIG was found to be between 8 and 9 mEq/l. These findings differ from those of Balsubramanian and colleagues [16], who found a mean base excess effect of

Table 2

Acid–base variables in acute renal failure patients and two control groups

Variable	Acute renal failure group	Matched controls	Intensive care unit controls	*P* value (analysis of variance)
pH*,**	7.30±0.13	7.38±0.12	7.43±0.08	<0.0001
pCO$_2$ (mmHg)	37.9±8.5	40.5±11.3	42.3±8.5	0.073
Bicarbonate (mmol/l)*,**	18.9±5.5	23.5±6.1	27.5±5.2	<0.0001
Base excess (mmol/l)*,**	−7.5±7.2	−1.5±7.2	2.9±5.3	<0.0001
Sodium (mmol/l)*	139.6±6.2	133.5±5.4	140.8±4.5	<0.0001
Potassium (mmol/l)**	4.7±0.8	4.3±0.9	4.1±0.4	0.0003
Chloride (mmol/l)*	102.5±7.8	95.5±5.5	102.0±4.6	<0.0001
Magnesium (mmol/l)a	1.05±0.40	0.88±0.34	0.94±0.28	0.065
Calcium (mmol/l)b,**	1.10±0.12	1.12±0.09	1.17±0.09	0.0009
Phosphate (mmol/l)*,**	2.08±0.92	1.30±0.64	1.13±0.50	<0.0001
Albumin (g/l)	22.6±6.3	25.2±5.9	23.9±5.8	<0.0001
Lactate (mmol/l)**	3.72±3.45	3.50±3.77	1.92±1.52	0.004
Anion gap (mEq/l)*,**	22.9±7.6	18.8±6.5	15.4±3.7	<0.0001
Apparent strong ion difference (mEq/l)**	42.4±4.4	42.8±4.4	45.2±3.7	<0.0001
Effective strong ion difference (mEq/l)*,**	29.0±5.1	33.4±6.3	36.9±5.5	<0.0001
Strong ion gap (mEq/l)*,**	13.4±5.5	9.5±4.4	8.3±3.6	<0.0001

All data presented as mean±standard deviation.
aMeasured as total magnesium.
bMeasured as ionized calcium.
*Significant difference between the acute renal failure group and matched controls.
**Significant difference between the acute renal failure group and intensive care unit controls.

−4.9 mEq/l due to unmeasured anions in their patients. However, these findings are in keeping with similar findings of Fencl and colleagues [17] and of Cusack and colleagues [18]. The nature of such unmeasured anions in control patients is unknown but might be similar to that of ARF patients and only differ quantitatively.

The application of quantitative biophysical methods also reveals the importance of a previously neglected contributor to the acidosis of ARF: phosphate. Our finding of hyperphosphatemia in patients with ARF is not surprising, as this disorder is well known to occur in patients with renal insufficiency [19]. In our patients, hyperphosphatemia accounted for approximately 20% of the difference in acid–base status between the ARF group and controls.

These acidifying disorders were attenuated by a concomitant metabolic alkalosis, which was essentially secondary to hypoalbuminemia. This disorder was also found in the other two ICU groups, and it accounted for approximately 5 mEq/l base excess. However, the severity of hypoalbuminemia appeared greater in ARF patients. This alkalinizing effect of hypoalbuminemia was responsible for changing the AG downward and for masking the presence of acidifying anions.

Patients with ARF also had a decreased SIDa compared with ICU controls. This acidifying change was mostly secondary to the accumulation of lactate (Table 2). Unlike the changes already described, however, such hyperlactatemia was not unique to ARF patients and was also seen to the same extent in APACHE II-matched controls. This observation supports the usefulness of different control groups in seeking to isolate the specific acid–base consequences of ARF in the setting of critical illness.

The present study has several limitations. It is observational and retrospective in design, and is therefore open to selection bias. However, our criteria for patient selection were objective and predefined. Furthermore, the matched control group and the ICU control group were made up of severely ill patients with a wide range of acute conditions. These control patients were from the same ICU, had variables measured in the same laboratories during the same time period, and had an ICU mortality of 30% and 18%, respectively. This mortality was similar to the ICU mortality of our ARF patients (28%). We studied a limited sample of patients. However, differences emerged and were strong. Furthermore, the approach developed by Stewart and Figge has increasingly been applied to elucidate areas of uncertainty in clinical acid–base

Figure 1
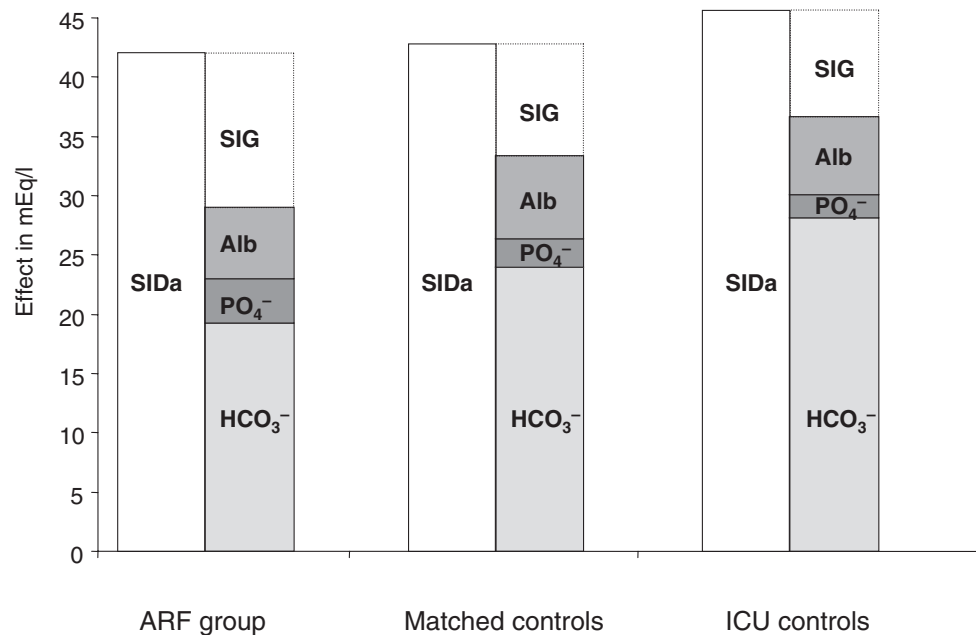
Anionic and cationic charges in the three study groups. The mean apparent strong ion difference (SIDa) and the mean effective strong ion difference (SIDe − or sum of ALb, PO_4^- and HCO_3^-) in the three groups: patients with acute renal failure (ARF), a control group matched for Acute Physiology and Chronic Health Evaluation score without ARF, and an intensive care unit (ICU) control group without ARF. Alb, albumin effect; PO_4^-, phosphate effect; HCO_3^-, CO_2 effect. The ARF group was associated with a high strong ion gap (SIG) and a high phosphate concentration compared with the other groups.

physiology [3–6] and, when so used, it has provided previously unavailable insights [17,18,20,21]. This also appears true of our investigation.

The choice of definition of ARF is open to disagreement as no consensus definition yet exists for this syndrome. We chose a definition that had previously been applied to critically ill patients to guide a randomized controlled trial [22] as one that had proved relevant and useful. There were differences in the diagnostic features of the three groups. We found it impossible, once one has to exclude ARF and to create an APACHE II-matched cohort, to achieve a balanced distribution of diagnoses. Accordingly, our findings may not apply to other populations of ICU patients. By creating two control groups we sought to overcome such limitations as much as possible. Finally, other workers have highlighted the limitations of the AG and have offered ways of correcting the AG for changes in albumin and phosphate [23]. The present study lends further support to the utility and necessity of such corrections, especially in the critically ill. It is disappointing that such corrections are not part of current medical teaching [11].

In conclusion, the typical acid–base picture of ARF of critical illness is one of mild acidemia due to moderate metabolic acidosis. Such acidosis is the result of the net balance of acidifying forces due to the accumulation of unmeasured anions, phosphate, and the attenuating effect of metabolic alkalosis

Key messages

• The acidosis of ARF is complex

• Unexcreted unmeasured anions are the major cause, followed by hyperphosphatemia

• These acidifying changes are attenuated by the alkalinizing effect of hypoalbuminemia

secondary to hypoalbuminemia. In ARF patients, the compensatory responses are inadequate both at a respiratory level and at a metabolic level. Understanding these abnormalities might assist physicians in making the correct physiological diagnosis and, perhaps, in avoiding unnecessary investigations or incorrectly targeted therapeutic interventions.

Competing interests

None declared.

Acknowledgement

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