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Acid-base variables in patients with acute kidney injury requiring peritoneal dialysis in the pediatric cardiac care unit

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Abstract
Purpose. We aimed to clarify the acid-base abnormalities of patients with acute kidney injury (AKI) requiring peritoneal dialysis (PD) in pediatric cardiac care units.
Methods. A retrospective observational study was conducted in a pediatric cardiac care unit in a tertiary care university hospital. The subjects were 40 patients with AKI requiring PD between 2003 and 2005, and controls matched by type of surgery and body weight. Acid-base variables, including blood gas data and electrolytes, were assessed. The Stewart-Figge variables, including strong ion difference apparent (SIDa), strong ion difference effective (SIDe), and strong ion gap (SIG), were calculated.
Results. Blood gas analyses showed that the PD group was more acidemic, with a lower mean bicarbonate and a lower mean base excess, typical features of metabolic acidosis. The strong ion analyses revealed that the PD group had lower mean sodium and albumin concentrations. Based on the Stewart-Figge methodology, SIDa was smaller in the PD group than in the control group, but SIG was similar in the two groups. Receiver-operating characteristic curve analyses showed that serum albumin was the only prognostic factor associated with PCCU mortality, even after adjustment for PD treatment.
Conclusion. Patients with AKI requiring PD in a pediatric cardiac care unit had significant metabolic acidosis compared to controls matched by the type of surgery and body weight. Hyponatremia and hypoalbuminemia were characteristics of these patients. The calculated SIDa was smaller in the PD than in the control group. Only the serum albumin had a significant prognostic value.

Key words Pediatric · Acute kidney injury · Peritoneal dialysis · Acid-base balance · Cardiac surgery

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Introduction

Renal dysfunction after pediatric cardiac surgery is a common complication that is associated with a high mortality [1,2]. Some patients require artificial renal support, and peritoneal dialysis (PD) is frequently chosen, especially in small infants [3–5]. It is well known that patients with acute kidney injury (AKI) develop a metabolic acidosis, and that the degree of this acidosis can predict the outcome [6,7]. However, there is little information about the cause of this acidosis, for which detailed physicochemical analysis is required.

Recently, the Stewart-Figge methodology [8–10] has been established and proven to be useful for understanding acid-base abnormalities in various fields [11–16]. Briefly, Stewart suggested that hydrogen ion concentration could be determined by three independent variables, i.e., strong ion difference (SID), total weak acid, and Pa_{CO_2} [8]. SID means the difference between strong cations (sodium, potassium, calcium, and magnesium) and strong anion (chloride). Total weak acid means the sum of weak acids such as bicarbonate, albumin, and phosphate. Figge and colleagues termed original SID "strong ion difference apparent (SIDa) and total weak acid calculated by the sum of effects of bicarbonate, albumin, and phosphate" as "strong ion difference effective (SIDe)" [9,10]. Once weak acids are quantitatively taken into account, the SIDa – SIDe should equal 0 (electrical charge neutrality) unless there are unmeasured charges to explain this "ion gap." Such charges are described by the "strong ion gap (SIG)" [16]. A positive value for SIG must represent unmeasured anions (sulfate, keto acids, citrate, pyruvate, acetate, gluconate, etc.) that must be included to account for the measured pH.

This approach emphasizes the importance of strong ions (sodium and chloride), weak acids (albumin and phosphate), and also unmeasured anions in metabolic acid-base abnormalities. Using this methodology, it was

shown that, in adult patients with acute renal failure, increased unmeasured anions and hyperphosphatemia were the two main components of the acidosis [12] and continuous renal replacement therapy, such as hemofiltration, improved the patients' acidosis and decreased unmeasured anion and phosphate levels [11].

In the present study, 40 patients with AKI requiring PD in a pediatric cardiac care unit were studied to clarify the acid-base abnormalities, using the Stewart-Figge methodology. Because acid-base abnormalities can be affected by the severity of the operation and the patient's age, appropriately matched controls were chosen.

Patients and methods

This retrospective study was conducted at the Okayama University Medical School. The data collected in this type of study were considered to have been audited by the Institutional Ethics Committee, which, therefore, obviated the need for informed consent. Thus, instead of obtaining informed consent, we prospectively published the study protocol on a website and accepted any comments from the study participants' parents or guardians.

Patients

We retrospectively reviewed the records of our pediatric cardiac care unit (PCCU) between 2003 and 2005. Forty patients requiring PD were identified. No specific criteria were used to define AKI. The indications for starting and stopping PD in our institution are shown in Table 1.

After collecting the patients' demographic data, we chose another 40 patients as matching controls. The type of surgery and body weight were used as matching variables. The types of surgery were assessed using the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) system [17–19]. This system consists of six categories ranked 1 to 6 for complexity; a higher category means more complex surgery. For example, atrial septal defect surgery is category 1, total repair of tetralogy of Fallot is category 2, Ross procedure is category 3, double switch is category 4, repair of truncus arteriosus and interrupted arch is category 5, and Norwood operation is category 6. In total, 80 postpediatric cardiac surgery patients (40 PD patients and 40 control patients) were studied.

In the PD group, acid-base variables before starting PD were collected, including blood gas data and electrolytes (sodium, potassium, chloride, ionized calcium, magnesium, lactate, albumin, phosphate). In the matched control group, the PCCU admission values of these variables were used.

Measurements

Blood gas analyses were routinely conducted by intensive care unit (ICU) staff using an ABL 630 blood gas analyzer (Radiometer Medical, Copenhagen, Denmark). The pH, Pa_{CO_2}, Pa_{O_2}, HCO_3^-, base excess (BE), lactate, and ionized calcium values were obtained based on these measurements. Simultaneously, another blood sample was sent to the central laboratory, and measurements were conducted by central laboratory staff using an automated biochemical analyzer (Clinical Analyzer 7350; Hitachi High-Technologies Tokyo, Japan). The results (sodium, potassium, chloride, magnesium, albumin, phosphate, blood urea nitrogen, creatinine) were electronically stored and then collected by the investigators. The quality of these values was confirmed by one of the investigators (H.M.).

Stewart-Figge methodology

Using the Stewart-Figge method [8–10], the strong ion difference apparent (SIDa), the strong ion difference effective (SIDe), and the strong ion gap (SIG) were calculated as described below.

$$SIDa = (Na^+) + (K^+) + (Ca^{2+}) + (Mg^{2+}) - (Cl^-) + (lactate^-)$$

$$SIDe = 1000 \times 2.46 \times 10^{-11} \times P_{CO_2}/(10^{-pH}) + 10 \times (Alb) \times (0.123 \times pH - 0.631) + (Phosphate) \times (0.309 \times pH - 0.469)$$

(P_{CO_2} = mmHg, (Alb) = 1g·dl^{-1}, (phosphate) = mmol·l^{-1})

$$SIG = SIDa - SIDe$$

Table 1. Indications for starting and stopping peritoneal dialysis (PD)

Indications for PD	Indications for stopping PD
1. Oliguria (<0.5 ml·kg^{-1}·h^{-1}) for more than 2 h OR 2. Hyperkalemia (more than 5.5 mmol·l^{-1}) despite aggressive diuretic therapy, optimization of inotropic support, and adjustment of fluid status	1. Return of sufficient urine output AND 2. Normalization of serum electrolytes AND 3. Normalization of serum acid-base status

Statistical analysis

Data are expressed as means with 95% confidence intervals (95% CIs). Comparisons between the groups were done using Student's *t*-test or Fisher's exact test, as appropriate. To assess prognostic significance, a logistic regression model for each of the acid-base variables was used. Then, receiver operating characteristic (ROC) curves were constructed, and the areas under the ROC curves were determined. To assess independent prognostic significances of acid-base variables, other logistic models were constructed putting PD treatment as an independent covariate into each model, and adjusted odds ratios were reported. $P < 0.05$ was considered statistically significant.

Results

Forty patients with peritoneal dialysis and 40 matching controls were studied. Thirty-two patients (80%) in the PD group were post-surgical and 8 were medical (these patients had deteriorated in the post-surgical ward). The patients' demographics were almost identical in the two groups (Table 2). The mean age of the PD group was 12.2 months (95% CI, 5.5 to 18.9 months), and the mean body weight was 5.6 kg (95% CI, 4.0 to 7.1 kg). Many patients had complicated surgery; 20 (50%) patients were in categories 4, 5, or 6 (Table 2).

In the PD group, mean blood urea nitrogen (BUN) and creatinine (Cr) levels were higher than in the control group. The PD group had a more positive fluid balance than the control group; however, this difference did not reach statistical significance. The mean urine volume was smaller in the PD group than in the control group (Table 3). These results confirmed that the PD patients had the typical features of AKI (higher BUN and Cr, more positive fluid balance, less urine output).

Compared to the control group, the PD group had a higher degree of acidemia (pH 7.348; 95% CI, 7.319 to 7.378) than the control group (pH 7.423; 95% CI, 7.406 to 7.441; $P < 0.0001$); bicarbonate levels were lower in the PD group (22.3 $mEq \cdot l^{-1}$; 95% CI, 21.2 to 23.4) than in the control group (26.4 $mEq \cdot l^{-1}$; 95% CI, 25.2 to 27.7; $P < 0.0001$), and the base excess (BE) was less in the PD group (–2.1; 95% CI, –3.3 to –0.9 $mEq \cdot l^{-1}$) than in the control group (2.5; 95% CI, 1.1 to 3.9 $mEq \cdot l^{-1}$; $P < 0.0001$; Table 4). Thus, the PD group showed the typical features of metabolic acidosis.

The mean serum sodium concentration was significantly lower in the PD group than in the control group (136 $mmol \cdot l^{-1}$; 95% CI, 135 to 138 $mmol \cdot l^{-1}$ in the PD group vs 141 $mmol \cdot l^{-1}$; 95% CI, 140 to 142 $mmol \cdot l^{-1}$ in the control; mean difference, –4.4; 95% CI, –6.7 to –2.2 $mmol \cdot l^{-1}$; P = 0.0002), and the mean albumin concentration was significantly lower in the PD group (3.7 $g \cdot dl^{-1}$; 95% CI, 3.5 to 4.0 $g \cdot dl^{-1}$) vs 4.1 $g \cdot dl^{-1}$ (95% CI, 3.9 to 4.4 $g \cdot dl^{-1}$); mean difference –0.4; 95% CI, –0.7 to –0.1 $g \cdot dl^{-1}$; P = 0.021). Also, the serum lactate concentration was higher in the PD group than in the control group (4.95 $mmol \cdot l^{-1}$; 95% CI, 3.04 to 6.86 $mmol \cdot l^{-1}$ vs 2.82 $mmol \cdot l^{-1}$; 95% CI, 1.80 to 3.83 $mmol \cdot l^{-1}$; mean difference 2.13; 95% CI, –0.07 to 4.33 $mmol \cdot l^{-1}$; P =

Table 2. Patients' characteristics

	PD	Control	*P* value
Sex (male)	16 (40%)	17 (42.5%)	>0.99
Age (months)	12.2 (5.5 to 18.9)	12.4 (4.6 to 20.2)	0.96
Body weight (kg)	5.6 (4.0 to 7.1)	5.8 (4.4 to 7.1)	0.88
Operation categories			
1	0	0	0.52
2	4	4	
3	8	4	
4	7	12	
5	2	2	
6	11	10	

PD, peritoneal dialysis

Table 3. Renal function by group

	PD	Control	*P* value
Blood urea nitrogen ($mg \cdot dL^{-1}$)	29.1 (21.1 to 37.0)	16.7 (13.7 to 19.7)	0.0046
Creatinine ($mg \cdot dL^{-1}$)	0.80 (0.57 to 1.03)	0.45 (0.38 to 0.52)	0.0039
Fluid balance ($ml \cdot kg^{-1} \cdot day^{-1}$)	8.8 (–8.1 to 25.6)	–0.1 (–9.1 to 8.9)	0.36
Urine ($ml \cdot kg^{-1} \cdot day^{-1}$)	25 (16 to 35)	66 (58 to 75)	<0.0001

PD, peritoneal dialysis

Table 4. Acid-base status by group

	PD	Control	*P* value
pH	7.348 (7.319 to 7.378)	7.423 (7.406 to 7.441)	<0.0001
Pa_{CO_2} (mmHg)	42.1 (39.4 to 44.8)	41.3 (39.3 to 43.4)	0.66
Pa_{O_2} (mmHg)	87 (60 to 114)	102 (77 to 128)	0.41
Bicarbonate ($mEq \cdot l^{-1}$)	22.3 (21.2 to 23.4)	26.4 (25.2 to 27.7)	<0.0001
Base excess ($mEq \cdot l^{-1}$)	–2.1 (–3.3 to –0.9)	2.5 (1.1 to 3.9)	<0.0001
Sodium ($mmol \cdot l^{-1}$)	136 (135 to 138)	141 (140 to 142)	0.0002
Potassium ($mmol \cdot l^{-1}$)	4.30 (3.92 to 4.67)	3.98 (3.80 to 4.12)	0.14
Chloride ($mmol \cdot l^{-1}$)	102 (100 to 104)	103 (101 to 105)	0.52
Calcium ($mmol \cdot l^{-1}$)	1.48 (1.40 to 1.56)	1.38 (1.32 to 1.45)	0.07
Magnesium ($mmol \cdot l^{-1}$)	0.49 (0.44 to 0.54)	0.51 (0.46 to 0.56)	0.55
Lactate ($mmol \cdot l^{-1}$)	4.95 (3.04 to 6.86)	2.82 (1.80 to 3.83)	0.057
Phosphate ($mmol \cdot l^{-1}$)	1.77 (1.47 to 2.08)	1.72 (1.54 to 1.91)	0.78
Albumin ($g \cdot dl^{-1}$)	3.7 (3.5 to 4.0)	4.1 (3.9 to 4.4)	0.021
SIDa ($mEq \cdot l^{-1}$)	39.1 (36.7 to 41.4)	42.7 (41.0 to 44.3)	0.011
SIDe ($mEq \cdot l^{-1}$)	37.3 (36.0 to 38.5)	41.8 (40.2 to 43.5)	<0.0001
SIG ($mEq \cdot l^{-1}$)	1.3 (–0.8 to 3.5)	1.0 (–0.5 to 2.4)	0.76

PD, peritoneal dialysis; SIDa, strong ion difference apparent; SIDe, strong ion difference effective; SIG, strong ion gap

Table 5. Prognostic significance of the acid-base variables

	Odds ratio	95% CI	AUC	95% CI	*P* value
pH	0.000072	$8.6*10^{-8}$ to 0.06	0.67	0.52 to 0.81	0.005
Pa_{CO_2}	1.01	0.95 to 1.08	0.52	0.36 to 0.68	0.69
Pa_{O_2}	1.00	1.00 to 1.01	0.54	0.38 to 0.71	0.17
Bicarbonate	0.80	0.68 to 0.93	0.71	0.59 to 0.83	0.004
Base excess	0.81	0.71 to 0.94	0.71	0.59 to 0.83	0.004
Sodium	0.89	0.80 to 0.98	0.68	0.55 to 0.81	0.02
Potassium	1.61	0.89 to 2.90	0.58	0.41 to 0.74	0.12
Chloride	0.94	0.86 to 1.03	0.59	0.45 to 0.72	0.21
Calcium	7.00	0.79 to 61.8	0.59	0.44 to 0.74	0.08
Magnesium	0.07	0.0006 to 9.61	0.59	0.40 to 0.78	0.29
Phosphate	1.30	0.60 to 2.81	0.51	0.33 to 0.69	0.5
Lactate	1.20	1.04 to 1.38	0.73	0.60 to 0.87	0.012
Albumin	0.31	0.13 to 0.70	0.69	0.56 to 0.82	0.005
SIDa	1.02	0.87 to 1.19	0.65	0.49 to 0.81	0.18
SIDe	0.83	0.71 to 0.96	0.72	0.59 to 0.84	0.01
SIG	1.08	0.93 to 1.25	0.57	0.43 to 0.70	0.30
	Adjusted odds ratio	95% CI			*P* value
pH	0.02	0.00 to 20.91			0.27
Bicarbonate	0.91	0.76 to 1.08			0.27
Base excess	0.91	0.78 to 1.07			0.27
Sodium	0.97	0.87 to 1.08			0.55
Albumin	0.33	0.12 to 0.92			0.035
Lactate	1.20	1.00 to 1.43			0.053
SIDe	0.92	0.77 to 1.11			0.39

95% CI, 95% confidence interval; AUC, area under the receiver-operating characteristic curve; SIDa, strong ion difference apparent; SIDe, strong ion difference effective; SIG, strong ion gap

0.057), though the difference was not statistically significant (Table 4).

Based on the electrolyte levels, the calculated SIDa was smaller in the PD group than in the control group (Table 4). However, the SIG was not different between the two groups (Table 4).

Twenty-two patients (55%) in the PD group and 2 patients (5%) in the control group died in the PCCU ($P < 0.0001$). The logistic regression models showed that pH, bicarbonate, and base excess were significantly associated with PCCU mortality (Table 5). Interestingly, serum sodium, albumin, and lactate levels were

also significantly related to PCCU mortality. SIDe was associated with PCCU mortality, but SIDa and SIG were not. Because PD patients had a ten times higher PCCU mortality than controls, the logistic model was adjusted for PD treatment. After adjustment for PD treatment, only the serum albumin concentration was independently associated with PCCU mortality.

Discussion

The acid-base variables of 40 patients requiring PD in the pediatric cardiac care unit (PCCU) were assessed. To identify the unique characteristics of these patients, a control group of 40 patients, matched by the type of surgery and body weight, was also studied. PD patients had a more severe metabolic acidosis than controls. The PD patients' acidosis was mainly due to a lower sodium concentration that was counteracted by the alkalinizing effects of a lower albumin concentration than in controls. The calculated SIDa was lower in the PD group than in the control group, suggesting that these patients had a strong ion acidosis that was induced by lower sodium concentration. Even after adjustment for PD treatment, the serum albumin concentration had a prognostic significance in these patients.

In the present case-vs-matched-control study, the most prominent difference between the two groups was the serum sodium concentration (mean difference 4.4 $mEq \cdot l^{-1}$). Patients with congestive heart failure are characterized by the presence of hyponatremia, which has prognostic significance [20–23]. Although signs of heart failure were not assessed, it is likely that PD patients would have more severe heart failure than non-PD patients. Therefore, the difference in the sodium concentrations between the groups may have been related to the difference in the severity of heart failure. The significant difference in the serum sodium concentration resulted in a significant difference in the calculated SIDa between the two groups. The PD patients had a so-called strong ion acidosis. In previous reports, strong ion acidosis was mainly due to hyperchloremia and hyperlactatemia [24–28]. To the best of our knowledge, this is the first report of strong ion acidosis induced by hyponatremia. In AKI patients with severe heart failure, the presence of hyponatremic acidosis should be properly recognized.

It was also found that the serum sodium concentration was related to PCCU mortality. However, after adjustment for PD treatment, this relationship was no longer significant. These results indicate that, even though the difference in serum sodium concentrations was large, this had only a minimal effect on prognosis.

The patients in the PD group had a lower serum albumin concentration than those in the control group, and the lower serum albumin concentration had prognostic significance. A lower serum albumin concentration may reflect the severity of heart failure by reflecting the degree of body water retention [29,30]. Although the difference between the groups was significant, there was only a 1.4 $mEq \cdot l^{-1}$ (95% CI, 0.5 to 2.4 $mEq \cdot l^{-1}$) difference (calculated by Figge's formula) between the two groups. Therefore, the effect of the difference in the albumin concentration on the acid-base status was not large. On the other hand, the prognostic value of the albumin concentration was significant even after adjustment for PD treatment. The patients had a relatively high albumin concentration, probably due to the aggressive use of albumin solution for fluid resuscitation. Even at this high serum albumin concentration, a higher albumin concentration was associated with a better prognosis (adjusted odds ratio, 0.33; 95% CI, 0.12 to 0.92; 67% mortality reduction for a 1 $g \cdot dl^{-1}$ increase in the serum albumin concentration). However, this finding should be interpreted with caution. Because our study was retrospective in nature, we could not reach a conclusion regarding the effectiveness of albumin administration in pediatric cardiac patients. Our study indicates the albumin concentration in pediatric cardiac patients could be important. The effectiveness of albumin administration should be pursued in a future randomized study.

In a previous study using the Stewart-Figge methodology in adult AKI patients [9,10,12], an increased SIG and a higher phosphate concentration were the major factors related to the patients' metabolic acidosis. However, no differences in these variables were observed in the present study. Instead, lower sodium and albumin concentrations were observed in the PD group. There are several potential explanations for the differences between our study and the above studies. First, pediatric AKI may be different from adult AKI. Although our pediatric patients had typical features of AKI and metabolic acidosis, renal electrolyte handling may differ between pediatric and adult patients. Second, in the present study, only patients in a cardiac care unit were included. These patients' AKI was primarily due to heart failure. Thus, our cohort had a highly specific AKI etiology. Differences in the etiology may have different effects on the acid-base status, even among patients with the same degree of AKI.

Our results have some important clinical implications. Appropriate diagnosis of metabolic acidosis in cardiac patients is clearly important to administer appropriate treatments and to avoid unnecessary treatments. If hyponatremia is a major factor of metabolic acidosis in these patients (which we found in this study), the administration of sodium bicarbonate to these patients can be a reasonable choice, because sodium bicarbonate would increase the serum sodium concen-

tration without the increase of strong anions [31]. Contrarily, if staff are unaware of hyponatremic acidosis in these patients, they will give more fluids, more inotropes, and sometimes start renal replacement therapy to correct the metabolic acidosis. Better understanding of acid-base abnormalities is clearly needed to give adequate treatments and to avoid potentially dangerous interventions.

Our study had some limitations. First, it was retrospective in nature, and was thus open to selection bias. However, this bias was reduced by the use of matched controls. In fact, during matching, the patients' outcomes and acid-base status were masked. Second, our study was conducted in a single tertiary center and included many cases with complex congenital cardiac diseases. Thus, the generalizability of our findings could be minimal. However, no previous studies of the acid-base status of pediatric PD patients in a PCCU have been published. The lower sodium and albumin concentrations that were found in the heart failure patients were quite reasonable. Our findings offer a new insight into the acid-base physiology of pediatric AKI patients.

Conclusions

Patients with AKI who required PD in a PCCU had a significant metabolic acidosis compared to controls that were matched by type of surgery and body weight. Hyponatremia and hypoalbuminemia were characteristics of pediatric patients with AKI requiring PD after cardiac surgery. The PD patients' acidosis was a strong ion acidosis that was mainly due to a lower sodium concentration. Of all the acid-base variables that were studied, only the serum albumin concentration had a significant prognostic value. In AKI patients with severe heart failure, hyponatremic acidosis should be properly recognized.

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