

# Defining acidosis in postoperative cardiac patients using Stewart's method of strong ion difference\*

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**Objective:** To define the true incidence and nature of acidosis in pediatric patients postcardiac surgery, using Stewart's direct method of measuring strong ion difference. We also wished to compare the ability of standard indirect methods (base deficit, lactate, anion gap, and corrected anion gap) to accurately predict tissue acidosis.

**Design:** A single-center prospective observational study.

**Setting:** A pediatric intensive care unit in a tertiary referral center.

**Patients:** Pediatric patients who had undergone cardiac surgery were studied in the immediate postoperative period. Patients who had undergone both open and closed cardiac surgery were included.

**Interventions:** Routine arterial blood gas analysis and laboratory electrolyte measurements were made in patients immediately on admission to the pediatric intensive care unit (PICU) after cardiac surgery and each morning until discharge from the PICU.

**Measurements and Main Results:** Figge's equations were used to calculate strong ion difference and total tissue acids (unmeasured acids and lactate). These direct methods then were compared to indirect measurements: base deficit, lactate anion gap,

and anion gap corrected for albumin. We collected 150 samples from 44 patients. Tissue acidosis occurred overall in 60 of 150 samples. This was due to raised unmeasured acids alone in 44 of 60 (73.3%), raised lactate alone in six of 60 (10%), and a combination of the two in ten of 60 (16.6%). Hyperchloremia occurred in 19 of 150 samples overall and 12 of 25 (48%) samples immediately after cardiopulmonary bypass. Measured base deficit showed a poor correlation with true tissue acidosis ( $r = -.48$ ,  $p < .001$ ) and the worst discriminatory ability (area under the curve, 0.72; 0.62–0.82). Anion gap corrected for albumin had the best correlation ( $r = .95$ ,  $p < .001$ ) and highest area under the curve (0.90; 0.85–0.95).

**Conclusions:** Metabolic acidosis occurs frequently postcardiac surgery and is largely due to raised unmeasured acids and less commonly raised lactate. Hyperchloremia is common, particularly after cardiopulmonary bypass. Base deficit correlates poorly with true tissue acidosis, and corrected anion gap offers the most accurate bedside alternative to Stewart's method of tissue acid calculation. (*Pediatr Crit Care Med* 2004; 5:240–245)

**KEY WORDS:** pediatric; intensive care; cardiac surgery; metabolic acidosis; strong ion difference

**M**etabolic acidosis is a frequent event following cardiac surgery, especially that involving cardiopulmonary bypass (CPB). Monitoring acid-base disturbances, and in particular defining the etiology of acidosis, are important parts of assessing a patient's cardiac output in the postoperative period (1). Traditional methods used to interpret acid-base data, such as observation of the base deficit (BD) or calculation of the anion gap (AG), give little insight

into the precise nature of the problem. The BD is a calculated figure, derived from  $Paco_2$  and arterial pH, but reliance on its use alone to quantify acidosis has a number of pitfalls. First, it cannot define whether an acidosis is due to increased tissue acids (lactate and keto acids), hyperchloremia, or a combination of both. Second, its calculation assumes normal water, plasma protein, and electrolyte content (2). The observed AG also ignores the role of the main nonbicarbonate buffers in blood plasma such as plasma proteins and inorganic phosphate. The common finding of hypoalbuminemia among critically ill patients, resulting in an alkalinizing effect on plasma pH, demands that AG must be adjusted for abnormal albumin concentrations to improve its usefulness (3).

In contrast to the Henderson-Hasselbach approach to interpreting acid-base data, the mathematical model based on physiochemical principles described by Stewart, and modified by Figge, proposes that three independent variables deter-

mine pH in plasma by primarily changing the degree of water dissociation into hydrogen ions: the  $Paco_2$ , the strong ion difference (SID), and the total weak acid concentration (4). This method allows the clinician to quantify individual components of acid-base abnormalities and provides insight into their pathogenesis. Although Stewart's strong ion theory has been used previously to better understand metabolic derangements in adult intensive care and pediatric hyperchloremic acidosis (4,5), studies have not been published evaluating its use after pediatric cardiac surgery.

Therefore, using Figge's equations to directly measure acidosis, the aim of our study was, first, to define the true incidence and nature of acidosis in pediatric patients after cardiac surgery, and second, to compare the ability of indirect measures (BD, anion gap, corrected anion gap, and lactate) to identify the presence of tissue acids (TA) in this population.

**\*See also p. 296.**

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## METHODS

We performed a prospective observational study in a single pediatric intensive care unit (PICU) in a university teaching hospital. Internal review board approval is not required for case reports at our institution. Routine arterial blood gas (ABG) analysis and laboratory electrolyte measurements were made in 44 consecutive patients after cardiac surgery. Patients who had undergone both "closed" surgery and "open" surgery on cardiopulmonary bypass were included. The first set of blood samples were taken immediately on admission to the PICU from cardiac theater. The subsequent samples were collected at 7:00 am each morning, until either PICU discharge or removal of the indwelling arterial catheter. PaO<sub>2</sub>, pH, HCO<sub>3</sub><sup>-</sup>, and lactate were measured with the ABL300 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark). Electrolytes (serum sodium, potassium, magnesium, phosphate, calcium, and chloride [Cl<sup>-</sup>]) and albumin were measured using an ion-selective electrode on an Olympus HBU 600 auto-analyzer. The ABG and laboratory measured values were entered into Excel (Microsoft) on the PICU. Figge's equations were used to calculate SID, TA, and unmeasured acids (UMA; Equations 1–3). The AG and the AG corrected for albumin (AGcorr) also were calculated (Equations 4 and 5). The patient's clinicians were blind to the calculated SID, TA, and UMA values.

$$\text{SID} = [\text{HCO}_3^-] + [\text{Alb}^-]^* + [\text{Pi}^-]^* \quad [1]$$

$$\text{TA} = ([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - \text{SID}) \quad [2]$$

$$\text{TA} = \text{UMA} + \text{lactate} \quad [3]$$

$$\text{AG} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] \quad [4]$$

$$\text{AGcorr} = \text{AG} + 0.25 \times [44 - \text{measured albumin}] \quad [5]$$

Significant tissue acidosis was defined as a TA >5 mEq/L. An increased UMA was defined as >3 mEq/L, abnormal lactate as >2 mmol/L, and an increased BD as ≤2 mEq/L. Hyperchloremia was defined as >110 mmol/L. A raised AG was defined as >16 mEq/L. The normal range for SID was defined as 38–42 mEq/L. These cut-off points were extrapolated from adult studies, as SID values have not, to date, been measured in healthy children. Cl and XA were corrected for dilution/concentration as per Figge's method using Equation 6:

$$[\text{Cl}^-] \text{ corrected} = [\text{Cl}^-] \text{ observed} \times ([\text{Na}^+] \text{ normal} / [\text{Na}^+] \text{ observed}) \quad [6]$$

where \* $[\text{Alb}^-]$  = negative electrical charge contributed by serum albumin (g/L) =  $[\text{Alb}] \times (0.123 \times \text{pH} - 0.631)$  and  $[\text{Pi}^-]$  = negative charge contributed by serum phosphate (mmol/L) =  $[\text{PO}_4] \times (0.309 \times \text{pH} \times -0.469)$ .

## Statistics

Data were assumed to be nonparametric. The strength of the relationship between TA and BD, AG, AGcorr, and lactate was assessed using Spearman's correlation coefficient. The ability of these variables to discriminate a true tissue acidosis (TA >5mEq/L) was quantified by the area under the receiver operator curve. Their predictive values were compared by calculating sensitivity, specificity, and positive and negative predictive values.

## RESULTS

One hundred fifty samples were collected from 44 patients during their intensive care stay after cardiac surgery. Their median age was 3.5 months (interquartile range, 1–36). The surgical procedures performed included Blalock-Taussig shunts, arterial switch procedures, and repair of truncus arteriosus, ventriculoseptal, and atrioseptal defects. Cardiopulmonary bypass was required in 25 of 44 patients.

The nature of metabolic derangement in our patient population postcardiac surgery was as follows. Tissue acidosis, in all its forms, occurred in 60 of 150 patient samples. This was due to raised UMA alone in 44 of 60 (73.3%), pure lactic acidosis in six of 60 (10%), and a combination of raised UMA and lactic acid (LA) in ten of 60 (16.6%). In 37 of 150 samples, the tissue acidosis reached a TA >5 mEq/L. Hyperchloremia occurred in 19 of 150 samples and in 15 of 19 samples; this was an isolated hyperchloremia with

no increased UMA or LA. In seven of these 15 samples, there was an associated increase in BD, despite the absence of measurable tissue acidosis.

We then compared our direct measurement of TA to indirect methods of measuring acidosis (Table 1). As can be seen, BD gave an apparent acidosis in 44 of 150 of samples, but in 21 of 44 (47%) this was not a true tissue acidosis as defined previously. Conversely, in the 106 samples with a normal BD, 14 (13%) had a true tissue acidosis when measured with Stewart's method. Regression analysis confirmed that BD and TA were poorly correlated ( $r_s = -.48, p < .001$ ) and showed that the closest correlation was seen between AGcorr and TA ( $r_s = .95, p < .001$ ; Table 2, Fig. 1).

The ability of each of the indirect methods to predict acidosis was compared by calculating the receiver operator characteristic curve analysis for each variable. Overall, AGcorr had the best discriminatory ability, with an area under the curve of 0.90 (confidence interval, 0.85–0.95; Table 3).

Last, the first postoperative samples of the 25 patients who had undergone CPB were analyzed. In this group, tissue acidosis occurred in 15 of 25 patients. This was due to raised UMA alone in 12 of 15 patients (80%), LA alone in one of 15 patients (6.6%), and a combination of raised UMA and LA in two of 15 patients (13.3%). In nine of 25 samples, TA was >5 mEq/L. Hyperchloremia occurred in 12 of 25 samples (48%), and this was an isolated hyperchloremia with no associated tissue acidosis in eight of 12 samples. Again in this subgroup, AGcorr showed the best association with true tissue acidosis ( $r_s = .926, p < .01$ ), and BD correlated poorly ( $r_s = .24, p = .3$ ). In 14 patients who had a normal BD, five had a

Table 1. Results of validation study comparing indirect measures of acidosis with direct measure of excess acids (tissue acids, or TA)

	Indirect Measure Acidosis					
	Base Deficit		Anion Gap		Corrected Anion Gap	
	Acidosis	No Acidosis	Acidosis	No Acidosis	Acidosis	No Acidosis
All samples	44	106	24	126	57	93
Direct measure acidosis						
Raised TA	37	23	14	13	37	0
Normal TA	113	21	92	113	20	93

Raised TA defined as >5 mEq/L.

true tissue acidosis as measured by Stewart's method. Conversely, in the 11 patients with an increased BD, indicating

Table 2. Results from Spearman's correlation analysis to describe the relationship between measured tissue acids (TA) and each of the indirect methods of acidosis measurement: base deficit, lactate, anion gap, and anion gap corrected for albumin

Variable	$r_s$ Value	$p$ Value
TA vs. base deficit	-.48	<.001
TA vs. lactate	.48	<.001
TA vs. anion gap	.88	<.001
TA vs. anion gap corrected	.95	<.001

acidosis, four did not have a tissue acidosis. These four patients were all hyperchloremic (Cl, 111, 111, 113, and 114 mmol/L). Overall, the mean serum Cl in the first samples post-CPB was  $109 \pm 3.2$  mmol/L, and this was significantly higher than the mean Cl seen in the total data set (mean Cl,  $105.8 \pm 4$  mmol/L).

## DISCUSSION

We have shown that it is feasible to directly calculate acidosis in a clinical setting using Figge's modification of Stewart's principles. This has allowed us to examine the incidence and nature of

true tissue acidosis in postoperative congenital heart surgery patients. In clinical practice, the presence of an acidosis is commonly used in such patients as an early indicator of low cardiac output and oxygen debt. A number of studies have shown that mean serum lactate concentrations are significantly higher in patients who die (6–8), whereas Charpie et al. (9) reported that changes in serum lactate measurements over time may be more helpful in accurately predicting poor outcome. However, other sources of acidosis also need to be considered. In critically ill adult patients, lactate accounts for less than half of the changes

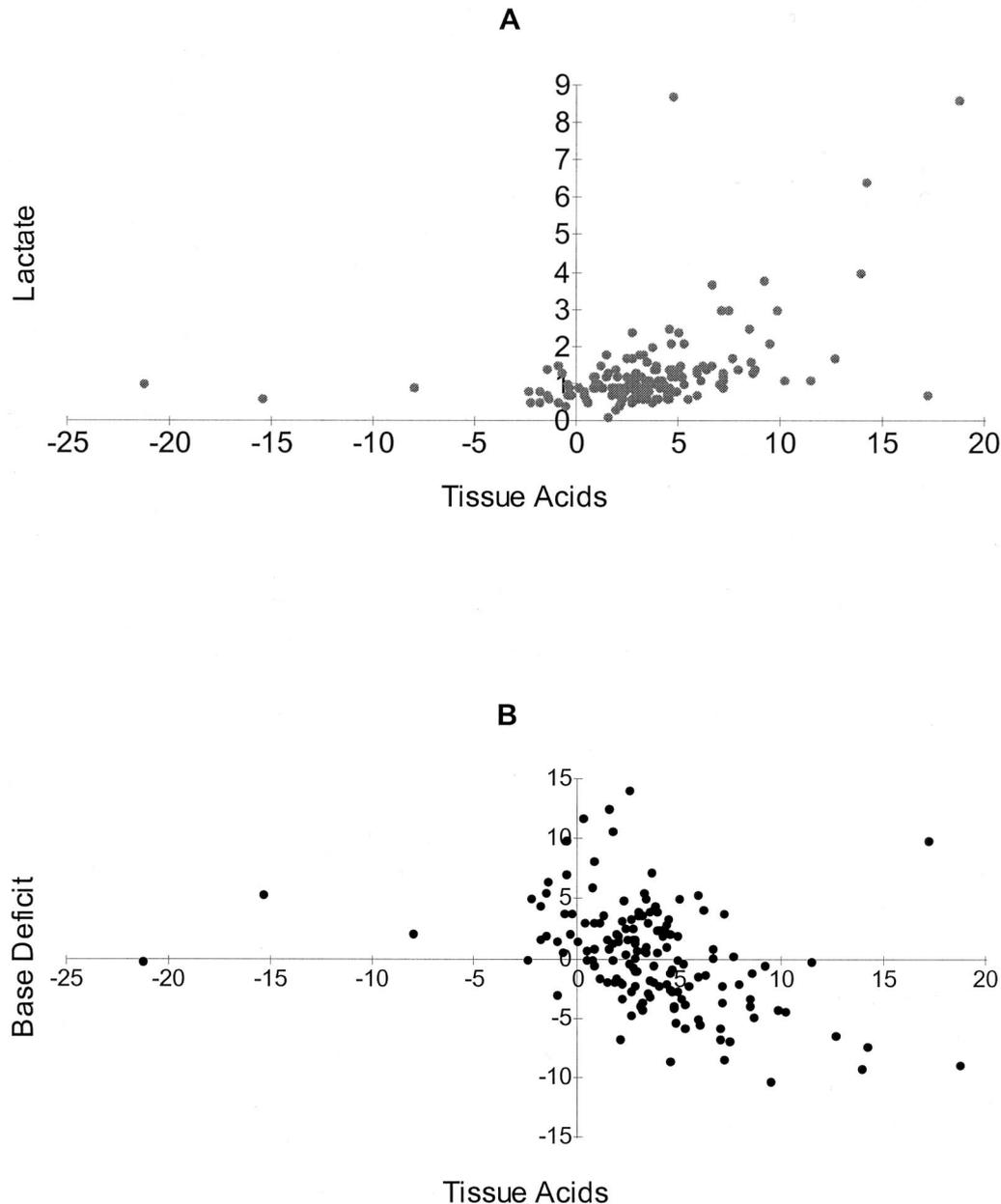


Figure 1. Scatterplots illustrating relationships between tissue acids and A, lactate; B, base deficit; C, anion gap; and D, anion gap corrected for serum albumin.

seen in raised AG acidosis (10). In our pediatric population, a pure lactic acidosis occurred in only 10% of children who had tissue acidosis, and the major contributor to acidosis after cardiac surgery was raised UMAs. The exact biochemical composition of UMA remains unclear, although speculated causes include keto acids and organic acids such as sulfate. The clinical significance of UMAs in post-congenital heart surgery patients has not been established. In our small study, we did not attempt to correlate clinical outcome with measured UMA. However, in general pediatric intensive care patients, unmeasured anions have been shown to

predict mortality rate more accurately than LA, BD, or AG (2).

The following clinical examples from our case series illustrate how the management of individual cases may be aided by the use of Stewart's method to define the cause of an acidosis.

*Case 1.* A 4-wk-old baby underwent repair of infracardiac total anomalous pulmonary venous drainage on CPB. Postoperatively, the patient had problems with suprasystemic pulmonary artery pressures, and he returned to the PICU with his chest open, atrially paced and on  $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  dopamine. The first postoperative ABG showed a falsely reas-

suring pH of 7.32,  $\text{HCO}_3^-$  21.3, Cl 97, BD 9.9, lactate 0.7, and albumin 33. Stewart's method revealed a raised TA of 17.2, a markedly raised UMA of 16.5, with a raised AG of 25 and AGcorr of 27.7. This child had a low cardiac output and ongoing problems with pulmonary hypertension in the first 24 hrs postoperatively despite a normal blood lactate. He required a noradrenaline infusion and eventually had his chest closed on day 3 in the PICU.

*Case 2.* A 4-wk-old infant underwent non-CPB cardiac surgery for repair of a coarctation of the aorta. On the first postoperative day, the morning ABG showed a

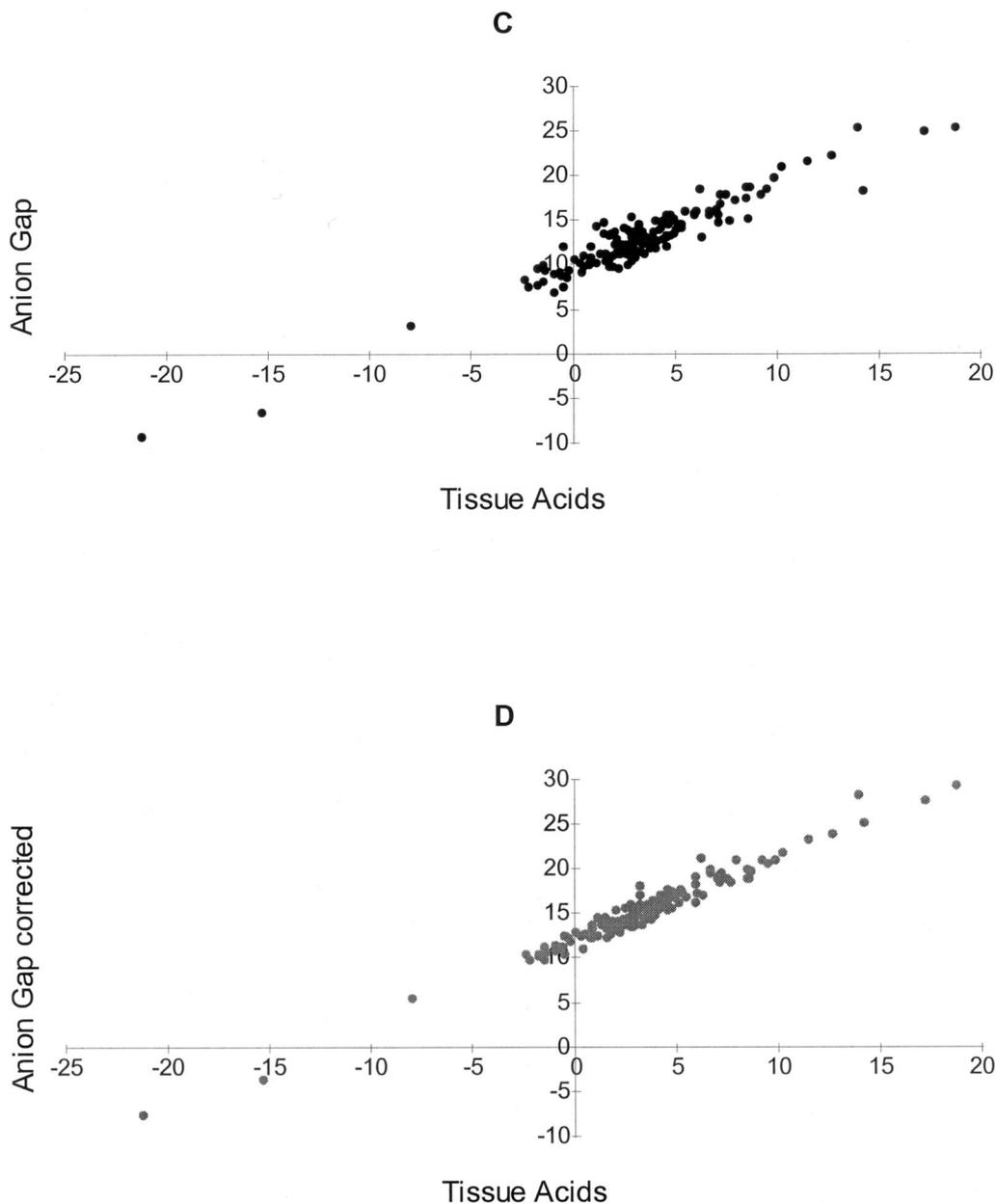


Figure 1. Continued.

**S**trong ion difference can be calculated on the intensive care unit from routine electrolytes and arterial blood gases.

**Table 3.** Area under curve (AUC) of calculated receiver operator characteristics curves for each of the variables examining their ability to predict a true acidosis (defined as excess acids tissue acidosis >5 mEq/L)

Variable	AUC	95% CI	Sens	Spec	PPV	NPV
Lactate	0.63	0.51–0.74	30	96	69	19
BD	0.72	0.62–0.82	62	81	52	87
AG	0.81	0.71–0.91	65	100	100	90
AGcorr	0.90	0.85–0.95	100	82	65	100
AGcorr (>17 mEq/L)	0.91	0.85–0.97	92	90	76	97

CI, confidence interval; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; BD, base deficit; AG, anion gap; AGcorr, corrected AG.

Values given for lactate >2 mmol/L, BD  $\geq$ 2 mEq/L, AG >16, AGcorr >16.

pH of 7.2, HCO<sub>3</sub> 21.3, Paco 55 mm Hg, and BD -6.7mEq/L, with a lactate of 0.9 mmol/L. Using Stewart's method, TA was calculated in the normal range at 1.4 mEq/L, and this was confirmed by an AG of 11.6 and AGcorr of 14.1. The patient had required several boluses of albumin overnight, and the most likely cause for the raised BD was therefore a hyperchloremic acidosis (serum Cl, 111 mmol/L). The patient did not require any further escalation in therapy.

Hyperchloremia occurred in 12.6% of samples overall and 48% of samples immediately post-CPB. This is clinically important, as it led to an apparent acidosis (raised BD, without measurable tissue acids) in almost half the samples that displayed an isolated hyperchloremia. In clinical practice, a measured acidosis such as this may be misinterpreted as an early sign of inadequate tissue oxygenation due to low cardiac output. Although hyperchloremic acidosis has been increasingly documented following fluid resuscitation in critically ill children (11), the exact cause of this post-CPB is unclear (12, 13). One potential source is the relatively high concentration of Cl (Clc) in the solution used to prime the CPB circuit during CPB. The constituents of the pump prime solution in our institution varied depending on the weight of the patient. CPB circuits for children <5 kg were primed with a volume of 400–500 mL, consisting of a combination of fresh frozen plasma and red blood cells, resulting in an approximately physiologic Clc. CPB circuits for children >5 kg were primed with 250 mL of red blood cells, 250 mL of 4.5% human albumin solution, and a combination of human albumin solution and crystalloid (Plasma-Lyte 148) to achieve a hematocrit of 0.27 l/L. Plasma-Lyte 148 contains a Clc of 98 mmol/L and human albumin solution a Clc of 100–160 mmol/L. Therefore, younger children would have received a

relatively physiologic solution, whereas older children would have received a Clc of approximately 120–130 mmol/L. In fact, we found no correlation between age and postoperative Clc, suggesting that other factors such as dilutional acidosis may be more important (12).

Our findings confirm those of Fencl et al. (4) in critically ill adult patients, in which they found that BD missed serious acid-base abnormalities in about one sixth of patients. A recent study in general pediatric patients found AGcorr to be the best discriminator for the presence of raised tissue acids and that BD and lactate performed poorly (5). We have confirmed these findings in children postcardiac surgery and post-CPB and have demonstrated the corrected AG to be a reliable and simple alternative to the calculation of TA. The clinical usefulness of corrected AG is demonstrated in Table 3. The high value for area under the curve indicates that within a population of patients, AGcorr is the best screening test for acidosis. However, positive/negative predictive values take into account the prevalence of the condition within the population and inform the clinician regarding the relevance of the test to the individual patient. In the case of AGcorr, a positive predictive value of 63% suggests that the test will pick up some patients who do not actually have a true acidosis in approximately 1:3 cases. Conversely, a negative predictive value of 100% suggests that every patient who tests negative will reassuringly not have an acidosis. If the cutoff for corrected anion gap is adjusted to 17, this increases the discriminatory ability and positive predictive value of the test but at the expense of accepting that you might “miss” some cases of true acidosis. The weight a clinician places on the significance of such a result will vary according to personal preference and the relevant

clinical setting. The importance of correcting AG for serum albumin is especially relevant in the critically ill child, due to the high incidence of hypoalbuminemia. In our patient group, hypoalbuminemia (albumin <33 g/L) occurred in 29.3% of all samples (44 of 150).

The limitations of this study are the relatively small number of patients and the lack of normal data for xanthurenic acid and UMA in healthy children. It would be interesting, in further studies, to obtain repeated samples over the first 6–12 hrs postoperatively, when the greatest deterioration in cardiac output is seen (14). Further work also is needed to determine the constituents of the other as yet undefined “unmeasured acids.”

## CONCLUSION

SID can be calculated on the intensive care unit from routine electrolytes and ABGs. Tissue acidosis occurs frequently postcardiac surgery, and in our patient group this was largely due to raised UMA and less commonly LA. Stewart's approach to acid-base disturbance has important treatment implications and can be used to differentiate between tissue acidosis and hyperchloremic acidosis. Last, BD correlates poorly with calculated TA, and corrected anion gap offers the most accurate bedside alternative to Stewart's calculation of tissue acidosis.

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