Unmeasured anions in children after cardiac surgery

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Objectives: Acidosis caused by increased unmeasured anion levels occurs frequently after cardiac surgery, with uncertain significance. We examined the ability of unmeasured anions and lactate to predict major events after cardiac surgery, in addition to lactate/increased unmeasured anion levels during low cardiac output states.

Methods: In the initial 6 months, all patients admitted after cardiac surgery were enrolled. Arterial samples were taken at 0, 4, 8, 12, 24, and 36 hours postoperatively. The Stewart method was used to calculate excess acid and unmeasured anion levels. Major adverse events were defined as low cardiac output states requiring cardiac massage or mechanical support. In the second 6-month period, data were collected from a further 8 infants during cardiac arrest/extracorporeal membrane oxygenation cannulation.

Results: One hundred thirteen patients were analyzed. Major adverse events occurred in 8 (7.1%) of 113 patients. On admission, metabolic acidosis occurred in 94 of 113 samples: lactate alone (n = 25); mixed lactate and unmeasured anions (n = 44); and unmeasured anions alone (n = 25). All of the patients who experienced major adverse events had unmeasured anion levels of greater than 3 mEq/L on admission. Initial unmeasured anion levels were significantly higher in those infants with major adverse events (10.6 mEq/L [standard deviation, 8.2 mEq/L] vs 4.8 mEq/L [standard deviation, 6.6 mEq/L], $P = .024$). Lactate levels did not differ between the 2 groups. In the 16 patients sampled during major adverse events, metabolic acidosis occurred in 15 of 16, with a mean excess acid level of 14.9 mEq/L (standard deviation, 8.3 mEq/L). Although unmeasured anions made a significant contribution, lactate was the predominant acid.

Conclusions: After cardiac surgery, unmeasured anion levels were significantly higher in those children with major adverse events. The greatest risk of major adverse events was found in children with both increased lactate levels and increased unmeasured anion levels on admission.

After cardiac surgery, a predictable decrease in cardiac output occurs.[1] Predicting which patients will succumb to this low cardiac output state is difficult. The development of metabolic acidosis, and in particular lactic acidosis, has been shown to predict major adverse events (MAEs) after cardiac surgery.[2,3] Serial lactate levels seem to be a better predictor of outcome than initial lactate levels alone.[4] Other sources of acidosis are more difficult to measure and are grouped together under the term *unmeasured anions* (UMAs). Quantification of UMAs can be achieved by using the Stewart method of calculating the strong ion difference. Stewart's biochemical theories have been modified by Figge to allow easy bedside calculation of UMAs by using routine electrolytes and albumin.[5,6] Using the Stewart method, we have previously shown that UMAs make a significant contribution to acidosis after cardiac surgery and that isolated lactic acidosis occurs infrequently.[7] The clinical importance of UMAs is still being delineated. A recent report suggests that UMA levels are better than lactate levels at predicting mortality

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after cardiac surgery.[8] We wished to examine serial UMA levels and the ability of increased UMA levels to predict MAEs after cardiac surgery. In addition, we measured the contribution of UMAs to acidosis during low cardiac output states after cardiac surgery.

Materials and Methods

The study took place in a large tertiary referral pediatric intensive care unit (PICU) over a 12-month period. Ethical approval was given by the local hospital ethics committee, and the need for written informed consent was waived because the data were collected as part of routine clinical care.

Post-cardiac Surgery Samples

In the initial 6 months of the study period, all patients admitted to the PICU after cardiac surgery were enrolled. Both cardiopulmonary bypass (CPB) and non-CPB procedures were included. Incomplete electrolyte data or nonarterial samples were excluded from analysis. Data were collected from routine arterial blood gases and electrolyte analysis at admission to the PICU and at 4, 8, 12, 24, and 36 hours postoperatively. Lactate levels were taken from arterial gases and analyzed by using an automated blood gas analyzer (Bayer 865). Electrolytes were measured as standard in our laboratory (Vitros 350 chemistry system; Na, K, and C l using potentiometric analysis and Ca, Mg, PO_4, and albumin using colorimetric analysis).

Our typical bypass prime consisted of 500 mL of plasmalyte, 100 mL of H_2O, 15 mmol of bicarbonate, 3 mmol of calcium, 20 mg of heparin, and 100 mL of 20% albumin. The circuit is surface coated with 1 unit (325 mL) of packed red blood cells. Excess prime (600 mL) was then hemofiltered off before CP

The Stewart method, as modified by Figge, was used to calculate total excess acid (XA) and UMA levels.[5,7] UMA and XA levels were calculated away from the bedside at a later stage and therefore did not influence patient care. Clinicians were aware of standard acidosis measures: pH, base deficit, and lactate. The equations to determine UMA and XA levels were as follows:

Equation 1: $SID = [HCO_3^-] + [Alb^-] + [Pi^-]$

Equation 2: $XA = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - [Cl^-]$ corrected $- SID$

Equation 3: $UMA = Xa - Lactate$

Equation 4: $[Cl^-]$ corrected $= [Cl^-]$ observed $\times (140/[Na^+]$ observed)

where SID is defined as strong ion difference, $[Alb^-]$ is defined as the negative electrical charge contribution by serum albumin (in grams per liter; $[Alb] \times ([0.123 \times pH] -0.631)$, and $[Pi^-]$ is defined as the negative charge contributed by serum phosphate (in millimoles per liter; $[PO_4] \times ([0.309 \times pH] \times -0.469)$.

An increased lactate level was defined as greater than 2 mmol/L, and an increased UMA level was defined as greater than 3 mEq/L. XA gives a measure of the total excess tissue acid, which consists of lactate and UMAs.

MAEs were defined as low cardiac output states requiring cardiac massage, chest opening, or mechanical support (extracorporeal membrane oxygenation [ECMO] or a left ventricular assist device). Other outcome measures were length of ventilation (in hours) and length of stay (in days).

Low Cardiac Output Samples

During the initial 6-month period, 3 patients had samples drawn at or immediately before an MAE. Retrospective data from ECMO cannulation records were available for a further 5 patients. During a second 6-month period, a further 8 patients experienced MAEs, and serial arterial samples were collected at 0, 4, 8, and 12 hours after cardiac arrest. This provided us with a second data set. Again, the Stewart method was used to calculate XA and UMA levels.

Statistical Analysis

Means (standard deviations [SDs]) were calculated for UMA and lactate levels at individual time points. Differences between continuous variables were determined by using the Mann-Whitney *U* test. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for MAEs. The Spearman rank sum test was used to assess correlation between linear variables. Analysis of variance between groups was determined where appropriate.

Results

During the initial 6-month period of recruitment, data were collected from 127 patients admitted to the PICU after cardiac surgery. The mean age was 38.4 months (range, 2 days to 23 years). Four patients were more than 16 years old, but the care of their long-standing congenital cardiac disease continued to be provided in the PICU, and they were therefore included in the analysis.

The surgical procedures were varied, and RACHS-1 categories were as follows: category 1, n = 8; category 2, n = 50; category 3, n = 48; category 4, n = 2; category 5, n = 0; and category 6, n = 5. CPB had been required during surgical intervention in 111 of 127 cases. Mean CPB time was 119.7 minutes (range, 0-373 minutes). Sufficient electrolyte data for analysis were available in 113 patients.

MAEs occurred in 8 (6.9%) of 113 patients. These major events involved loss of cardiac output and need for cardiac massage. In response, 6 of these 8 patients underwent emergency chest reopening, 3 were cannulated for rescue ECMO, and 4 died subsequent to their arrest.

On the initial arterial blood samples taken on admission to the PICU, the mean lactate level was 3.1 mmol/L (SD, 2.3 mmol/L), and the mean UMA level was 5.18 mEq/L
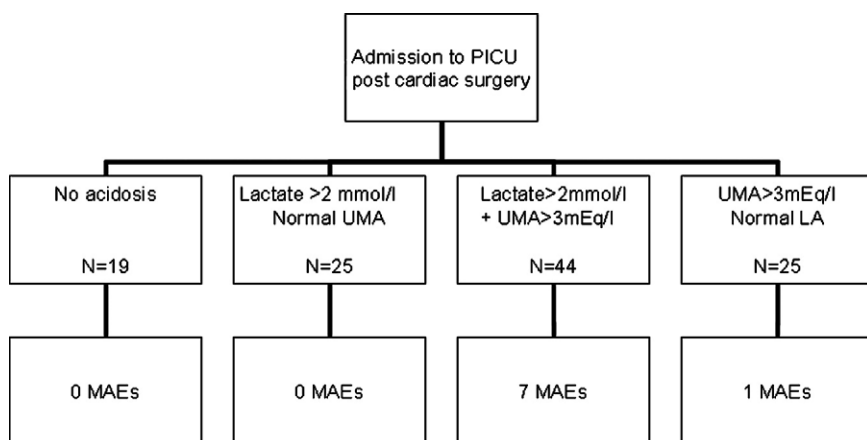
Figure 1. Occurrence of major adverse events *(MAEs)* in infants arranged according to their acidosis profile on admission to the pediatric intensive care unit *(PICU)* after cardiac surgery. *UMA,* Unmeasured anions; *LA,* lactate.

(SD, 6.8 mEq/L). Of the 113 samples, UMA levels were increased (>3 mEq/L) in 69 patients. All of the patients who later went on to have MAEs had UMA levels of greater than 3 mEq/L on initial arterial sampling (Figure 1), and therefore RRs compared with patients with UMAs of less than 3 mEq/L could not be calculated. At a cutoff point of a UMA level of greater than 6 mEq/L, the RR of an MAE was 2.13 (95% CI, 1.3-3.4). An increased lactate level was less predictive, with an RR for MAE of 1.48 (95% CI, 1.09-2.01) if the initial lactate level was greater than 2 mmol/L and an RR of 1.3 (95% CI, 0.76-2.21) if the initial lactate level was greater than 6 mmol/L.

On admission, the mean UMA level differed significantly between those infants who would proceed to MAEs (10.6 mEq/L [SD, 8.2 mEq/L]) and those who would not (4.8 mEq/L [SD, 6.6 mEq/L]; $P = .024$). Initial lactate level did not differ significantly between the 2 groups. The profile of UMA and lactate levels over time (after cardiac surgery) is displayed in Figure 2. A trend for higher UMA levels in those patients with MAEs continued up to 36 hours but was only statistically significant on admission.

Although CPB time correlated with initial lactate level ($R = 0.311$, $P = .001$), there was no correlation between UMA levels and CPB time ($R = 0.061$, $P = .52$).

At all time points, UMA levels did not correlate significantly with length of stay or length of ventilation. Although lactate levels on admission did not correlate with length of stay or length of ventilation, subsequent levels at 6, 12, and
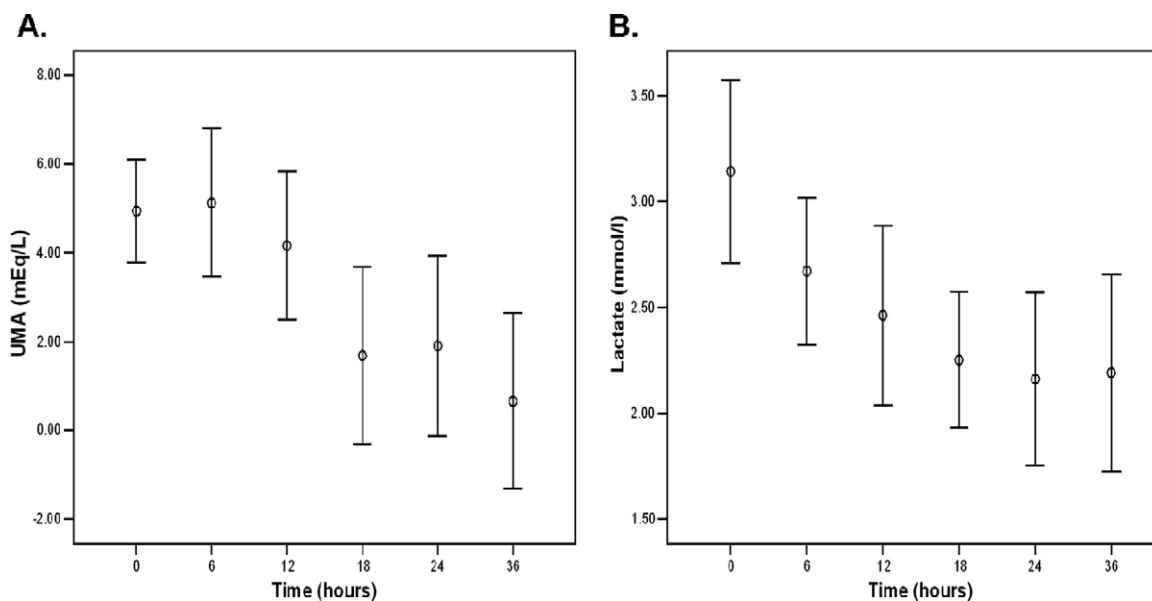

Figure 2. A, Time trend of mean unmeasured anion *(UMA)* levels after cardiac surgery. B, Time trend of lactate levels after cardiac surgery. *Error bars* represent 95% confidence intervals.

TABLE 1. Demographics, operative details, and outcomes of 16 patients with cardiac arrest or a low cardiac output event requiring mechanical support after cardiac surgery

Study no.	Age	Sex	Diagnosis	CPB (min)	Postop day	Event	Support	LOS (d)	LOV (h)	Survival
1	3 d	F	HLHS	198	0	CA	ECMO	7	160	No
2	3 d	F	HLHS	184	2	CA	ECMO	7	157	No
3	10 d	M	TV dysplasia	0	1	LCO	ECMO	2	72	No
4	19 d	M	HRHS	81	0	CA	LVAD	12	280	No
5	2 d	F	HLHS	201	1	CA	ECMO	42	622	Yes
6	46 d	F	PA	0	2	CA	ECMO	24	528	Yes
7	1 d	M	TAPVD	132	0	LCO	ECMO	23	540	No
8	9 d	M	HLHS	203	1	CA	ECMO	17	408	No
9	2.5 mo	F	PA, VSD, MAPCAs	305	0	CA	ECMO	9.5	138	Yes
10	19 mo	F	Ebstein's anomaly	0	5	CA	ECMO	33	333	No
11	3 y	F	Sennings	282	0	LCO	LVAD	28	220	Yes
12	8 d	F	HLHS	299	3	CA	ECMO	140	3309	No
13	17 d	F	MAPCAs	139	1	CA	ECMO	2	41	No
14	4 d	M	PA, VSD, PDA	127	0	CA	ECMO	5	620	No
15	56 d	M	Truncus arteriosus	184	0	CA		0.2	3	No
16	56 d	M	ASD + VSD	117	0	CA		10	240	Yes

CPB, Cardiopulmonary bypass time; *Postop day*, day after cardiac surgery when arrest/event occurred; *LOS*, length of stay; *LOV*, length of ventilation; *HLHS*, hypoplastic left heart syndrome; *CA*, cardiac arrest; *ECMO*, extracorporeal membrane oxygenation; *TV*, tricuspid valve; *LCO*, low cardiac output; *HRHS*, hypoplastic right heart syndrome; *LVAD*, left ventricular assist device; *PA*, pulmonary atresia; *TAPVD*, total anomalous venous drainage; *VSD*, ventricular septal defect; *MAPCA*, major aorto-pulmonary collateral arteries; *PDA*, patent ductus arteriosus; *ASD*, atrial septal defect.

18 hours after surgical intervention correlated significantly with length of stay ($R = 0.223$ and $P = .021$ at 6 hours; $R = 0.265$ and $P = .007$ at 12 hours, and $R = 0.313$ and $P = .007$ at 18 hours).

The acidosis profiles in neonates were examined and compared with those of older patients. Although the initial lactate level was higher in neonates than in patients older than 1 month (4.5 mmol/L [SD, 2.7 mmol/L] vs 2.9 mmol/L [SD, 2.2 mmol/L], $P = .003$), there was no significant difference between UMA levels in the 2 groups (5.1 mEq/L [SD, 7.4 mEq/L] vs 5.7 mEq/L [SD, 6.7 mEq/L], $P = .943$).

Others risk factors were examined. There was no correlation between age or weight and MAEs. There were significant correlations between both RACHS-2 category and CPB time and MAEs ($R = 0.184$, $P = .048$ and $R = 0.204$, $P = .03$, respectively). However, our numbers in RACHS-2 categories 5 and 6 are small, and analysis of variance testing showed no significant difference in UMA levels across the differing RACHS-2 categories ($P = .176$).

During the 6-month study period, 3 patients had arterial blood gas analysis and electrolyte sampling at or immediately before cardiac arrest. We examined these samples and calculated XA and UMA levels for each case. In addition, we retrospectively collected data from 5 infants at the time of cardiac arrest and cannulation for ECMO and prospectively collected data from 8 patients who experienced cardiac arrest or severe low cardiac output states over a further 6 months. In total, this allowed us to examine the acid-base

profiles in 16 children at the time of cardiac arrest. Their details and outcomes are displayed in Table 1.

At the time of arrest, 15 of 16 patients had metabolic acidosis (defined as an XA levels of >5 mEq/L), with a mean XA level of 14.9 mEq/L (SD, 8.3 mEq/L). Lactate made up the highest proportion of calculated excess tissue acid. In 5 of 16 patients, the acidosis was almost entirely a lactic acidosis, and in 10 of 16 patients there was a mixed acidosis. In no case was the acidosis entirely caused by UMAs (Figure 3). Patients remained acidotic 12 hours after MAEs, and lactate remained the predominant acid (Figure 4 and Table 2).

During the study period, only 3 patients recruited underwent deep hypothermic circulatory arrest during their surgical procedures. The small number did not allow us to comment on the nature of UMAs in these patients.

Discussion

We have shown that UMAs make a significant contribution to acidosis immediately after cardiac surgery. This contribution continues up to 36 hours after surgical intervention. Patients who have higher levels of UMAs and lactate postoperatively have an increased risk of MAEs and death. Mean UMA levels were higher in those infants who sustained MAEs throughout the first 36 hours after surgical intervention. Our findings are consistent with those of Durward and colleagues,[8] who recently reported that UMA levels at 0 and 24 hours postoperatively were superior to lactate levels as a predictor of death.
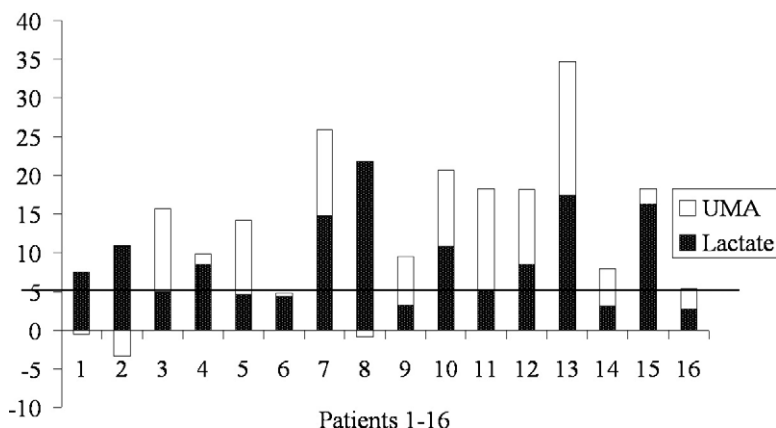
Figure 3. Acidosis at the time of cardiac arrest/low output state in each of 16 patients. Unmeasured anion *(UMA)* levels are measured in milliequivalent units per liter, and lactate levels are measured in millimoles per liter. The **thick black line** denotes the upper limit of normal for acidosis (excess acid = 5 mEq/L).

Surprisingly, initial lactate levels were not useful in predicting outcome. Subsequent lactate levels from 6 to 18 hours correlated with length of stay but not with MAEs. Previous studies have indicated that serial lactate levels are a better predictor than initial lactate levels alone.[4] Initial lactate levels might reflect lactate levels of the red blood cell prime solution used during CPB, whereas subsequent lactate levels are a consequence of ongoing oxygen debt.[9] The importance of UMAs as a morbidity predictor might be due to their occult nature. We are aware of the importance of an increasing lactate level, can measure it easily, and can recognize it as a danger sign. Lactic acidosis is generally reacted to promptly, with escalation in therapy. UMA levels are not routinely calculated, and nonlactic acidosis might not be treated as aggressively. Our study highlights the importance of both lactate and nonlactate acidosis. The majority of MAEs occurred in the group, with increased levels of both lactate and UMAs on admission. This group needs to be recognized as being at increased risk.

However, the majority of patients with increased UMA levels on admission had uneventful postoperative courses. We did not find any UMA level above which the predictive

ability was clinically useful. Similarly, in general intensive care patients, studies examining the ability of UMA levels and strong ion gap to predict mortality have had mixed results.[10-12] Perhaps it is too much to ask of a single isolated biochemical measurement to predict the course of a complex, critically ill patient. An increased UMA level should therefore be seen as an indicator of risk and acted on in conjunction with the patient's lactate level and his or her overall clinical condition. Although not yet part of routine clinical care, Stewart's strong ion difference has allowed us to quantify the contribution of differing sources of acidosis in important clinical situations.[13-15]

The origin of UMAs is unknown, and they are most likely a combination of exogenous and endogenous acids.[16] Although we did not find any correlation with CPB time, it is likely that parts of the CPB prime add exogenous acids, such as citrate and acetone, to the immediate postoperative sample. This will add to the endogenous acid load of ketones, sulfates, and the negative charge of inflammatory proteins. Decreased clearance by the liver and kidney might also decrease the ability to clear UMAs. None of these sources of acid have been quantified in the postoperative cardiac patient. The increase in UMA levels during cardiac arrest cannot be blamed on the bypass prime and gives a clearer reflection of endogenous acid production.
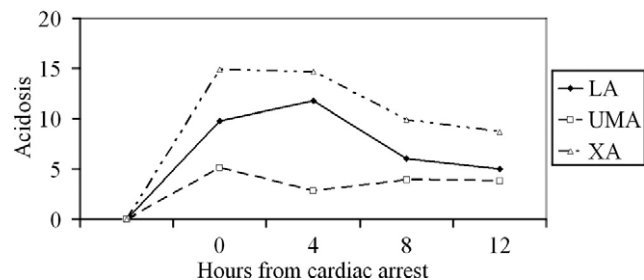

Figure 4. Acidosis at the time of cardiac arrest and 12 hours after arrest. *LA*, Mean arterial lactate level (in millimoles per liter); *UMA*, mean unmeasured anion level (in milliequivalent units per liter) calculated from arterial sample; *XA*, mean excess acids calculated from arterial sample.

TABLE 2. Acidosis at and after cardiac arrest (n = 16)

Hours from cardiac arrest	XA (mEq/L), mean (SD)	LA (mmol/L), mean (SD)	UMA (mEq/L), Mean (SD)
0	14.9 (8.3)	9.8 (6.0)	5.1 (6.0)
4	14.7 (7.6)	11.8 (6.8)	2.9 (6.8)
8	9.9 (6.7)	6.0 (4.6)	3.9 (4.2)
12	8.7 (5.3)	5.0 (2.4)	3.8 (4.1)

Data were available from 16 patients at 0 hours, 9 patients at 4 hours, and 8 patients at 8 and 12 hours. *XA*, Excess acids calculated from arterial blood samples; *SD*, standard deviation; *LA*, arterial lactate; *UMA*, unmeasured anions calculated from arterial samples.

Importantly, we have shown that during severe low output states, lactate is the predominant source of acid and remains so for the subsequent 12 hours. It is useful to recognize that UMAs make a significant contribution in two thirds of patients, but no patients had isolated UMA acidosis at the time of their MAE. Similarly, a recent study of adults during cardiac arrest found that lactate accounts for only 50% of metabolic acidosis, with strong ion gap accounting for most of the remainder.[17]

Although all of our patients with MAEs had significant events requiring cardiac massage, mechanical support, or both, we do not routinely use invasive methods of quantifying cardiac output. The availability of reliable continuous cardiac output monitoring would be the ideal and would allow us to accurately track the development of acidosis and its clinical relevance during these crucial postoperative hours.

Conclusions

Increased UMA levels after cardiac surgery are associated with an increased risk of morbidity and mortality. The greatest risk for MAEs was seen in those patients with both lactate acidosis and increased UMA levels. We have also demonstrated that UMAs make a significant contribution to acidosis during low cardiac output states, albeit secondary to that of lactate.

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