Intraoperative Plasma Lactate as an Early Indicator of Major Postoperative Events in Pediatric Cardiac Patients

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Hyperlactatemia and unmeasured anions (UMA) have been suggested to be useful predictors of outcomes after pediatric cardiac surgery in the ICU. However, if we detect high-risk patients in the operating room, we could practice early intervention to decrease mortality and morbidity. The purpose of this study was to determine whether the intraoperative lactate or UMA levels can predict adverse outcomes in pediatric cardiac patients with undergoing cardiopulmonary bypass (CPB). We studied 102 patients with congenital heart disease. Arterial blood samples were obtained after inducing anesthesia, 5 min after weaning from CPB and after chest closure. Major adverse events (MAEs) were defined as cardiac compression, re-sternotomy due to hemodynamic instability, extra-corporeal membrane oxygenator support, creatinine levels greater than 2 mg/dL, or death. Patients were divided into MAE group (8 patients, 7.8%) and non-MAE group. Six patients with MAEs died. Importantly, the lactate levels (mmol/L) at weaning from CPB (4.19 vs 2.1; MAE group vs non-MAE group), chest closure (5.76 vs 2.39; MAE group vs non-MAE group) and the intraoperative increases in lactate levels were significantly higher in the MAE group than in the non-MAE group. However, there was no significant difference in the UMA levels or their changes between the groups. The increase in the lactate level from CPB weaning to chest closure was the best predictor of MAEs (AUC: 0.810). In conclusion, the intraoperative plasma lactate levels were more closely associated with MAEs, and they are more useful for predicting the outcome of pediatric cardiac patients than the UMA levels.

Keywords: congenital heart disease; lactate; perioperative care; predictor of outcome; unmeasured anions

An early indicator of adverse outcomes following open heart surgery should help identify patients at high risk who may benefit from early intervention. Postoperative hyperlactatemia as a result of tissue hypoperfusion is associated with high morbidity and mortality, and the serum or plasma lactate level in the intensive care unit (ICU) has prognostic value after pediatric cardiac surgery (Cheifetz et al. 1997; Charpie et al. 2000, Cheung et al. 2005, Basaran et al. 2006). In addition, hyperlactatemia during cardiopulmonary bypass (CPB) is an early predictor of morbidity and mortality in pediatric patients (Munoz et al. 2000, Ranucci et al. 2006). However, some confounding factors, such as the inhibition of pyruvate dehydrogenase, enhanced glycolysis, and an exogenous lactate load from red blood cells, can decrease the predictive power of lactate levels (McAuliffe et al. 1986, Gilfix et al. 1993).

One alternative marker of tissue hypoxia, another source of acidosis that is difficult to measure, is the level of unmeasured anions (UMA). UMA include anions such as sulfates and negatively charged proteins that produce hydrogen ions. Stewart’s biochemical theories, as modified by Figge et al. (Fencl et al. 2000), allow the easy bedside calculation of the UMA level from routine blood gas and chemistry analysis (Fencl et al. 2000, Murray et al. 2004). The UMA level makes a significant contribution to acidosis, and its values in the ICU are significantly higher in children with major adverse events (MAEs) after cardiac surgery (Murray et al. 2004; Murray et al. 2007). Another report suggests that an elevated strong ion gap is superior to lactate levels as a predictor of mortality after cardiac surgery (Durward et al. 2005). However, some reports have questioned the role of the UMA level as a predictor of outcome in critically ill patients (Cusack et al. 2002; Hatherill et al. 2003; Rocktaeschel et al. 2003).
Both lactate and UMA levels might be useful for predicting postoperative outcomes. If we could identify high-risk patients earlier, e.g., in the operating room rather than in the ICU, we could practice early intervention to decrease morbidity and mortality. However, there is little information regarding whether intraoperative lactate or UMA levels predict adverse outcomes or on which is the superior predictor. The purpose of this study was to determine whether intraoperative lactate or UMA levels can predict adverse outcomes and to determine which is superior in pediatric patients undergoing cardiac surgery.

Materials and Methods

This prospective, observational study enrolled 102 nonconsecutive pediatric patients requiring cardiac surgery under CPB in a large tertiary-referral pediatric hospital during a 2-year period. Ethics approval was obtained from the Institutional Review Board. Written informed consent was obtained from the parents or from both the subjects and the parents if the children understood the study protocol. Exclusion criteria included non-CPB cardiac surgery and preoperative renal dysfunction with a serum creatinine level higher than 2 mg/dl.

The patients were anesthetized using thiopental, midazolam, sufentanil, fentanyl, vecuronium and sevoflurane. Monitoring consisted of electrocardiography, pulse oximetry, capnography, continuous arterial pressure monitoring and central venous pressure monitoring. A median sternotomy was made, and CPB was established via cannulation of the ascending aorta and both caval veins after systemic heparinization. Perfusion rates were maintained at 1.8-2.2 L/min/m². During perfusion, the hematocrit was maintained at 20-25%. Hypothermic cardiac arrest was not used in any case. Modified ultrafiltration was performed in all cases. After weaning from CPB, inotropic agents were infused, and the patient was transfused at the attending anesthesiologist’s discretion.

All biochemical information was obtained routinely from arterial blood samples collected in heparinized blood-gas syringes and blood specimen tubes after inducing anesthesia, 5 min after weaning from CPB and after chest closure. If the patient could not be weaned from CPB, weaning from CPB was considered to be 5 min after trying to wean the patient from CPB, and T3 was set at the time of chest closure before the patient left the operating room with an extracorporeal membrane oxygenator (ECMO). The clinicians involved in the care of the patients had full access to the real-time results of the laboratory data. Ionized calcium, lactate levels and pH were analyzed using a blood gas analyzer (GEM Premier 3000, Blood/Gas Electrolyte analyzer Model 5700, Instrumentation Laboratory, Lexington, MA). Electrolytes and albumin were measured in a standard manner in our laboratory (200FR Auto Chemistry Analyzer, Toshiba, Japan). Changes in the lactate and UMA levels from induction to CPB weaning, from induction to chest closure and from CPB weaning to chest closure were also determined.

The physicochemical results were analyzed quantitatively using Stewart’s method, as modified by Figge and colleagues (Fencel et al. 2000), to incorporate the effects of plasma proteins. We calculated the apparent strong ion difference (SIDe), which is the difference between the sums of all measured strong cations and strong anions, as follows:

$$SID_e = [Na^+] + [K^+] + [Mg^{++}] + [Ca^{++}] - [Cl^-]_{correct} - [lactate]$$

Finally, SIG (which represents UMA) was determined as SIDe – SIDa.

A MAE was defined as any condition requiring cardiac compression, chest opening, or extracorporeal membrane oxygenator (ECMO) support; renal dysfunction with a creatinine level higher than 2 mg/dL; or death. MAEs were defined as events occurring within 24 hours of ICU arrival. The patients were divided into MAE and non-MAE groups accordingly. The lactate, UMA, albumin, bicarbonate and phosphorus levels and their intraoperative changes were compared between the two groups. Intraoperative and postoperative hemodynamic variables (arterial blood pressure, heart rate and central venous pressure) were also compared.

Statistical Analysis

The distributions of the data were evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used to compare the two independent groups. The predictability for MAEs was assessed using the area under the receiver operating characteristic (ROC) curve. Univariate binary logistic regression analysis was used to examine the relationship between the parameters and MAEs. P-values < 0.05 were considered significant. All data are presented as the mean ± standard deviation (median [range]). Statistical analyses were performed using SPSS 18.0 (IBM SPSS, Somers, NY, USA), and ROC curve analysis was performed using MedCalc 12 (MedCalc Software, Mariakerke, Belgium).

Results

MAEs occurred in 8 (7.8%) of the 102 patients. These events consisted of the loss of cardiac output and the need for cardiac massage. Six patients underwent cardiac massage in the ICU (in one case, the serum creatinine level was above 2 mg/dL; one patient was cannulated for rescue ECMO after an emergency chest opening in the ICU). Six of the eight patients with MAEs died.

The surgical procedures varied, and the risk adjustment for congenital heart surgery (RACHS)-1 categories is summarized in Table 1. There was no significant difference in the severity of the primary disease between the MAE and non-MAE groups. The demographic and perioperative characteristics of the MAE and non-MAE groups are compared in Table 2. MAEs occurred more frequently in younger and smaller patients. In addition, the durations of CPB, mechanical ventilation and the ICU stay were significantly longer in the MAE group than in the non-MAE group.

The lactate and UMA levels in the two groups are shown in Fig. 1. The lactate levels at weaning from CPB...
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and chest closure and intraoperative increases were significantly greater in the MAE group than in the non-MAE group. Conversely, there were no significant differences in UMA levels or its changes between the groups.

The changes in major anions related to the UMA level are shown in Fig. 2. There was a significant difference only in the intraoperative change in bicarbonate from induction to chest closure.

Fig. 3 shows the perioperative hemodynamic variables. Systolic blood pressure was significantly lower in the MAE group than in the non-MAE group during the study period. CVP was higher in non MAE group than in the MAE group 1 hr after ICU admission.

Fig. 4 shows the discriminatory and predictive values for MAEs determined using ROC curve analysis. The intraoperative lactate levels were better than the intraoperative UMA levels at predicting MAEs. Lactate at chest closure and the change in the lactate level from CPB weaning to chest closure showed moderate diagnostic value (AUC: 0.788 and 0.810, respectively). The AUCs for the changes in the lactate level from CPB weaning to chest closure and from induction to chest closure were significantly greater than those for the changes in the UMA level from CPB weaning to chest closure and from induction to chest clo-

Table 1. Risk adjustment for congenital heart surgery for the study population.

<table>
<thead>
<tr>
<th>Category</th>
<th>MAE (n = 8)</th>
<th>no MAE (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Coarctoplasty (&gt; 30d) = 1, total repair of PAPVR = 1</td>
<td>Coarctoplasty (&lt; 30d) = 1, total repair of TOF = 8, VSD repair = 24, BCPS + aortic valve repair = 1, carpal-pulmonary artery anastomosis = 1, ASD + VSD repair = 7, total repair of TAPVR = 1, Coarctoplasty = 2, pulmonary artery angioplasty = 2, total correction of coarctation of aorta = 1, aortic valvuloplasty = 2</td>
</tr>
<tr>
<td>Category 2</td>
<td>Coarctoplasty (&lt; 30d) = 1, ASD&amp;VSD repair = 1</td>
<td>total repair of pulmonary atresia = 1, total repair of TOF = 8, VSD repair = 24, BCPS + aortic valve repair = 1, carpal-pulmonary artery anastomosis = 1, ASD + VSD repair = 7, total repair of TAPVR = 1, Coarctoplasty = 2, pulmonary artery angioplasty = 2, total correction of coarctation of aorta = 1, aortic valvuloplasty = 2</td>
</tr>
<tr>
<td>Category 3</td>
<td>MAP+TVP = 1</td>
<td>Fontan = 7, BT shunt = 1, RVOT widening = 1, AVSD repair = 1, biventricular repair = 1, AVR = 1, Rastelli’s Op = 2, LVOT myectomy + MVP, MAP = 1, Coarctoplasty = 5, valvuloplasty of MV&amp;TV = 1, PA - VSD + PDA total correction = 1, ASO = 7, MVR = 2, LA membrane excision = 1</td>
</tr>
<tr>
<td>Category 4</td>
<td>Rastelli’s Op = 2, ASO = 1</td>
<td>Rastelli’s Op = 1, ASO+RVOT reconstruction = 1, ASO+VSD repair = 5</td>
</tr>
<tr>
<td>Category 5</td>
<td>MVP + PAB + RA reduction = 1</td>
<td></td>
</tr>
<tr>
<td>Category 6</td>
<td>Norwood = 1</td>
<td>DKS + BCPS = 2, Norwood = 1</td>
</tr>
</tbody>
</table>

Table 2. Patients, CPB, and ICU characteristics.

<table>
<thead>
<tr>
<th>MAE (n = 8)</th>
<th>Non-MAE (n = 94)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>1.6 ± 2.3 (0.8 [0.1 - 7.0])</td>
<td>22.8 ± 43.1 (5.0 [0.1 - 204.0])</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.6 ± 0.7 (3.6 [2.8 - 4.7])</td>
<td>10.3 ± 11.4 (6.9 [2.0 - 78.9])</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>51.1 ± 3.7 (51.5 [45.0 - 57.0])</td>
<td>75.3 ± 27.7 (66.3 [43.0 - 171.9])</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>240 ± 126 (225 [106 - 473])</td>
<td>156 ± 67 (150 [64 - 392])</td>
</tr>
<tr>
<td>ACC time (min)</td>
<td>109 ± 84 (68 [25 - 255])</td>
<td>87 ± 47 (87 [24 - 248])</td>
</tr>
<tr>
<td>Induction-CPB weaning (min)</td>
<td>300.6 ± 142.5 (275.0 [142 - 573])</td>
<td>258.7 ± 80.0 (246.0 [118 - 505])</td>
</tr>
<tr>
<td>CPB weaning-chest closure (min)</td>
<td>74.3 ± 59.7 (56.0 [18 - 189])</td>
<td>64.1 ± 28.2 (60.0 [22 - 186])</td>
</tr>
<tr>
<td>Chest closure-ICU (min)</td>
<td>37.8 ± 22.0 (33.0 [16 - 80])</td>
<td>37.6 ± 15.0 (38.0 [10 - 69])</td>
</tr>
<tr>
<td>MV time (hr)</td>
<td>450 ± 326 (416 [48 - 1074])</td>
<td>75 ± 105 (31 [3 - 852])</td>
</tr>
<tr>
<td>ICU time (hr)</td>
<td>589 ± 346 (498 [48 - 1074])</td>
<td>125 ± 109 (96 [18 - 501])</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; ASO, arterial switch operation; AVSD, atrioventricular septal defect; AVR, aortic valve replacement; BCPS, bidirectional cavopulmonary shunt; BT shunt, Blalock-Taussig shunt; DKS, Damus-Kaye-Stansel procedure; LVOT, left ventricular outflow tract; MAP, mitral annuloplasty; MVP, mitral valvuloplasty; MVR, mitral valve replacement; PAB, partial anomalous pulmonary venous return; RA, right atrium; RVOT, right ventricular outflow tract; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; TVP, tricuspid valvuloplasty; VSD, ventricular septal defect.

Data are expressed as the mean ± standard deviation (median [range]).

CPB, cardiopulmonary bypass; ACC, aorta cross clamping; MV, mechanical ventilation; ICU, intensive care unit; MAE, major adverse event; Induction, time point of inducing anesthesia; CPB weaning, 5 min after weaning from CPB; Chest closure, time point of chest closure.
sure \((P = 0.012\) and 0.048, respectively). The cut-off values for lactate at chest closure and the change in the lactate level from CPB weaning to chest closure were 6.6 and 0.5 mmol/L, respectively. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each measurement are shown in Table 3. Lactate at chest closure and the change in the lactate level from CPB weaning to chest closure had high NPV (95.8% and 97.5%, respectively).

Table 4 shows the discriminatory value for MAEs determined using univariate binary logistic regression analysis. The lactate levels at CPB weaning and chest closure and the changes in the lactate level from induction to CPB weaning, from CPB weaning to chest closure and from induction to chest closure were significantly associated with MAEs.

Discussion

This study showed that higher levels of lactate and intraoperative increases in the lactate level are more closely associated with MAEs than the UMA levels and the changes in these levels.

There has been some controversy regarding whether lactate or UMA level is a better predictor of adverse outcomes. The UMA level measured in the ICU was found to be superior to the lactate level as a predictor of MAEs after
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Fig. 3. Perioperative hemodynamic variables in the MAE group and non-MAE group

The systolic blood pressure at induction, CPB weaning, chest closure, 1 hour after ICU admission and 6 hour after ICU admission, and CVP at 1 hour after ICU admission were significantly greater in non-MAE group than in the MAE group.

SBP, systolic blood pressure; HR, heart rate; CVP, central venous pressure; bpm, beats per minutes; Induction, time point of inducing anesthesia; CPB weaning, 5 minutes after weaning from CPB; chest closure, time point of chest closure; ICU1, 1 hour after ICU admission; ICU6, 6 hours after ICU admission; MAE, major adverse event.

*P < 0.05.

Fig. 4. Receiver operating characteristic curve comparing the intraoperative lactate and UMA levels and changes as predictors of major adverse events.

The lactate level at CPB weaning, chest closure and change in the lactate level from induction to chest closure, and change in the lactate level from CPB weaning to chest closure can be indicators of the major adverse events. AUCs of change in the lactate level from CPB weaning to chest closure and change in the lactate level from induction to chest closure were significantly greater than those of change in the UMA level from CPB weaning to chest closure and change in the UMA level from induction to chest closure respectively.

Induction, time point of inducing anesthesia; weaning, 5 min after weaning from CPB; closure, time point of chest closure; UMA, unmeasured anions; Change in lactate induction-weaning, change in the lactate level from induction to CPB weaning; Change in lactate induction-closure, change in the lactate level from induction to chest closure; Change in UMA induction-weaning, change in the UMA level from induction to CPB weaning; Change in UMA induction-closure, change in the UMA level from induction to chest closure; AUC, area under curve; P\textsubscript{AUC}, P value of the comparison of AUCs between lactate and UMA at each time point.
pediatric cardiac surgery in some studies (Durward et al. 2005; Murray et al. 2007), whereas other studies showed that the UMA level offers no additional advantage over the lactate level in predicting surgical outcomes (Cusack et al. 2002; Hatherill et al. 2003; Rocktaeschel et al. 2003). Both of these reports focused on postoperative or critically ill patients in the ICU. In contrast, our study is the first study to investigate the relationship between intraoperative UMA levels and adverse outcomes and to compare intraoperative lactate and UMA levels as indicators of adverse outcomes.

An increase in the lactate concentration can be caused by a decrease in oxygen delivery to a tissue; therefore, lactate can increase whenever tissue hypoxia occurs (i.e., preoperatively, intraoperatively or postoperatively). Eventually, a shortage of oxygen to vital organs can result in a MAE.

Table 3. Sensitivity, specificity, and predictive values of lactate at chest closure and change in the lactate level from 5 min after weaning from CPB to chest closure.

<table>
<thead>
<tr>
<th>parameter</th>
<th>cut-off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate at chest closure</td>
<td>&gt; 6.6</td>
<td>50</td>
<td>97.8</td>
<td>57.1</td>
<td>95.8</td>
</tr>
<tr>
<td>Change in lactate CPB weaning - chest closure</td>
<td>&gt; 0.5</td>
<td>75</td>
<td>77.7</td>
<td>20.7</td>
<td>97.5</td>
</tr>
</tbody>
</table>

CPB weaning, 5 min after weaning from CPB; chest closure, time point of chest closure.
Change in lactate level CPB weaning - chest closure, changes in the lactate level from 5 min after weaning from CPB to chest closure; MAE, major adverse event; PPV, positive predictive value; NPV, negative predictive value.

Induction, time point of inducing anesthesia; CPB weaning, 5 min after weaning from CPB; chest closure, time point of chest closure; Change in lactate induction - CPB weaning, change in the lactate level from time point of inducing anesthesia to 5 min after weaning from CPB; Change in lactate CPB weaning - chest closure, change in the lactate level from 5 min after weaning from CPB to time point of chest closure; Change in lactate induction - chest closure, change in the lactate level from time point of inducing anesthesia to time point of chest closure.

Table 4. Discriminatory value for major adverse events using univariate binary logistic regression analysis for lactates.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Significance</th>
<th>OR (95% C.I.)</th>
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</thead>
<tbody>
<tr>
<td>Lactate at CPB weaning</td>
<td>0.004</td>
<td>1.62 (1.17 - 2.25)</td>
</tr>
<tr>
<td>Lactate at chest closure</td>
<td>0.001</td>
<td>1.53 (1.18 - 1.98)</td>
</tr>
<tr>
<td>Change in lactate induction - CPB weaning</td>
<td>0.011</td>
<td>1.55 (1.10 - 2.18)</td>
</tr>
<tr>
<td>Change in lactate CPB weaning - chest closure</td>
<td>0.002</td>
<td>2.64 (1.44 - 4.84)</td>
</tr>
<tr>
<td>Change in lactate induction - chest closure</td>
<td>0.002</td>
<td>1.15 (1.16 - 1.97)</td>
</tr>
</tbody>
</table>

Induction, time point of inducing anesthesia; CPB weaning, 5 min after weaning from CPB; chest closure, time point of chest closure; Change in lactate induction - CPB weaning, change in the lactate level from time point of inducing anesthesia to 5 min after weaning from CPB; Change in lactate CPB weaning - chest closure, change in the lactate level from 5 min after weaning from CPB to time point of chest closure; Change in lactate induction - chest closure, change in the lactate level from time point of inducing anesthesia to time point of chest closure.

Although no single intraoperative biochemical marker can predict patient outcomes with perfect accuracy, intraoperative lactate levels may be superior to the UMA levels for predicting the postoperative course of cardiac patients. Munoz et al. demonstrated that an increase in lactate level during CPB is an early indicator of a poor outcome (Munoz et al. 2000). We showed that lactate measurements were more predictive of MAEs in the early post-CPB period. Although the oxygen delivery may be adequate for the metabolic demands during CPB, the low cardiac output following CPB can cause progressive hyperlactetemia.
Cut-off values of 6.6 mmol/L lactate at chest closure and a 0.5 mmol/L change in the lactate level from CPB weaning to chest closure have low positive predictive value but high negative predictive value. Therefore, these criteria are more useful for excluding patients at low risk.

There are several limitations of this study. First, the number of subjects was small, and a completely homogenous group could not be created. Second, there could be a selection bias toward patients with more complicated congenital heart disease because of the nonrandomized method of patient selection; further study of less complex cases is needed. Third, the cut-off values of 6.6 mmol/L lactate at chest closure and a 0.5 mmol/L change in the lactate level from CPB weaning to chest closure have low positive predictive value.

In conclusion, the intraoperative lactate levels and the changes in these levels are more closely associated with adverse outcomes than are UMA levels. An elevated lactate level during surgery should be considered a serious indicator of an adverse outcome. Early aggressive intervention in these patients may decrease the morbidity and mortality after pediatric cardiac surgery.

Acknowledgments
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Conflict of Interest
The authors declare no conflict of interest.

References


