Rate of increase in serum lactate level risk-stratifies infants after surgery for congenital heart disease

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Objective: Increased blood lactate levels reflect tissue oxygen debt and might be indicative of low cardiac output. We hypothesized that the rate of increase in serum lactate would be an ideal marker to discriminate between infants at high and low risk of a poor outcome after surgical repair of congenital heart disease using cardiopulmonary bypass.

Methods: In the present prospective, observational study in a pediatric cardiac intensive care unit, infants (aged <12 months) undergoing cardiac surgery had serial whole blood lactate levels measured with every arterial blood gas drawn for the first 24 postoperative hours. The composite poor outcome included death, the need for extracorporeal support, and dialysis.

Results: The lactate levels were measured in 231 infants; 19 infants (8.2%) had a poor outcome. A lactate increase rate of 0.6 mmol/L/h had very good discriminatory ability (area under the curve [AUC], 0.89) with a sensitivity of 90%, specificity of 84%, positive predictive value (PPV) of 34%, and negative predictive value (NPV) of 99%. Similar results were obtained for subgroups stratified by 1- or 2-ventricle heart disease and risk adjustment for congenital heart surgery (RACHS-1) score. In neonates (age <30 days) with single-ventricle physiology (n = 43, poor outcome = 8), a lactate increase of 0.6 mmol/L/h had near perfect discriminatory ability (AUC 0.99) with a sensitivity of 100%, specificity of 51%, PPV of 32%, and NPV of 100%. In 2-ventricle neonates (n = 43, poor outcome = 5), a lactate increase of 0.6 mmol/L/h also had near perfect discriminatory ability (AUC, 0.99), with a sensitivity of 100%, specificity of 90%, PPV of 56%, and NPV of 100%.

Conclusions: The postoperative lactate increase rate allows discrimination between infants at high and low risk of morbidity and mortality after congenital heart disease surgery, and the lactate level can be followed serially for the treatment response. (J Thorac Cardiovasc Surg 2014;148:589-95)

Clinical indicators reflecting tissue perfusion and systemic oxygen delivery are needed after surgery for congenital heart disease (CHD). The ideal indicator would have a high predictive value for outcome, would allow for early detection of tissue ischemia before injury, and could be monitored serially to assess the response to therapeutic interventions. Blood lactate has been studied as a potential clinical marker, particularly in children after cardiac surgery. Lactate is formed from pyruvate as the final product of glycolysis. Under aerobic conditions, lactate is converted back to pyruvate by mitochondrial oxidation. Under anaerobic conditions, cellular lactate levels increase, leading to increased serum lactate levels.[1] Thus, hyperlactemia might reflect tissue oxygen debt.

Multiple studies in the pediatric data have examined the utility of blood lactate levels as both positive and negative predictors of outcome after surgery for CHD.[2-10] However, most of these studies had important limitations, including low patient numbers, that compromised their ability to adequately assess the predictive value of an elevated lactate level. Furthermore, several studies combined data from children of all ages in their analyses. This could have been problematic because the susceptibility to tissue oxygen debt and normal lactate levels vary with age.[11,12] Finally, the point at which the lactate level is measured during the clinical course and the chronicity of the lactate measurements differed from study-to-study, making comparisons among smaller studies difficult.

More than 1 decade ago, we published a prospective study on the predictive value of serial lactate levels in a small cohort of 46 neonates after complex congenital heart surgery at the University of Michigan.[13] In that limited sample, the rate of increase in serum lactate was identified as an early marker of increasing tissue oxygen debt that was predictive of poor outcome. Despite the potential benefits of an increase in lactate as a predictor of poor outcome, these results have not been reproduced on a larger

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Abbreviations and Acronyms

AUC = area under the curve
CBP = cardiopulmonary bypass
CHD = congenital heart disease
CICU = cardiac intensive care unit
ECMO = extracorporeal membrane oxygenation
ICU = intensive care unit
IQR = interquartile range
NPV = negative predictive value
PPV = positive predictive value
RACHS-1 = risk adjustment for congenital heart surgery

scale or in a broader patient population. In the present study, we sought to re-evaluate the utility of both initial and serial lactate measurements in a larger cohort of infants after cardiopulmonary bypass (CPB) for congenital heart surgery. We hypothesized that rate of increase in serum lactate would have a strong predictive value for the outcome and would proceed maximal tissue oxygen debt.

METHODS

Patients

We conducted a prospective, observational study of infants (<12 months of age) after surgical repair of CHD requiring CPB. A total of 231 nonconsecutive infants were enrolled in the study from June 2010 to September 2011. Nonconsecutive enrollment resulted because of parental refusal (3 infants) or parental unavailability for consent (18 infants). Parental consent was obtained before data collection, and the institutional review board of the University of Michigan approved the research protocol. All infants were required to be ≥37 weeks' corrected gestational age and to weigh >2 kg before enrollment. Infants requiring extracorporeal membrane oxygenation (ECMO) in the operating room before arrival in the cardiac intensive care unit (CICU) were excluded from the study. Only those patients in whom ECMO was initiated emergently after postoperative CICU admission were included in the present analysis.

Lactate Measurements

Serial, arterial, whole blood lactate levels were collected per CICU protocol at the discretion of the treating clinician. At our center, lactate levels were obtained routinely with each arterial blood gas drawn. All lactate levels measured in the initial, postoperative 24 hours were included in the present study. Whole blood lactate was measured using a pediatric blood gas analyzer (ABL 800 Flex; Radiometer, Brønshøj, Denmark) for each sample. For serum lactate levels within a range of 0 to 30 mmol/dL, this pediatric blood gas analyzer is accurate, with an r^2 of 0.95, and precise, with a coefficient of variance of 0% to 2% compared with laboratory-measured lactate values. A priori analyses were planned to assess the predictive values of both the initial postoperative lactate level and the maximal rate of increase in the lactate level. The initial lactate level was drawn within 1 hour of arrival in the CICU postoperatively. The lactate increase rate was calculated as the difference between the consecutive lactate measurements divided by the interval between the measurements. The maximal rate of lactate increase was expressed as the largest increase between 2 consecutive measurements divided by interval during the first 24 postoperative hours.

Outcome Variable

The primary outcome variable ("poor outcome") was a composite of death during hospitalization, the need for ECMO support initiated after admission to the CICU, and the initiation of renal dialysis. In our CICU, few infants have significant preoperative kidney disease, and most cases of renal injury requiring dialysis result from acute kidney injury caused by tissue ischemia, which has been reported in other studies.[14] Although not inclusive of all significant postoperative events that could result from postoperative ischemia, this composite outcome was specifically selected because the individual outcomes can be easily assessed as positive or negative, and the endpoints are clinically relevant. A subject was classified as having a poor outcome based on the appearance of any 1 component of the composite outcome. Secondary outcomes included the need for an unplanned cardiac reoperation, duration of tracheal intubation, and length of intensive care unit (ICU) and total hospital stays.

Statistical Analysis

Descriptive statistics are reported as frequencies with percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. The demographic and patient surgical characteristics between the 2 outcome groups (poor and good outcome) were compared using the chi-square test or Fisher's exact test, as appropriate, for the categorical variables and the Wilcoxon rank sum test for continuous variables. Using receiver operating characteristic curves, the optimal levels for the initial postoperative lactate level and maximal hourly increase in lactate were determined as the best combination of sensitivity and specificity for significant discrimination between patient outcomes. To ascertain the predictive ability of the optimal levels, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each optimal value were calculated, and the relative risks with the 95% confidence intervals (CIs) for a poor outcome are also reported. Similarly, additional subgroup analyses planned a priori included evaluating the predictive value of the initial lactate level and increase in lactate stratified by single- and 2-ventricle subjects, single- and 2-ventricle neonates (age <30 days), and risk adjustment for congenital heart surgery (RACHS-1) score.[15] Finally, after stratifying the cohort by the high- and low-risk lactate measurements, other clinical outcomes were compared using the chi-square test or Fisher's exact test, as appropriate, for the categorical variables and the Wilcoxon rank sum test for continuous variables. All analyses were performed using Statistical Analysis Systems, version 9.3 (SAS Institute, Cary, NC), with statistical significance set at $P < .05$ using 2-sided tests.

RESULTS

A total of 231 subjects were analyzed in the present study. Of these 231 subjects, 212 had good outcomes and 19 (8.2%) met ≥1 of the criteria for a composite poor outcome, including 9 (3.9%) who required post-CICU admission ECMO support, 7 who required renal dialysis (3.0%), and 11 (4.8%) who died (Figure 1). The interval between surgery and the occurrence of the composite poor outcome was a median of 1 day (IQR, 0-63). Specifically, the interval from surgery to a poor outcome was a median of 1 day (range, 0-2) for patients needing ECMO support, a median of 3 days (range, 2-15) for patients requiring renal dialysis, and a median of 24 days (range, 1-197) for the patients who died. Six additional subjects whose parents had agreed to the study were excluded from the analysis after requiring ECMO support in the operating room before the CICU admission.

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