Postoperative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: A cohort follow-up to 18 months

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Objectives: An observational cohort study was conducted in infants less than 6 weeks of age undergoing intracardiac surgery to examine the predictive value of serial postoperative lactate determination on survival and early childhood neurodevelopment.

Methods: A total of 85 infants with congenital heart disease underwent intracardiac surgery between 1996 and 1999. Differences in serial lactate concentrations after surgery among 3 outcome groups were compared. The predictive value of plasma lactate concentration on outcome (1) at discharge from initial hospitalization and (2) 18 to 24 months postnatal age was examined.

Results: Compared with survivors, the nonsurvivors had higher lactate concentrations on admission to the pediatric intensive care unit at day 1 peak and area under the curve of the lactate profile than those of adverse and intact survivors (all $P < .001$, analysis of variance). Significant differences in the time for lactate concentrations to return to 2 mmol/L or less during the first postoperative day were observed among the groups: nonsurvivors > adverse survivors > intact survivors. Lactate concentrations of less than 7 mmol/L on admission or less than 8 mmol/L at day 1 peak predicted survival with 82% sensitivity and 83% specificity, and positive and negative predictive values of 97% and 43%, respectively ($P < .001$, χ^2). Plasma lactate concentrations were associated with adverse outcome but had lower predictive values compared with that for nonsurvival.

Conclusions: Serial lactate determination accurately predicts survival and may help differentiate survivors with adverse outcome from those with intact neurodevelopment in early childhood.

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Over the past 2 decades, the perioperative care of infants with complex congenital heart disease has improved and led to decreased mortality.¹ Increasing attention is now being given to the outcome of infants surviving after intracardiac surgery.² Acute mortality during initial hospitalization usually relates to the perioperative severity of the illness and is associated with multiorgan failure.³ However, the determinants of developmental outcome of infants surviving intracardiac surgery are multifactorial, including brain injury before, during, and after surgery, as well as environmental factors such as the socioeconomic status of the family.⁴

Intraoperative risk factors, such as the deep hypothermic circulatory arrest time^{5,6} and neuroimaging⁷ and electrophysiologic^{5,8} findings, have been shown to correlate with mortality rates and neurodevelopmental morbidity after intracardiac surgery in infants. Recently, in a prospective study of young infants (<2 years of age) with complex congenital heart disease excluding hypoplastic left heart syndrome (HLHS) and other congenital anomalies, Limperopoulos and associates⁹ identified the following clinical characteristics that increase the risk for persistent developmental

deficits: preoperative and acute postoperative neurodevelopmental status, microcephaly, type of heart lesion, length of deep hypothermic circulatory arrest, age at operation, and days in the intensive care unit. Some of these factors, however, are observer-dependent or occur late in the course of initial hospitalization.

Plasma lactate is a conventional indicator of tissue hypoxia¹⁰ and has been widely used in the management of critically ill patients. Hyperlactatemia correlates with mortality in adults, children, and neonates.¹¹⁻¹⁴ After intracardiac surgery in young infants, the predictive value (PV) of lactate concentration on postoperative mortality is supported by some studies,¹⁵⁻¹⁸ whereas Hatherill,¹⁹ Munoz,²⁰ and their associates, both reported low positive PV (32%-45%) for mortality despite an optimal sensitivity and specificity of approximately 80%. Although the discrepancy may be related to developmental changes in lactate metabolism, a detailed examination of plasma lactate profile during the postoperative period and its relationship with the neurodevelopmental outcome in this population may help establish its value in patient management.

To date, limited information is available on the relationship between postoperative plasma lactate profile and the outcome of neonates undergoing intracardiac surgery and followed prospectively with comprehensive and standardized neurodevelopmental assessment. In our previous report on outcome predictors in a cohort of 85 infants, preliminary findings suggested plasma lactate as an independent predictor.²¹ Therefore, we investigated the PV of serial lactate determination on the mortality and neurodevelopment in early childhood of neonates with complex congenital heart disease who underwent intracardiac surgery within 6 weeks of age. We hypothesized that infants with persistently elevated plasma lactate concentrations had a higher likelihood of dying during the acute hospitalization period and had abnormal neurodevelopmental outcome in early childhood if they survived.

Patients and Methods

This study was approved by the Health Research Ethics Board of the University of Alberta, Edmonton, Alberta, and the institutional ethics committee of associated follow-up programs.

From September 1996 to August 1999, after informed consent, all infants with complex congenital heart disease who were admitted to the Stollery Children's Hospital and who underwent intracardiac surgery at the age of 6 weeks or less were prospectively included in a multicenter cohort study to examine predictors associated with outcome.²¹ During the 3-year study period, 85 consecutively admitted, eligible infants (68% were male, 81% were white) were enrolled in the study. Primary cardiac diagnoses included transposition of great arteries with or without ventricular septal defect (23, 27%), HLHS (26, 31%), total anomalous pulmonary venous drainage (6, 7%), truncus arteriosus (9, 10%), complex anomalies involving the aortic arch or mitral valve (16, 19%), and other complex cardiac lesion (5, 6%).

As part of the postoperative management of these sick infants, plasma lactate concentrations were measured on or soon after admission to the intensive care unit and frequently during the first 72 postoperative hours to assess tissue oxygenation. Any decision to withdraw or discontinue treatment was not based solely on plasma lactate concentration. Because this was a retrospective analysis of convenient sampling of lactate levels, patients who had normal lactate levels or died soon after admission had few lactate determinations. The blood samples were preserved on ice, if not run immediately, and sent for plasma lactate concentration assay immediately by enzymatic spectrometric methods (normal range: 0.5-2.0 mmol/L). For this study, serial plasma lactate concentrations of individual patients obtained during the entire postoperative period were plotted on individual time-scaled charts for subsequent calculations as appropriate.

Multidisciplinary assessments were performed at 18 to 24 months of age at the Neonatal and Infant Follow-up Clinic at the Glenrose Rehabilitation Hospital, Edmonton, Alberta (42%), or associated follow-up clinics of the Western Canadian Complex Pediatric Therapies Project (58%), with no knowledge of the clinical course of these infants except for the intracardiac surgery. The comprehensive assessment has been described.^{14,21} In brief, Mental Developmental Index and Performance Developmental Index were determined by the administration of Bayley Scales of Infant Development²² by certified examiners with experience in testing children with both normal and abnormal outcomes. Neurologic and developmental examinations were completed by a pediatrician experienced in neurodevelopmental follow-up. Behavioral hearing tests were completed in a sound booth by a certified clinical audiologist experienced in testing young children.

The following definitions were used in this study:

1. *Nonsurvivor* was defined as any infant who died during the initial hospitalization, regardless of cause.
2. *Adverse survivor* was defined as an infant who died after discharge from the hospital or who survived with motor or sensory disability or neurodevelopmental delay. *Disability* included the following: (1) cerebral palsy of all types or severity²³ that was diagnosed by a constellation of clinical neuromotor abnormalities at 18 to 24 months as agreed by 2 physicians (a neurodevelopmental pediatrician and pediatric neurologist/physiatrist); (2) legal blindness (corrected visual acuity of the better eye <20/200); and/or (3) hearing loss (sensorineural hearing of >40 dB in the better ear). *Neurodevelopmental delay* was defined as either Mental Developmental Index and/or Performance Developmental Index greater than 2 SD below the mean for normative data (<70) without disability.
3. *Intact survivor* was defined as a survivor free of disability and neurodevelopmental delay.
4. *Adverse outcome* referred to the combined group of nonsurvivors and adverse survivors.

The clinical characteristics of the 3 study groups (nonsurvivors, adverse and intact survivors) have been reported²¹ and are shown in Table 1.

Data Handling of Postoperative Plasma Lactate Profile

For this study, plasma lactate concentration on admission to the intensive care unit; peak postoperative concentration during hos-

TABLE 1. Demographic and clinical characteristics in 85 infants who underwent intracardiac surgery at 6 weeks of age or less (mean $\pm$ SD)

	Nonsurvivors	Adverse survivors	Intact survivors
N	14	28	43
Gestational age (wk)¶	38 $\pm$ 1	39 $\pm$ 2	40 $\pm$ 1
Birth weight (g)	3120 $\pm$ 550	3280 $\pm$ 750	3430 $\pm$ 530
Apgar score at 1 min	7 $\pm$ 1	7 $\pm$ 2	7 $\pm$ 2
Apgar score at 5 min	9 $\pm$ 1	8 $\pm$ 1	8 $\pm$ 1
Age at intracardiac surgery (d)	13 $\pm$ 12	11 $\pm$ 9	9 $\pm$ 9
Duration of CPB (min)¶	157 $\pm$ 82	105 $\pm$ 52*	97 $\pm$ 29*†
Duration of hypothermic arrest (min)¶	57 $\pm$ 19	34 $\pm$ 24*	25 $\pm$ 24*
Crossclamp time (min)	69 $\pm$ 21	56 $\pm$ 22	54 $\pm$ 20
Preoperative peak lactate (mmol/L)	3.9 $\pm$ 4.3	2.6 $\pm$ 1.8	2.7 $\pm$ 2.4
Duration of hospitalization (d)¶	30 $\pm$ 25	54 $\pm$ 46	22 $\pm$ 12

CPB, Cardiopulmonary bypass. * $P < .05$ versus nonsurvivors, † $P < .05$ versus adverse survivors (Scheffé, analysis of variance [ANOVA]). ¶These characteristics have been reported.²¹

pitalization, day 1 (D1 peak), days 2 to 5, and 6 days after intracardiac surgery; lactims; and area under the curve of the lactate profile during postoperative day 1 were compared. Lactime was defined as the time required for the plasma lactate concentration to decrease to 5 or 2 mmol/L or less. The area under the curve was determined from the lactate profile and expressed in mmol/L $\cdot$ h.

Statistical Analysis

Data are expressed as mean $\pm$ SD. Differences in the clinical and biochemical measurements between the 3 groups (nonsurvivors, adverse and intact survivors) were compared using 1-way analysis of variance (ANOVA) followed by Scheffé multiple comparison testing. To examine predictability of plasma lactate, concentrations of 4 to 10 mmol/L and 15 mmol/L were used, based on the available literature¹⁵⁻²⁰ and general consensus of a poor chance of survival, respectively. Their PVs for nonsurvival or adverse outcome were calculated and analyzed with Fisher's exact test. Comparison between 2 proportions was performed with the z test. Statistical software programs, SPSS version 10.07 for Windows (SPSS Inc, Chicago, Ill) and SigmaStat version 2.0 (Jandel Scientific Corp, San Rafael, Calif), were used. Statistical significance was set at P less than .05 except for post hoc Scheffé testing, which was set at P less than .10 as recommended.

Results

Among 85 patients enrolled, 14 infants (16%) died during the initial hospitalization after intracardiac surgery (4 on the operative day, 2 between postoperative days 2 and 5, and 8 after postoperative day 5). Among these, 4 received extracorporeal membrane oxygenation postoperatively. The causes of nonsurvival included multiple organ dysfunction syndrome (10, 71%) and acute hemodynamic decompensation (4, 29%). Four children with HLHS (3) and transposition of great arteries (1) died of cardiorespiratory failure before 18 months of age. The remaining 67 survivors received follow-up at 18 to 24 months of age. Of the study population, 28 children (33%) survived with adverse outcome including 4 late deaths and 24 with neurodevelopmental

disability (3) or delay (21). Forty-three children (51%) were considered intact survivors. The clinical characteristics of the 3 study groups were not different (Table 1).

Survivors had shorter cardiopulmonary bypass times and hypothermic arrest times than the nonsurvivors (Table 1). During the early postoperative period, they also had higher arterial pH than the nonsurvivors (7.36 ± 0.08 and 7.33 ± 0.07 of the intact and adverse survivors, respectively, vs 7.26 ± 0.13 of the nonsurvivors, $P < .05$, ANOVA),²¹ but the PAO_2 and base deficit were not different between groups (data not shown).

Plasma Lactate Profile of Infants Treated With Intracardiac Surgery

There were 8 ± 4 (1-22) lactate determinations during the first postoperative day with no differences between groups. Infants of the nonsurvivor group had significantly higher lactate concentrations on admission, at D1 peak, and during hospitalization (highest concentrations) when compared with the adverse and intact survivors, whose lactate concentrations were not different (Table 2). The lactate concentrations on days 2 to 5 and 6 days after intracardiac surgery were also higher in the nonsurvival group.²¹ Similar patterns were observed in the subgroup of infants without HLHS; for those with HLHS, nonsurvivors had significantly longer lactime for plasma lactate concentration of 2 mmol/L or less and higher peak lactate during hospitalization than those of intact survivors. The nonsurvivor group also had longer lactimes and greater area under the curve of the lactate profile during day 1 after intracardiac surgery than adverse and intact survivors ($P < .001$) (Table 2). Adverse survivors had a significantly longer lactime for plasma lactate concentration of 2 mmol/L or less than intact survivors (Table 2). Two nonsurvivors (14%) had lactate concentrations returned to 2 mmol/L or less within 24 hours

TABLE 2. Postoperative plasma lactate concentrations of infants who underwent intracardiac surgery at 6 weeks of age or less (mean $\pm$ SD)

	Nonsurvivors	Adverse survivors	Intact survivors
N	14	28	43
On admission (mmol/L)*	10.7 $\pm$ 4.9	6.3 $\pm$ 2.4	5.5 $\pm$ 2.6
Highest during day 1 (mmol/L)*,¶	14.2 $\pm$ 8.8	6.8 $\pm$ 3.4	6.2 $\pm$ 3.6
Highest during hospitalization (mmol/L)*	15.8 $\pm$ 8.9	7.9 $\pm$ 4.6	6.5 $\pm$ 3.7
Lactime to $\leq$ 5 mmol/L (h)*	11 $\pm$ 11	4 $\pm$ 4	3 $\pm$ 6
Lactime to $\leq$ 2 mmol/L (h)*,†	23 $\pm$ 9	16 $\pm$ 10	11 $\pm$ 9
AUC of day 1 (mmol/L $\cdot$ h)*	220 $\pm$ 200	80 $\pm$ 30	70 $\pm$ 50

AUC, Area under the curve. * $P < .05$ adverse or intact survivors versus nonsurvivors (Scheffé, analysis of variance [ANOVA]). † $P = .07$, adverse versus intact survivors (Scheffé, ANOVA). Definitions of nonsurvivors and adverse and intact survivors are described in the text. ¶These characteristics have been reported.²¹

postoperatively compared with 19 adverse survivors (68%) and 37 intact survivors (86%).

Prediction of Outcome Using Plasma Lactate

To investigate whether plasma lactate had a practical prognostic implication during the early postoperative period, we examined the PVs of plasma lactate concentrations on admission and at D1 peak. The PVs of lactate concentrations from 6 to 15 mmol/L, on admission and at D1 peak, on nonsurvival are shown in Table 3. The relationship between these plasma lactate concentrations and nonsurvival was significant (Fisher exact test). Increasing the cutoff concentration of plasma lactate decreases sensitivity and negative PV but increases specificity and positive PV. Plasma lactate concentrations of 15 mmol/L or greater on admission (but not at D1 peak) provided a 100% specificity and positive PV with poor sensitivity (Table 3). Optimal PVs were obtained with plasma lactate concentrations of 7 mmol/L or greater on admission or 8 mmol/L or greater at D1 peak (Table 4,

$P < .001$, Fisher's exact test) (Figure 1). Lactate concentrations of 7 mmol/L or greater on admission and 8 mmol/L or greater at D1 peak predicted nonsurvival with 83% sensitivity and 82% specificity, which was higher than the specificity with a lactate concentration of 7 mmol/L or greater on admission ($P = .07$, $\beta = 0.6$, z test). The correct prediction of outcome was 82%. Lactate concentrations of less than 7 mmol/L on admission or less than 8 mmol/L at D1 peak predicted survival with 82% sensitivity and 83% specificity, and positive and negative PVs of 97% and 43%, respectively.

Plasma lactate determination was also significantly related to adverse outcome (Table 4, Fisher's exact test). Lactate concentration of 4 mmol/L or greater on admission had a sensitivity or more than 80%, but low specificity, which was significantly improved with D1 peak lactate concentration of 6 mmol/L or greater ($P < .001$, z test). The use of either D1 peak lactate concentration of 6 mmol/L or greater or combined lactate concentrations of 4 mmol/L or

TABLE 3. Prediction of nonsurvival in 85 infants who underwent intracardiac surgery at 6 weeks of age or less by plasma lactate concentrations (6-15 mmol/L) on admission and at day 1 peak

	Sensitivity	Specificity	Positive PV	Negative PV	Accuracy
Admission					
≥ 6 mmol/L‡	92%	56%	26%	98%	61%
≥ 7 mmol/L‡	92%	69%	33%	98%	72%
≥ 8 mmol/L‡	67%	82%	38%	94%	77%
≥ 9 mmol/L‡	58%	90%	50%	93%	86%
≥ 10 mmol/L‡	50%	96%	57%	89%	94%
≥ 15 mmol/L‡	25%	100%	100%	89%	89%
D1 peak					
≥ 7 mmol/L‡	92%	63%	30%	98%	67%
≥ 8 mmol/L‡	83%	78%	38%	96%	78%
≥ 9 mmol/L‡	75%	79%	38%	95%	78%
≥ 10 mmol/L*	50%	83%	33%	91%	78%
≥ 11 mmol/L*	42%	86%	33%	90%	80%
≥ 15 mmol/L‡	33%	99%	80%	90%	89%

PV, Predictive value; D1, day 1. * $P < .05$, † $P < .01$, ‡ $P < .005$ as related to the outcome, Fisher's exact test.

TABLE 4. Predictive values of plasma lactate in 85 infants who underwent intracardiac surgery at 6 weeks of age or less

	Sensitivity	Specificity	Positive PV	Negative PV
Nonsurvival				
Admission ≥7 mmol/L*	92%	69%	33%	98%
D1 peak ≥8 mmol/L*	83%	78%	38%	96%
Admission ≥7 mmol/L and D1 peak ≥8 mmol/L*	83%	82%‡	43%§	97%
Adverse outcome				
Admission ≥4 mmol/L†	85%	35%¶	55%	71%
D1 peak ≥6 mmol/L*	73%	65%	66%	72%
Admission ≥4 mmol/L and D1 peak ≥6 mmol/L*	73%	67%	67%	73%

PV, Predictive value; D1, day 1. * $P < .001$, † $P < .05$ as related to the outcome, Fisher's exact test. ‡ $P < .05$, § $P < .01$, || $P < .001$ versus the corresponding PV for adverse outcome, z test. ¶ $P < .001$ versus the corresponding PV using both admission and D1 peak lactate concentrations, z test.

greater on admission and 6 mmol/L or greater at D1 peak had similar PVs. The sensitivity was lower than that of using lactate concentration on admission alone ($P = .08$, $\beta = 0.6$, z test). Compared with the PVs for nonsurvival, the specificity and positive and negative PVs were significantly lower for the prediction of adverse outcome (Table 3, z test). The accuracy was also lower for the prediction of adverse outcome (70%) than that of nonsurvival ($P = .10$, $\beta = 0.6$, z test).

Discussion

Our study, based on a structured comprehensive follow-up program, provides initial data supporting the PV of serial

plasma lactate determination in young infants undergoing intracardiac surgery at an age of 6 weeks or less. It has been suggested that neonates requiring intracardiac surgery are at a higher risk for neurodevelopmental disabilities than older children.⁹ Several studies have demonstrated an association between hyperlactatemia and mortality after intracardiac surgery in children.^{12,15-20} Our findings support the use of plasma lactate concentrations to predict early survival with an accuracy of more than 80%. Specifically, plasma lactate of less than 7 mmol/L on admission or less than 8 mmol/L at D1 peak predicts survival with a positive PV of 97% in contrast with the prediction of nonsurvival with a positive PV of only 43% for plasma lactate exceeding these levels. In addition, serial plasma lactate determination may help identify those survivors with neurodevelopmental disability or delay as having a longer lactime for the lactate concentration to decrease to 2 mmol/L or less during the first postoperative day than did the intact survivors. Plasma lactate measurement, which is readily available in all hospitals, has the potential to objectively provide predictive information on the outcome of these critically ill neonates during the early postoperative period.

The PV of plasma lactate on mortality has been extensively studied in critically ill adults, but less so in the pediatric population. Several studies confirmed the PV of hyperlactatemia in *selected* groups of neonates, including those with severe hypoxemia²⁴ or hypoxemic-ischemic encephalopathy,¹³ and after extracorporeal membrane oxygenation.¹⁴ Our results support the use of plasma lactate as an early predictor of outcome in a selected population of critically ill neonates and adds to the literature on predictors of mortality in neonates after intracardiac surgery.^{12,15-20} The nonsurvivors had higher plasma lactate on admission and at D1 peak after intracardiac surgery. Although similar patterns were observed in the subgroup of infants without HLHS and to a lesser extent for those with HLHS, our sample size was too small for further analysis of individual cardiac defects. As shown by the lactimes, nonsurvivors also had a slower rate of decline in plasma lactate postoperatively, which was also observed by Munoz and associ-

Figure 1. Plasma lactate concentrations on admission and at day 1 peak of 85 infants with complex congenital heart disease who underwent intracardiac surgery at 6 weeks of age or less. Lines of admission lactate of 7 mmol/L and day 1 peak lactate of 8 mmol/L are placed for reference. Circles, normal survivors; triangles, adverse survivors; diamonds, nonsurvivors.

ates²⁰ in 174 children undergoing operations for congenital heart disease. Munoz and colleagues²⁰ also noted that hyperlactatemia during cardiopulmonary bypass in 174 patients with intracardiac surgery was associated with postoperative mortality. Charpie and coworkers¹⁵ suggested that serial lactate determination might be an accurate predictor of death within 72 hours postoperatively or requirement for extracorporeal membrane oxygenation support in a prospective study of 46 infants who underwent complex neonatal cardiac surgery.

Siegel and colleagues¹² reported high PVs of lactate concentration in 41 children with intracardiac surgery and indicated that using an admission lactate concentration of greater than 4.2 mmol/L predicted postoperative deaths with a positive PV of 100%. In a study with results similar to ours, Hatherill and associates¹⁹ reported that an initial lactate concentration of greater than 6 mmol/L had poor positive PV (32%) for mortality in a prospective observational study of 99 young children aged 0.38 to 31 months. However, by using admission lactate of 7 mmol/L or greater, we reported higher sensitivity (vs 78%), lower specificity (vs 83%), and similar negative PV (vs 97%). Nonetheless, the overall accuracy of prediction is similar between studies at greater than 80%. The “poor” positive PV may undermine the usefulness of plasma lactate concentration to identify nonsurvivors because of other confounding issues and advances in surgical and perioperative care, which may explain the different and apparent contrasting observations between studies and surgical populations. Indeed, the positive PV value remains less than 100% despite lactate concentrations 15 mmol/L or greater, which may indicate a dismal chance of survival (Table 3). *With recognition of this weakness, plasma lactate concentration may predict which infants survive the immediate postoperative course after intracardiac surgery. Lactate concentrations of 7 mmol/L or less on admission or 8 mmol/L or less at D1 peak predicts survival accurately, with a sensitivity of 82% and a positive PV of 97% as shown in our study.* Furthermore, although there is a wide range of plasma lactate concentrations used in the prediction (4–7 mmol/L),^{12,15–20} the lactate concentration used in our study is consistent with others reporting a mortality of 10% or more.^{18,19} Indeed, Munoz and coworkers²⁰ observed an association between the complexity of intracardiac surgery and the lactate concentration. Therefore, a heterogeneous population of infants with intracardiac surgery may explain the variation in the lactate concentrations used in prediction that may need modification according to institutional experience.

Predicting the neurodevelopmental outcome in critically ill neonates is difficult. From our previous report, almost 40% of the total variance of the long-term outcome remained unaccounted for by known risk factors identified during the preoperative, intraoperative, and postoperative

periods.²¹ Nonetheless, various risk factors including the deep hypothermic circulatory arrest time,⁶ neuroimaging,⁷ and electrophysiologic⁸ findings, and certain clinical features⁹ have been shown to be associated with subsequent neurodevelopmental outcome after intracardiac surgery. The current study is the first we are aware of to examine the PV of plasma lactate on neurodevelopmental outcome in early childhood after intracardiac surgery. This provides an objective assessment that is available early in the course after intracardiac surgery. However, consistent with our previous observation in those neonates requiring extracorporeal membrane oxygenation,¹⁴ the PVs for adverse outcome are lower than those for early mortality. Although mortality is usually related to the extent of organ failure or irreversible dysfunction of multiple organs, which may be reflected in the plasma lactate concentration, the plasma lactate concentration may not indicate the severity of organ-specific hypoxia. Therefore, plasma lactate determination has a lower predictability of the degree of cerebral hypoxic-ischemic insult in patients with nonlethal systemic hypoxemia. We suggest that serial lactate determination including a detailed examination of the lactate profile may help predict adverse outcome soon after admission to the intensive care unit with an accuracy of 70%. Indeed, the use of lactate concentrations on postoperative days 2 to 5 after cardiac surgery significantly improved the prediction of neurodevelopmental outcome of these patients.²¹

In this study, we used the definitions of lactime and area under the curve for the lactate profile in similar fashion to the report by Bakker and coworkers.²⁴ Bakker's group used the lactime for plasma lactate concentration to decrease to 2 mmol/L or less. They also calculated the theoretical area under the curve assuming a linear regression of the lactate concentration in contrast with our direct measurement using the lactate profile charted individually. In this study, we provided a detailed examination of the role of lactime and a more accurate estimation of the area under the curve of the lactate profile to examine the PV of serial lactate determination. Furthermore, it is important to study the PV of lactate concentrations in neonates rather than in a heterogeneous population of different developmental ages. Lactate metabolism is influenced by developmental changes including maturation of liver enzymes involved in the glucose hexaphosphate shunt. This may explain the high lactate concentrations during the immediate perinatal period that decrease with increasing age.²⁵ Indeed, because of these developmental changes, a careful interpretation of the lactate concentration profile rather than individual values is warranted, as suggested by Saugstad.²⁶

Conclusion

In addition to its conventional use as a biochemical marker of tissue oxygenation for the management of critically ill

neonates, plasma lactate can also be used as an early outcome predictor, particularly of survival, for neonates with complex congenital heart disease who undergo intracardiac surgery within 6 weeks of age. Further multicenter studies are required to confirm our observations and to examine the value of plasma lactate in the decision-making process.

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References

- McElhinney DB, Wernovsky G. Outcomes of neonates with congenital heart disease. *Curr Opin Pediatr*. 2001;13:104-10.
- Ferry PC. Neurologic sequelae of cardiac surgery in children. *Am J Dis Child*. 1990;144:369-73.
- Seghaye MC, Engelhardt W, Grabitz RG, Faymonville ME, Hornchen H, Messmer BJ, et al. Multiple system organ failure after open heart surgery in infants and children. *Thorac Cardiovasc Surg*. 1993;41:49-53.
- Bloom AA, Wright JA, Morris RD, Campbell RM, Krawiecki NS. Additive impact of in-hospital cardiac arrest on the functioning of children with heart disease. *Pediatrics*. 1997;99:390-8.
- Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban CK, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med*. 1993;329:1057-64.
- Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N Engl J Med*. 1995;334:549-55.
- Ashwal S, Holshouser BA, Hindshaw DB, Schell RM, Bailey L. Proton magnetic resonance spectroscopy in the evaluation of children with congenital heart disease and acute central nervous system injury. *J Thorac Cardiovasc Surg*. 1996;112:403-14.
- Rosenblatt B. Monitoring the central nervous system in children with congenital heart defects: clinical neurophysiological techniques. *Semin Pediatr Neurol*. 1999;6:27-31.
- Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C, et al. Predictor of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr*. 2002;141:51-8.
- Perret C, Enrico JF. Lactate in acute circulatory failure. In: Bossart H, Perret C, editors. *Lactate in acute conditions*. New York: S Karger AG; 1979. p. 69-82.
- Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med*. 1983;11:449-51.
- Siegel LB, Dalton HJ, Hertzog JH, Hopkins RA, Hannan RL, Hauser GJ. Initial postoperative serum lactate levels predict survival in children after open heart surgery. *Intensive Care Med*. 1996; 22:1418-23.
- da Silva S, Hennebert N, Denis R, Wayenberg JL. Clinical value of a single postnatal lactate measurement after intrapartum asphyxia. *Acta Paediatr*. 2000;89:320-3.
- Cheung P-Y, Etches PC, Weardon M, Reynolds A, Finer NN, Robertson CMT. The use of plasma lactate to predict early mortality and adverse outcome after neonatal extracorporeal membrane oxygenation: a prospective cohort in early childhood. *Crit Care Med*. 2002;30:2135-9.
- Charpie JR, Dekeon MK, Goldberg CS, Mosca RS, Bove EL, Kulik TJ. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*. 2000;120:73-80.
- Duke T, Butt W, South M, Karl TR. Early markers of major adverse events in children after cardiac operations. *J Thorac Cardiovasc Surg*. 1997;114:1042-52.
- Shemie SD. Serum lactate predicts postoperative complications after pediatric cardiac surgery [abstract]. *Pediatr Res*. 1996;39:54A.
- Cheifetz IM, Kern FH, Schulman SR, Greeley WJ, Ungerleider RM, Meliones JN. Serum lactates correlate with mortality after operations for complex congenital heart disease. *Ann Thorac Surg*. 1997;64:735-8.
- Hatherill M, Sajjanhar T, Tibby SM, Champion MP, Anderson D, Marsh MJ, et al. Serum lactate as a predictor of mortality after paediatric cardiac surgery. *Arch Dis Child*. 1997;77:235-8.
- Munoz R, Laussen PC, Palacio G, Zienko L, Piercey G, Wessel DL. Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: an early indicator of morbidity and mortality. *J Thorac Cardiovasc Surg*. 2000;119:155-62.
- Robertson CMT, Joffe A, Sauve R, Rebecka IM, Phillipos EZ, Dyck JD, et al. Outcomes from an interprovincial program of newborn open heart surgery. *J Pediatr*. 2004;144:86-92.
- Bayley N. Bayley Scales of Infant Development, second edition manual. (Dr. James Gyarke, BSID-II project director.) San Antonio (TX): The Psychological Corporation, Harcourt Brace & Co; 1993.
- Bax MCO. Terminology and classification of cerebral palsy. *Dev Med Child Neurol*. 1964;6:259-67.
- Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial Blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg*. 1996;171:221-6.
- Jung D, Lun A, Zinsmeyer J, Grauel EL, Gross J. The concentration of hypoxanthine and lactate in the blood of healthy and hypoxic newborns. *J Perinat Med*. 1985;13:43-50.
- Saugstad OD. Is lactate a reliable indicator of tissue hypoxia in the neonatal period? *Acta Paediatr*. 2002;91:17-9.