Frequency, Risk Factors, and Outcome of Hyperlactatemia After Cardiac Surgery*

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Study objective: To determine the respective frequencies, risk factors, and outcomes of no hyperlactatemia (NHL), immediate hyperlactatemia (IHL), or late hyperlactatemia (LHL) > 3 mmol/L after cardiac surgery.

Design: Prospective and observational study.

Setting: Cardiac surgery ICU in a 130-bed private community nonteaching hospital.

Patients: Consecutive patients (n = 325) undergoing cardiopulmonary bypass (CPB) for cardiac surgery.

Intervention: None.

Measurements: Arterial blood gas levels and lactate concentrations were measured at ICU admission, 4 h after surgery, between 6 h and 16 h after surgery, and on day 1.

Main results: Sixty-seven patients (20.6%) had an IHL on ICU admission, and 56 patients (17.2%) acquired LHL during their ICU stay. ICU mortality was 1.5% for NHL, 3.6% for LHL, and 14.9% for IHL groups (p < 0.0001). The three groups differed significantly for elective surgery, type of operation, CPB duration, intraoperative mean arterial pressure, and intraoperative and postoperative use of vasopressor. Independent risk factors for IHL were nonelective surgery, CPB duration, and intraoperative use of vasopressor. Logistic regression identified hyperglycemia and epinephrine therapy for LHL as postoperative risk factors. Receiver operating characteristic curves showed that IHL more accurately predicted ICU mortality than LHL.

Conclusions: Hyperlactatemia is common after cardiac surgery. A lactate threshold of 3 mmol/L at ICU admission is able to identify a population at risk of morbidity and mortality after cardiac surgery.

Key words: cardiac surgery; lactate acidosis; outcome; risk factor

Abbreviations: ALT = alanine aminotransferase; AUC = area under the receiver operating characteristic curve; CI = confidence interval; CPB = coronary artery bypass; IHL = immediate hyperlactatemia; LHL = late hyperlactatemia; MAP = mean arterial pressure; MV = mechanical ventilation; NHL = no hyperlactatemia; OR = odds ratio; ROC = receiver operator characteristic

Although hyperlactatemia is a common metabolic disturbance after cardiac surgery,1 its physiopathogenesis remains controversial.2 It is classically associated with tissue hypoxia (type A), but data3 suggest that type B (absence of tissue hypoxia) may be involved after cardiac surgery. In particular, metabolic effects of epinephrine are being also debated.3–6 Hyperlactatemia associated with metabolic acidosis is a major predictor of mortality of patients with sepsis or after cardiovascular shock,7,8 and the evolution of the lactate concentration after therapeutic management is able to predict more accurately the outcome.9 The aims of this study were to evaluate the frequency of a moderate increase of arterial lactate concentration > 3 mmol/L after normothermic cardiopulmonary bypass (CPB), to determine whether no hyperlactatemia (NHL), immediate (IHL) at ICU admission, or late hyperlactatemia (LHL)
during the ICU stay was associated with a different ICU outcome, and whether these populations shared the same risk factors for hyperlactatemia.

Materials and Methods

Patient Selection

We prospectively studied 325 unselected, consecutive patients undergoing cardiac surgery with normothermic CPB during a 6-month period. Patients with off-pump coronary artery bypass were not included in the study (n = 26).

Hyperlactatemia was defined as an arterial lactate concentration > 3 mmol/L. Patients were studied prospectively and classified according to their NHL, IHL, or LHL status. Because of the type of the data collected and the observational design of the study with normal management that included sequential lactate measurements, institutional review board approval was not required at our institution.

Surgery-Related Details

All surgical procedures were performed by two surgeons (A.L. and P.N.). Anesthesia techniques and medications were similar for all patients. Anesthesia was induced and maintained using a combination of sufentanil, propofol, or midazolam, and neuromuscular paralytic agent. Most patients received an inhaled anesthetic (sevoflurane). Standard median sternotomy and arteriovenous cannulation were performed for CPB. Body temperature was maintained between 34°C and 37°C. Warm blood cardioplegia was usually delivered retrograde via the coronary sinus or intermittent arteriograph. The bypass pump was primed with a combination of lactated Ringer solution and Elohes (Fresenius Kabi; Louviers, France). Nonpulsatile blood flow was calculated as a function of theoretical cardiac output and adapted to maintain a venous saturation of > 60%. Norepinephrine was administered intermittently to maintain a perfusion pressure > 50 mm Hg. Aprotinin was administered to 90% of the patients. All patients were retransfused with lost blood (Medtronics France; Boulogne-Billancourt, France). A pulmonary catheter was inserted preoperatively into 92 patients, and placement was verified by chest radiography on admission to the ICU. All patients were sent to the ICU postoperatively.

Data Collection

For each patient, the following information was recorded preoperatively: age; sex; obesity, defined as body mass index ≥ 30; presence of arterial hypertension; diabetes; current smoking; echocardiographic or angiographic left ventricular ejection fraction ≥ 60%; elective surgery (programmed surgery); and type of operation. We noted the following intraoperative variables: CPB and aortic cross-clamp duration; average blood flow during CPB; hemodynamic instability, defined as mean arterial pressure (MAP) on pump ≤ 50 mm Hg; and use of vasopressor. During the first 24 h after surgery, in the ICU, we recorded the following: prolonged MAP < 70 mm Hg (≥ 30 min); fluid resuscitation; use of vasopressor > 3 h; type of vasopressor; hyperglycemia, defined as two consecutive blood glucose concentrations ≥ 11 mmol/L; and alanine aminotransferase (ALT) [normal value ≤ 50 IU/L] at ICU admission and on day 1.

Fluid resuscitation was obtained with crystalloid solution and/or gelatin. Vasopressors were used when hypotension (MAP < 70 mm Hg) proved unresponsive to fluid infusions at the discretion of intensivist.

Mechanical ventilation (MV) duration, ICU length of stay, postsurgical ICU and hospital length of stay, and hospital mortality were also collected. We recorded the following major postoperative complications: myocardial infarction documented by an elevation of troponin I associated with a new Q wave in two adjacent derivations, low cardiac output, neurologic complications (confusion, documented focal, or overall deficit), and infections (pneumonia, mediastinitis, catheter-related infection, or bacteremia) using Centers for Disease Control and Prevention (Atlanta, GA) definitions, and acute renal insufficiency (twice preoperative creatinine or postoperative hemofiltration).

Specific Measurements

Arterial and mixed venous blood gas analyses and arterial lactate concentrations (normal lactate value ≤ 2 mmol/L) were performed using a commercial blood gas analyzer (Rapidlab 864; Chiron Diagnostics, Bayer; Leverkusen, Germany).

Cardiac output was measured using the thermodilution technique, and recorded values represent the average of at least three measurements. All flow and resistance values were corrected for body surface area. MAP was obtained via the radial artery catheter inserted preoperatively. For all patients, blood samples were obtained and hemodynamic variables systematically determined at admission to the ICU, at the fourth postoperative hour, and on day 1 postoperatively. A single lactate concentration was also determined between 6 h and 16 h postoperatively.

Statistical Analyses

Values are expressed as number of patients (percentage) or mean ± 1 SD. The associations between IHL or LHL and potential risk factors identified by univariate analysis were assessed with either the Fisher exact test or Kruskal-Wallis test and Mann-Whitney test, as appropriate. For each time point, analysis of variance was performed among the three different groups to compare pH values, lactate concentrations, and base excesses using an a posteriori Fisher test. A p value ≤ 0.05 was considered to be statistically significant. All tests were two tailed. Logistic regression multivariate analysis was performed separately for IHL and LHL, including preoperative and intraoperative factors (IHL) and preoperative, intraoperative, and postoperative factors (LHL) associated with p values ≤ 0.05 according to our univariate analysis. Odds ratios (OR) and their 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC) was determined to assess the ability of the lactate concentration measured at ICU admission or during the ICU stay to predict ICU mortality. An AUC of 1 would signify a 100% accuracy predicting death, and an AUC of 0.5 would indicate a completely random event. Sensitivity, specificity, negative predictive value, and positive predictive value to predict ICU mortality were calculated using a lactate threshold of > 3 mmol/L at ICU admission or during the ICU stay. Statistical analyses were performed with Statview version 5.1 (SAS Institute; Cary, NC) and SPSS version 11.0 (SPSS; Chicago, IL).

Results

Demographic characteristics of the 325 patients included in this study are presented in Table 1. IHL was found in 67 patients (20.6%), and 56 patients (17.2%) acquired LHL during their ICU stay. The three groups had similar preoperative characteristics, except for the frequencies of elective surgery and the type of operation.
Intraoperative Course

Surgery was more complicated for IHL than NHL and LHL patients, as assessed by the longest CPB duration and the more frequent intraoperative administration of vasopressor (Table 2). Vasopressor use was more common in the IHL and LHL patients because of their hemodynamic instability.

Postoperative Lactate Concentration and Metabolic Parameters

Evolution of lactate concentrations, pH values, and base excess during the first 24 postoperative h are illustrated in Figure 1. For IHL and LHL patients, elevated lactate concentrations were associated with metabolic acidosis. On day 1, IHL and LHL patients had comparable lactate concentrations, which remained significantly higher than those of NHL patients. Without sodium bicarbonate injection, all arterial blood gas parameters were normal for the three groups except for base excess.

ICU Characteristics

Postoperative episodes of hypotension and hyperglycemia were more frequent for IHL and LHL than NHL patients, as were epinephrine, norepinephrine and dobutamine use (Table 2). The percentages of IHL and LHL patients unresponsive to fluid challenge were comparable but significantly higher than for patients with NHL. All invasive hemodynamic values (data not shown) and ALT concentrations at ICU admission and on day 1 were similar for the three groups.

Risk Factors Associated With Hyperlactatemia

Independent risk factors associated with an IHL identified by logistic regression were as follows: nonelective surgery (OR, 6.6; 95% CI, 2.8 to 15.6), CPB duration (per minute) [OR, 1.02; 95% CI, 1.01 to 1.03], and intraoperative vasopressor (OR, 2.7; 95% CI, 1.2 to 5.9). For LHL patients, multivariate analysis retained two independent risk factors: postoperative epinephrine administration (OR, 6.0; 95% CI, 2.2 to 16.4) and postoperative hyperglycemia (OR, 4.4; 95% CI, 2.2 to 8.9).

Postoperative Course

The ICU mortality rate differed significantly among the three groups: 1.5% for NHL, 14.9% for IHL, and 3.6% for LHL (p < 0.0001) and between IHL and LHL groups (p = 0.03). Duration of MV, ICU, and postoperative lengths of stay were similar for patients acquiring hyperlactatemia at any time but significantly longer than those who did not (Table 2). Major postoperative complications occurred significantly more frequently for IHL and LHL patients.

Prediction of ICU Mortality Based on Lactate Concentration

The lactate value at ICU admission was the best predictor of ICU mortality (AUC, 0.84; 95% CI, 0.73 to 0.95), as compared to lactatemia measured during the ICU stay (AUC, 0.72; 95% CI, 0.57 to 0.88) [Fig 2]. Using the a priori threshold of 3 mmol/L, sensitivity for ICU mortality on ICU admission was...
Our observations suggest that hyperlactatemia occurs frequently after normothermic cardiac surgery. A threshold of 3 mmol/L at ICU admission enable us to identify patients with a poorer outcome and a higher risk of mortality. Pertinently, development of lactatemia > 3 mmol/L during the ICU stay was not associated with a poorer outcome.

Hyperlactatemia observed in our study was mostly the consequence of excess lactate production as previously described after cardiac surgery. Although a reduction of hepatic lactate clearance might have contributed, it has been documented only for patients with severe liver dysfunction, and no evidence of impaired liver function was detected in our patients, as illustrated by the comparable ALT values at ICU admission and on day 1 for the three groups.

The need for nonelective surgery was sixfold higher for patients with IHL. Urgent or emergency surgery is usually performed for patients with unstable hemodynamics. Therefore, we can hypothesize that the preoperative lactate values of some patients might have already been abnormal. Unfortunately, the lactate concentration was not measured preoperatively in our study. Prolonged CPB duration was also associated with IHL. Nonpulsatile CPB has also been associated with regional hypoperfusion, which has been incriminated in postoperative hyperlactatemia. Intraoperative vasopressor use was also an independent risk factor of IHL and reflects intraoperative hemodynamic instability, and difficulty to wean the patient off CPB could potentially be responsible for an intraoperative oxygen debt.

Postoperative epinephrine administration and hyperglycemia were independent risk factors of LHL. The authors of some clinical studies argued for epinephrine-induced hyperlactatemia. After cardiac surgery, epinephrine and hyperglycemia were identified by Raper et al as factors frequently associated with a lactate concentration ≥ 5 mmol/L, but no statistical analysis was performed. β2-Agonists are well known to induce severe lactic acidosis in patients with acute asthma, and epinephrine has a powerful β2 mimetic activity responsible for increased glycolysis, gluconeogenesis, and lipolysis. Increased intracellular concentrations of the free fatty acids inhibit conversion of pyruvate to acetyl-coenzyme A, leading to increased lactic acid production. Moreover, stimulation of β-adrenergic receptors raises the plasma glucose concentration, thereby increasing the substrate for glucoysis. Post-
operative hyperglycemia was a powerful independent risk factor associated with LHL and emphasizes the potential role of epinephrine to trigger the onset of hyperlactatemia. Hyperglycemia is frequently associated with normothermic CPB and per se may induce hyperlactatemia. Enhanced endogenous glucose levels have been described in cardiac surgery patients with normal hemodynamics and attributed to endogenous secretion of stress hormone and cytokine leading to insulin resistance. Chioléro et al demonstrated that after cardiac surgery, hyperglycemia and increased nonoxidative glucose availability may contribute significantly to hyperlactatemia in patients with cardiogenic shock.

Although the lactate concentration is a good marker of disease severity for ICU patients, its prognostic value after cardiac surgery has not been clearly demonstrated. Mild hyperlactatemia is usually considered to be benign. Our findings indicate that a mild increase of lactate concentration on ICU admission (>3 mmol/L) was able to identify patients early with a poorer outcome: higher morbidity and ICU mortality rates. However, patients who subsequently acquired hyperlactatemia in the ICU had higher morbidity and ICU mortality comparable to that of patients with NHL.

We prospectively tested a mildly elevated lactate level (3 mmol/L), which is 50% higher than the upper normal limit in our laboratory. Analysis of ROC curves of lactate concentration to predict ICU mortality showed that this arbitrary value was the best compromise of sensitivity and specificity. A higher value (eg, 5 mmol/L) would have slightly increased the specificity but at the expense of a sharp loss of sensitivity. When the lactate concentration was measured also influenced prediction of ICU mortality. Detection of IHL was the best predictor of ICU mortality as compared to later determinations.

Some of our results might contribute to modifying the management of cardiac surgery. Hemodynamic stabilization before CPB, in particular for nonelective surgery, might lower or prevent IHL with, for example, more frequent use of intra-aortic balloon pump support for high-risk patients. Limiting on-pump hypotension would avoid potential intraoperative visceral oxygen debt. Improvement of myocardial protection would facilitate weaning from CPB and prevent or attenuate postoperative low cardiac output. An aggressive strategy of monitoring postoperative hyperglycemia, even for nondiabetic patients, and treating it with continuous IV insulin therapy should improve the prognosis. In addition, first-line

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**Figure 1.** Lactate concentration, base excess, and pH, expressed as means ± SEM, at the times indicated in patients with NHL (black squares), IHL (black circles), and LHL (white circles).

* *p < 0.05 vs NHL group. † *p < 0.05 between IHL and LHL groups. H0 = admission to the ICU; H4 = 4 h after surgery; H6–16 = 6 to 16 h after surgery.

**Figure 2.** ROC curves of lactate values at ICU admission (solid line) and during ICU stay (dashed line) for ICU mortality. Sensitivity and 1—specificity for 3 mmol/L (black squares) and 5 mmol/L (black circles) of lactate are shown.
Epinephrine therapy should be re-evaluated, and the combination of norepinephrine and dobutamine might be administered to hypotensive patients with preserved left ventricular function but unresponsive to fluid management.\textsuperscript{6,21}

**Conclusion**

Hyperlactatemia is frequent after cardiac surgery. Based on our analyses, postoperative measurement of lactatemia appears to be clinically useful. A threshold of 3 mmol/L at ICU admission was able to identify a subpopulation of patients at higher postoperative risk. Sequential determinations identified patients at higher risk for major complication and thus the need for closer surveillance of their therapeutic responses and their metabolic consequences. Further studies are needed to determine whether correction of some risk factors could control or prevent this metabolic disturbance and thereby improve prognosis.

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**References**


