J Anesth (2012) 26:174–178
DOI 10.1007/s00540-011-1287-0

ORIGINAL ARTICLE

The impact of hyperlactatemia on postoperative outcome after adult cardiac surgery

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Received: 20 April 2011 / Accepted: 31 October 2011 / Published online: 24 November 2011

Abstract
Purpose To evaluate the value of blood lactate value in predicting postoperative mortality (primary outcome), duration of ventilation, and length of stay in an intensive care unit (ICU) and hospital (secondary outcomes).
Methods We performed a prospective observation study on 1,820 consecutive patients undergoing open heart surgery in a tertiary university medical center. Blood lactate levels were obtained from patients on admission to the cardiac surgical ICU and measured serially.
Results All patients were divided into three groups according to their maximum blood lactate levels: group I (normolactatemia, lactate $\leq$2.2 mmol/l), 332 patients; group II (mild hyperlactatemia, lactate 2.2–4.1 mmol/l), 1,054 patients; and group III (severe hyperlactatemia, lactate $\geq$4.4 mmol/l), 434 patients. Maximum blood lactate levels $\geq$4.4 mmol/l during the first 10 h post admission were associated with prolonged ventilation time, longer ICU stay, and increased mortality ($P < 0.001$).
Conclusions Hyperlactatemia is common after cardiac surgery. Maximal lactate threshold $\geq$4.4 mmol/l in the first 10 h after operation accurately predicts postoperative mortality.

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Keywords Lactate · Postoperative care · Cardiac anesthesia

Introduction

Hyperlactatemia, a well-recognized marker of hypoperfusion, has been associated with mortality in various clinical settings and is a common metabolic disturbance following cardiac surgery. Postoperative blood lactate levels are associated with outcome after both adult [1, 2] and pediatric cardiac surgery [3, 4]. Postcardiac surgery outcome is determined by the preoperative status of the patient, as well as by technical factors in the operating room and intensive care unit (ICU). The most common methods of preoperative risk stratification are clinical scoring systems such as EuroSCORE [5] and Parsonnet [6] score. However, morbidity and mortality are also influenced by surgical and anesthetic techniques, including time on cardiopulmonary bypass (CPB), completeness of revascularization, efficacy of myocardial protection, hemodynamic management and unforeseen events in the operating room. Patient prognosis upon arrival at the ICU may differ from the preoperative prognosis. We hypothesized that hyperlactatemia after surgery may be connected with intraoperative problems, and therefore decided to evaluate the impact of early postoperative lactate levels on patient outcome.

The aim of our study was to evaluate whether postoperative blood lactate levels are associated with mortality, ventilation time, and prolonged ICU and hospital stay.

Materials and methods

This prospective observational study was approved by the local ethics committee and received a waiver for informed

consent. All patients who underwent cardiac surgery during 36 months between 1 August 2009 and 31 July 2011 at our tertiary-care, university-affiliated medical center were enrolled into the study.

Patients undergoing off-pump cardiac surgery and patients with previous liver disease were excluded from the study.

All 1,820 study patients received a standard anesthetic protocol: 5–10 mg diazepam was used for premedication, and anesthesia was induced with 10–15 μg/kg fentanyl and 0.01–0.02 mg/kg midazolam; 0.1 mg/kg pancuronium was given to facilitate endotracheal intubation. The lungs were ventilated with an oxygen/air mixture to maintain normocapnia. Anesthesia was maintained with isoflurane, fentanyl, and midazolam. The total fentanyl and midazolam doses were 25.8 ± 12.9 μg/kg and 0.02 ± 0.03 mg/kg, respectively. Monitoring included a five-lead electrocardiogram, pulse oximetry, nasal temperature, invasive arterial pressure, and central venous pressure. A pulmonary artery catheter was also used in patients with heart failure or pulmonary hypertension. All patients undergoing valve procedures were assessed by transesophageal echocardiography.

Before initializing CPB, systemic heparinization was accomplished with a heparin dose of 400 U/kg. Additional heparin was administered during CPB to maintain an activated coagulation time of >480 s. CPB was maintained at a cardiac index of 2.4 l/min/m^2 with a Sarns heart–lung roller pump (Terumo CV Systems, Ann Arbor, MI, USA). Only the membrane oxygenator (Jostra-Bentley, Irvine, CA, USA) was heparin coated; circuit tubing and arterial filter (Jostra-Bentley) were without heparin. The pump prime consisted of 1,000 ml lactated Ringer's solution and 100 ml 20% mannitol, to which 10,000 U heparin was added. The mean arterial pressure was maintained between 60 and 80 mmHg using boluses of phenylephrine as required. Serum glucose levels were controlled with intermittent administration of insulin. Hematocrit was maintained at 22% with the administration of packed red blood cells as necessary. Epsilon-aminocaproic acid was administered in doses of 50–60 mg/kg to all patients. Cardiac arrest was achieved by anterograde or retrograde blood cardioplegia. Topical cooling was not used, and core temperature was around 34.5°–35°C. Before discontinuation of CPB, patients were warmed to 37°C, and returned to the cardiothoracic ICU while still intubated, where they were managed by an attending intensivist or surgical fellow.

Standard postoperative care consisted of mechanical ventilation in the assist-control mode at 8–10 ml/kg, 10–12 breaths/min, positive end-expiratory pressure of 4–5 cmH_2O; warm air heaters maintained normothermia. Sedation was provided with propofol in a dose of 0.5–1.0 mg/kg and analgesia with morphine boluses as required. Cardioactive drugs such as epinephrine, norepinephrine, dobutamine, or milrinone were administered according to the hemodynamic status of the patient. As part of postoperative management, blood lactate concentrations were measured immediately after admission to the ICU and every 1–3 h thereafter during the first 24 postoperative h, or up to ICU discharge, if patients were released early from the ICU. Arterial blood gas analyses and arterial lactate concentrations (normal lactate value, 2.2 mmol/l) were performed using a blood gas analyzer (Rapidlab 864; Chiron Diagnostics, Bayer, Leverkusen, Germany).

Weaning from the ventilator was commenced in the presence of hemodynamic stability (without or decreasing use of cardioactive drugs), absence of significant bleeding (100 ml/h), absence of significant arrhythmias, adequate urine output (1 ml/kg/h), and oxygen saturation of 95% with FiO_2 0.50.

Data collection

The following perioperative variables were obtained: sex, presence of congestive heart failure [New York Heart Association (NYHA) class III–IV], need for intraaortic balloon pump, presence of diabetes mellitus, presence of chronic obstructive pulmonary disease, presence of renal failure, left ventricular function, priority of surgery (elective or urgent), type of surgery, and duration of cross-clamping and CPB. Renal failure was defined as creatinine level >1.4 mg/dl. Postoperative variables included the duration of mechanical ventilation, duration of initial ICU stay, volume of bleeding, need for revision, inotropic support (epinephrine, norepinephrine, dobutamine) during the initial 24-h period, postoperative renal failure, and hospital mortality.

Statistical analysis

Values are expressed as number of patients (percentage) or mean ± 1 SD. Numeric variables were analyzed with analysis of variance (ANOVA) and post hoc tests. We compared preoperative, operative, and postoperative parameters. Analysis was performed for each parameter in each of the three groups, and patients were divided by their peak postoperative lactate values. Following, we performed uni- and multivariate analyses based on the Cox proportional hazards regressions model. The univariate parameters with $P < 0.05$ were used in the multivariate analyses using backward selection. The variables were tested for interaction and the assumption for proportional hazards was verified. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 16.0 (SPSS, Chicago, IL, USA).

Results

The study comprised 1,820 consecutive patients undergoing open heart surgery. Analysis of postoperative lactate values revealed two major patterns: 1,488 (81.8%) patients with elevated postoperative lactate levels and 332 (18.2%) patients demonstrating lactate levels within normal range. Postoperative peak lactate levels were seen after 3.36 ± 3.13 h; 7.34 ± 6.56 h elapsed before lactate values returned to within normal range after reaching peak levels.

All patients were divided into three groups according to peak blood lactate levels: group I (normolactatemia, lactate ≤2.2 mmol/l), 332 patients; group II (mild hyperlactatemia, lactate 2.21–4.4 mmol/l, 1,054 patients; and group III (severe hyperlactatemia, lactate ≥4.4 mmol/l), 434 patients. Preoperative and intraoperative data are presented in Table 1. Postoperative data are presented in Table 2. There were no significant statistical differences between the groups in the following parameters: diabetes, chronic obstructive pulmonary disease, number of active smokers, preoperative functional capacity as average and in each NYHA class, preoperative renal failure, priority for surgery (elective, during hospitalization, urgent, or emergent) and hospital stay (days), during the postoperative period.

There was a significant statistical difference in the following parameters: sex, logistic and standard EuroSCORE, type of surgery, cardiopulmonary bypass time (min), cross-clamp time (min), bleeding (ml), use of β-agonist (epinephrine, norepinephrine, dobutamine), postoperative renal failure, ICU length of stay (days), ventilation time (h), and hospital mortality rate between groups I and II compared with group III. Overall, postoperative mortality was 2.36% (43 patients). At proportional hazards regressions analysis, the following parameters were univariate predictors of in-hospital mortality (Table 3): lactate >4.4 mmol/l, congestive heart failure (NYHA III–IV), severe left ventricular (LV) dysfunction [ejection fraction (EF) <30%), and preoperative renal failure (serum creatinine >1.4 mg/dl). At multivariate analysis (Table 4) only lactate >4.4 mmol/l and congestive heart failure (NYHA III–IV) were still independent predictors of in-hospital mortality.

Discussion

Blood lactate levels are simple to obtain, and results are quickly available in most institutions. An increase in blood lactate levels could result from increased production or decreased clearance, or a combination of both processes. The nature of elevated blood lactate levels during and after cardiac surgery is still controversial. Tissue perfusion is at risk during cardiac surgery and in the immediate postoperative period. Takala et al. [7] suggest that hyperlactatemia after cardiac surgery is a sign of inadequate tissue perfusion of the hepatosplanchnic region. Perner et al. [8] found that increasing intraluminal lactate in the rectum during CPB indicates metabolic dysfunction of the intestinal mucosa. In contrast, Haisjackl et al. [9] and Braun

Table 1 Preoperative and intraoperative data for normolactatemia (group I), mild hyperlactatemia (group II), and severe hyperlactatemia (group III)

	Group I Lactate ≤2.2 mmol/l), n = 332	Group II Lactate 2.21–4.4 mmol/l, n = 1,054	Group III Lactate ≥4.4 mmol/l, n = 434	P value
Age (years)	62.5 ± 13.4	63.9 ± 13.9	64.2 ± 13.7	0.132
Male gender, n (%)	253 (76)	719 (68.1)	275 (63.1)	<0.01*
Diabetes, n (%)	93 (28.2)	382 (36.2)	148 (34)	0.022
Hypertension, n (%)	235 (71.2)	781 (75.6)	339 (77.8)	0.065
Smoking, n (%)	159 (48)	450 (43)	164 (38)	0.019
Severe COPD[a], n (%)	18 (5)	68 (6)	35 (8)	0.321
New York Heart Association class	2.0 ± 0.8	2.1 ± 0.8	2.2 ± 0.9	0.024
Preoperative renal failure, n (%)	3 (1)	12 (1)	6 (1)	0.826
Ejection fraction, n (%)	56 ± 10	55 ± 11	52 ± 14	0.121
Preoperative intraaortic balloon pump, n (%)	6 (2)	25 (2)	17 (4)	0.139
Standard EuroSCORE	4.7 ± 3	4.9 ± 3	6.2 ± 4	<0.05*
Logistic EuroSCORE	7 ± 8	7.1 ± 9	11 ± 14	<0.01*
CABG, n (%)	135 (41)	423 (40)	162 (37)	0.544
Aortic valve surgery ± CABG[b], n (%)	87 (26)	258 (24)	69 (16)	<0.01*
Mitral valve surgery ± CABG, n (%)	36 (11)	94 (9)	41 (9)	0.577
Aortic surgery, n (%)	20 (6)	82 (8)	45 (10)	0.079
Other surgery, n (%)	54 (16)	197 (19)	117 (28)	<0.05*

Results are presented as average ± SD or percentage

[a] Chronic obstructive pulmonary disease

[b] Coronary artery bypass graft

* Groups I and II compared with group III

Table 2 Postoperative data for normolactatemia (groups I), mild hyperlactatemia (group II), and severe hyperlactatemia (group III)

	Group I Lactate ≤2.2 mmol/l), $n = 332$	Group II Lactate 2.21–4.4 mmol/l, $n = 1{,}054$	Group III Lactate ≥4.4 mmol/l, $n = 434$	*P* value
Bypass time (min)	76 ± 38	91 ± 38	109 ± 53	<0.01*
Cross-clamp time (min)	55 ± 29	66 ± 32	74 ± 63	<0.01*
Bleeding during first 24 h (ml)	385 ± 479	389 ± 295	576 ± 708	<0.01*
Postoperative renal failure, *n* (%)	12 (3.61)	49 (4.65)	40 (9.22)	<0.05*
Using of *β*-agonists, *n* (%)	26 (7.83)	218 (20.68)	123 (28.34)	<0.01**
Ventilation time (h)	12 ± 7	20 ± 50	45 ± 109	<0.01*
ICU length of stay (h)	38 ± 29	59 ± 123	107 ± 210	<0.01*
Postoperative hospital stay (days)	7 ± 4	8 ± 9	11 ± 13	0.067
Hospital mortality, *n* (%)	3 (0.9)	8 (0.76)	32 (7.37)	<0.01*

Results are presented as average ± SD or percentage

* Groups I and II compared with group III; ** group I compared with groups II and III

Table 3 Risk factors for mortality: univariate analysis

Risk factors	Hazard ratio	95% CI	*P*
Congestive heart failure (NYHA III–IV)	1.95	1.25–3.04	0.003
Severe left ventricular (LV) dysfunction [ejection fraction (EF) <30%]	1.75	1.11–2.77	0.016
Preoperative renal failure (Cr >1.4 mg/dl)	1.71	1.15–2.54	0.008
Hyperlactatemia (lactate >4.4 mmol/l)	1.96	1.27–3.02	0.002

Table 4 Risk factors for mortality: multivariate analysis

Risk factors	Hazard ratio	95% CI	*P*
Congestive heart failure (NYHA III–IV)	1.86	1.12–3.11	0.017
Hyperlactatemia (lactate >4.4 mmol/l)	40.96	6.67–250.593	0.002

et al. [10] demonstrated that cardiac surgery was not associated with deterioration in splanchnic oxygen delivery and hyperlactatemia, but a manifestation of systemic inflammatory response to CPB. Dixon et al. [11] found that marked prothrombotic response after CPB is associated with elevated lactate levels. Gasparovic et al. [12] maintain that the lungs are an additional possible source of lactate during CPB. Besides anaerobic glycolysis, increased aerobic glycolysis by catecholamine-stimulated Na^+–K^+ pump may account for hyperlactatemia after cardiac surgery [13]. However, in our study the number of patients receiving a catecholamine was similar in groups II and III.

Measurement of blood lactate levels is widely used to assess the adequacy of tissue perfusion. Experimental studies have clearly confirmed the relationship between tissue hypoxia and hyperlactatemia. Traditionally, hyperlactatemia in critically ill patients was interpreted as a marker of anaerobic metabolism resulting from inadequate oxygen supply [14]. Maillet et al. [1] found that hyperlactatemia, >3 mmol/l, occurs frequently (17.2–20.6%) after cardiac surgery. In our study, severe hyperlactatemia, >4.4 mmol/l, was observed in 26.6% of patients. Arnold et al. [15] and Shapiro et al. [16] support the employment of lactate levels >4 mmol/l to be a marker for severe tissue hypoperfusion and hence a predictor of mortality. Irrespective of the origin of increased blood lactate levels, hyperlactatemia in septic [17], trauma [18], and emergency department patients [15, 16] is always associated with unfavorable outcome, compared to similar patients with normal blood lactate levels. Several studies have demonstrated that hyperlactatemia in the early postoperative period following pediatric cardiac surgery [3, 4, 19–22] and adult cardiac surgery [1] is associated with an increased risk of mortality and morbidity. The link between tissue hypoperfusion and hyperlactatemia is evident. Studies of acute myocardial infarction, trauma, sepsis, and stroke have been translated into improved outcomes by earlier diagnosis and early treatment [23]. Recognition of abnormally high blood lactate levels might facilitate earlier and more effective intervention in the immediate postoperative period. Jones et al. [24] shows that among patients with septic shock, lactate-directed management is equivalent to management directed to normalize central venous oxygen saturation ($ScvO_2$). Pölönen et al. [25] found that goal-oriented (lactate and $ScvO_2$) therapy during the immediate postoperative period after cardiac surgery could

decrease morbidity and reduce length of hospital stay. In our study, peak lactate values were seen after 3.4 ± 2.8 h postoperatively and decreased to normal range during the following 6.4 ± 5.7 h.

A serious limitation of our study was the lack of a specific goal-oriented protocol in our department. Patients were treated according to hemodynamic parameters and urine output, regardless of blood lactate levels.

Our results support the need for a large multicenter study using lactate-directed therapy in early postoperative hours after adult cardiac surgery.

Conclusions

Hyperlactatemia is common after cardiac surgery and may be a useful early-warning signal for further investigation. A maximal lactate threshold ≥4.4 mmol/l accurately predicts postoperative mortality in adult patients undergoing cardiac surgery with CPB. Hyperlactatemia is also significantly associated with prolonged ICU and hospital stay. Initial lactate levels, however, are poor predictors of mortality. Further studies are needed to establish a lactate-directed treatment protocol.

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