

## Lactic Acidosis after Cardiac Surgery Is Associated with Adverse Outcome

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### ABSTRACT

**Background:** The accurate identification of patients who have the potential to further deteriorate after cardiac surgery is difficult. Elevated serum lactate level after cardiac surgery is an indicator of systemic hypoperfusion and tissue hypoxia. The aim of this study was to investigate the effect of increased serum lactate on outcome after on-pump coronary artery bypass grafting.

**Methods:** Serum lactate level was measured in 776 patients within half an hour after surgery. Lactate level was less than or equal to 2 mmol/L in 534 patients (low lactate group) and more than 2 mmol/L in 242 patients (high lactate group). Continuous variables were analyzed with the Student *t* test. The  $\chi^2$  test and Fisher exact test were used to compare categorical variables.

**Results:** Demographic characteristics and details of surgery were similar in both groups. Increased cross-clamp and cardiopulmonary bypass times and highly positive fluid balance at the end of surgery were associated with a significant rise in postoperative lactate levels, which leads to increased need for intraaortic balloon pump support (odds ratio [OR], 5.9,  $P = .006$ ), increased likelihood of >24 h intensive care unit stay (OR, 3.4,  $P = .0001$ ), greater need for red blood cell transfusion (OR, 1.6,  $P = .002$ ), increased length of hospital stay, and higher mortality rates (OR, 5.6,  $P = .04$ ).

**Conclusions:** This study has demonstrated that elevated blood lactate level is associated with adverse outcome, and monitoring the blood lactate level during and after cardiac surgery is a valuable tool in identifying the patients who have the potential to deteriorate.

*Presented at the 18th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA), Prague, Czech Republic, May 25-28, 2003.*

*Received January 5, 2004; accepted January 14, 2004.*

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### INTRODUCTION

Identification of predictors of morbidity and mortality is an important issue for the optimal management of cardiac surgical patients. Stratification of risk in the cardiac surgical population involves mainly preoperative factors. However, intraoperative events related to surgical technique, myocardial protection, and cardiopulmonary bypass (CPB) may modify the postoperative course [Higgins 1997].

Elevated blood lactate level associated with metabolic acidosis is common among ill patients with systemic hypoperfusion and tissue hypoxia [Mizock 1992]. This situation represents type A lactic acidosis, resulting from an imbalance between supply and demand for tissue oxygen. Lactate production results from cellular metabolism of pyruvate into lactate under anerobic conditions. Therefore, blood lactate level in type A lactic acidosis is related to the total oxygen debt and the magnitude of tissue hypoperfusion [Mizock 1992, Broder 1964, Weil 1970]. Several studies have suggested that blood lactate concentration has prognostic value in patients with circulatory shock [Broder 1964, Weil 1970, Bitek 1971]. It has also been speculated that blood lactate concentration monitoring during CPB might be a sensitive tool to detect an imbalance between oxygen supply and demand [Fiaccadori 1989, Landow 1991].

The aim of this study was to investigate whether increased serum lactate level is associated with an adverse outcome after on-pump coronary artery bypass grafting.

### METHODS

#### Patients

Serum lactate level was measured before anesthetic induction and within half an hour after surgery in 776 consecutive patients undergoing isolated on-pump coronary artery bypass grafting (CABG) surgery between February 1999 and February 2002. Lactate level was less than or equal to 2 mmol/L in 534 patients (low lactate group) and more than 2 mmol/L in 242 patients (high lactate group). Use of inotropic agents and intraaortic balloon pump (IABP), time to extubation, and lengths of intensive care unit (ICU) and hospital stay were recorded. All data were collected prospec-

tively. Patients with hepatic dysfunction were excluded from the study.

### **Anesthesia and Operative Technique**

On the night previous to the operation, all patients received alprazolam (Xanax) 0.5 mg orally. Midazolam 125 µg/kg intramuscularly (IM) was given 30 minutes before the operation. In all patients, a 16-gauge intravenous (IV) cannula was inserted in the operating room. The IV drip was NaCl 100 mL/hour. Anesthetic induction consisted of midazolam 50 µg/kg, pancronium 0.15 mg/kg, and fentanyl 25 to 35 µg/kg. After endotracheal intubation, 50% O<sub>2</sub>, 50% N<sub>2</sub>O, and 3% to 4% desflurane was used for all hemodynamically stable patients. Desflurane and N<sub>2</sub>O were discontinued at times of hemodynamic instability. Maintenance anesthesia and muscle relaxation were accomplished with midazolam and vecuronium 80 µg/kg per hour. Furosemide 0.5 mg/kg was routinely administered. Priming solution for CPB included 900 mL Ringer's lactate solution, 150 mL 20% mannitol, and 60 mL sodium bicarbonate (8.4%). During CPB, hematocrit, mean arterial pressure, and pump flow were kept between 20% to 30%, 50 to 80 mm Hg, and 2 to 2.5 L/m<sup>2</sup>, respectively. Adequacy of tissue perfusion was monitored with arteriovenous partial carbon dioxide difference, lactate level, urine output, and base deficit. Moderate hypothermia was used during CPB, and midazolam and vecuronium dose was decreased to 60 µg/kg per hour when the body temperature reached to 32°C. Myocardial viability was preserved with topical hypothermia and antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol; Abbott Laboratories, Abbott Park, IL, USA) except in patients with an left ventricular ejection fraction less than 0.25 in whom antegrade and retrograde blood cardioplegia associated with terminal warm blood cardioplegia was used. During rewarming, midazolam and vecuronium dose was increased back to 80 µg/kg per hour. After the termination of CPB, midazolam and vecuronium dose was decreased to 50 µg/kg per hour and discontinued at skin closure.

### **Postoperative Clinical Management**

On arrival in the ICU, patients were placed on mechanical ventilation. The ventilator mode was switched to synchronous intermittent mandatory ventilation, and pressure support and ventilator settings were adjusted to a respiratory rate of 12/min; tidal volume, 8 to 10 mL/kg; FIO<sub>2</sub>, 0.6; positive expiratory-end pressure, 0 to 5 mm Hg; pressure support, 10 mm Hg; and trigger sensitivity, -2 cm H<sub>2</sub>O. All patients were warmed with forced-air warming until the rectal temperature reached 37°C. Basic fluid substitution during the first 20 postoperative hours was 40 mL/kg per day. Six hundred to 800 mL of this solution was the autologous blood derived from the CPB circuit, and the rest was balanced crystalloid solution. Meperidine, 0.4 mg/kg IV to a total dose of 50 mg over 6 hours, was used to treat shivering. All patients were evaluated for extubation every half an hour. As soon as spontaneous breathing resumed, respiratory rate was gradually decreased to 4/min and pressure support to 4 mm Hg. If there were no contraindications for the use of β-blockade, metoprolol was used intravenously to control hypertension.

All hemodynamically stable patients without excessive chest tube drainage and with PaCO<sub>2</sub> <48 mm Hg, pH >7.30, and PaO<sub>2</sub>/FIO<sub>2</sub> >250 were extubated. After the patient was extubated, 40% to 50% oxygen was administered by face mask. Oxygen hemoglobin saturation and respiratory rate were continuously monitored. Arterial blood gases were obtained at 30, 60, and 120 minutes postextubation. Repeated doses of diclofenac sodium 1.25 mg/kg IM were used for postoperative analgesia. Patients older than 70 years with a hemoglobin value less than 8 g/dL and patients aged 70 years or less with a hemoglobin value less than 7 g/dL received packed red blood cells. Patients with a tendency to bleed were treated by transfusion of fresh frozen plasma. Inotropes were used only when hemodynamic stabilization could not be achieved by fluid administration or when there was other evidence of impaired contractility. In case of an insufficient response to inotropes, intraaortic balloon counterpulsation was initiated. We aimed to discharge all patients on the fifth postoperative day. The decision to discharge was based on a satisfactory routine checkup on day 4, consisting of clinical examination, full blood cell count, urea and electrolyte levels, electrocardiogram, and chest roentgenogram. If the patient was medically unfit on day 4, hospitalization was prolonged, and further investigations were performed depending on the clinical status. Because the objective of our fast-track recovery protocol was to extubate the patients within 6 hours of the completion of cardiac procedure, to discharge from the ICU within 24 hours, and to discharge from the hospital on the fifth postoperative day, these time points were taken as references in this study.

### **Definitions**

Data characterizing perioperative clinical outcome were entered prospectively. Hospital mortality included all deaths within 30 days of surgery, irrespective of where the death occurred, and all deaths in the hospital after 30 days among patients who had not been discharged after undergoing surgery. Postoperative blood loss was defined as total chest tube drainage.

### **Statistical Analysis**

Data are reported as a percentage or as a mean ± SD. Univariate comparisons were computed using the  $\chi^2$  test or Fisher exact test for categorical variables and *t* tests for continuous variables. Statistical analysis was performed using SPSS statistical software (SPSS, Chicago, IL, USA). Variables were considered significant at *P* values less than .05.

## **RESULTS**

In the low and high lactate groups, the mean age (59 ± 12 versus 58 ± 12 years), female sex (29% versus 25%), and the mean EuroSCORE (2.9 ± 2.1 versus 3.4 ± 2.4) were similar (*P* > .05). Operative and postoperative data are shown in Tables 1 and 2. Demographic characteristics and details of surgery were similar in both groups. Increased cross-clamp and CPB times and highly positive fluid balance at the end of surgery were associated with a significant rise in postoperative lactate levels, which led to increased need for IABP sup-

Table 1. Operative Data\*

	Low Lactate (n = 534)	High Lactate (n = 242)	P
Preoperative hematocrit, %	40 ± 8	40.5 ± 5	NS
Hematocrit during CPB	27 ± 4	26.7 ± 4	NS
Preoperative lactate level, mmol/L	1.0 ± 0.7	1.1 ± 0.7	NS
Lactate level during CPB, mmol/L	1.2 ± 0.7	1.3 ± 0.8	NS
SBE during CPB, mmol/L	0.1 ± 2	-0.1 ± 2	NS
Cross-clamp time, min	34 ± 14	48 ± 29	.0001
CPB time, min	53 ± 19	76 ± 38	.0001
No. of distal anastomoses	2.9 ± 1	3.3 ± 1	NS
Fluid balance at the end of operation, mL	44 ± 512	205 ± 729	.0001

\*CPB indicates cardiopulmonary bypass; SBE, standard base excess.

port (odds ratio [OR] = 5.9, *P* = .006), >24 hour ICU stay (OR = 3.4, *P* = .0001), and red blood cell transfusion (OR = 1.6, *P* = .002); longer hospital stay; and higher mortality rates (OR = 5.6, *P* = .04).

**DISCUSSION**

The accurate identification of patients who have the potential to further deteriorate after cardiac surgery is difficult. Traditional endpoints of resuscitation such as heart rate, blood pressure, urine output, and peripheral perfusion remain insensitive indicators of underlying physiological disturbance [Parker 1987, Davis 1994, Bernardin 1996]. Many investigators have therefore used a variety of tools to predict which patients are likely to deteriorate, and these tools include physiological scoring systems, hemodynamic variables and their response to therapy, gastric mucosal pH, and the regional-to-arterial pCO<sub>2</sub> gap [Knaus 1981, Doglio 1991]. When an imbalance between oxygen supply and demand exists, anaerobic respiration commences and metabolic acidosis develops. This metabolic acidosis can be quantified from direct arterial blood gas analysis by examination of the base excess and the serum lactate concentration. Although there are a variety of other causes for metabolic acidosis, the early identification of those patients with tissue dysoxia would enable better triage decisions to be made with regard to future management. Hyperlactatemia may occur with or without concomitant metabolic acidosis. When hyperlactatemia occurs in the setting of good tissue perfusion, for example, catecholamine administration, alkalosis, or increased metabolic activity due to sepsis or burns, the buffering mechanisms can compensate for any fall in pH. When lactate levels increased because of poor tissue perfusion, however, the buffering systems are unable to cope and acidosis develops. Critically ill patients can have a variety of mechanisms as underlying causes of hyperlactatemia resulting from both types of mechanisms outlined above [Mizock 1992]. Although some investigators have found single time-point measurements of lactate early in the course of the illness to be predictive for mortality [Bakker 1991, Friedman 1995], this finding is not universal [Marik 1993, Bernardin 1996, Joynt 1997]. Previous workers have demonstrated that

Table 2. Postoperative Data\*

	Low lactate (n = 534)	High Lactate (n = 242)	P
Postoperative hematocrit, %	34.5 ± 5.4	34.0 ± 5.2	NS
Postoperative lactate level, mmol/L	1.3 ± 0.3	2.7 ± 1.1	.001
Postoperative SBE, mmol/L	-1.8 ± 2.7	-3.4 ± 4.6	.0001
Total chest tube output, mL	599 ± 339	778 ± 523	.0001
Patients received red blood cells, %	14	21.1	.016
Intraaortic balloon pump, %	0.6	3.2	.006
Time to extubation, min	247 ± 271	376 ± 571	.001
Length of intensive care unit stay, h	20.6 ± 11.2	25.6 ± 31.7	.02
Length of intensive care unit stay >24 h, %	2.7	8.7	.0001
Length of hospital stay, d	5.4 ± 2.8	6.2 ± 4.5	.013
Mortality, %	0.4	2	.035

\*SBE indicates standard base excess.

as the lactate level rises from 2.0 to 8.0 mmol/L, the probability of survival decreases from 90% to 10%, but this prognostic implication is dependent on the cause of the rise in lactate [Weil 1970, Bitek 1971]. High lactate levels due to hemorrhagic shock appear to be associated with better outcomes than increases in lactate due to either cardiogenic or septic shock, and this finding can be attributed to a potentially reversible cause of the shock due to hemorrhage [Bitek 1971]. Morbidity related to CPB, frequently referred to as the post-pump syndrome, ranges from mild capillary leakage to multiple organ system failure. The postpump syndrome has been attributed to exposure of blood cells to foreign surfaces and the release of inflammatory mediators [Harris 1970, Kirklin 1983, Seghaye 1993, McGiffin 1994]. In addition to post-pump syndrome, many patients develop metabolic acidosis and increased serum lactate levels during and just after CPB [Litwin 1959, Fiaccadori 1989, McGiffin 1994]. This acidosis is secondary to tissue hypoperfusion, which occurs despite the use of hypothermia to reduce metabolic demands and the maintenance of normal mixed venous oxygen saturation levels during CPB [Schiavello 1984, Fiaccadori 1989, Ariza 1991]. Previous studies have demonstrated that metabolic acidosis occurs during CPB through peripheral hypoperfusion [Clowes 1958, Shepard 1969, Fiaccadori 1989] and persists in the early postoperative period [Ariza 1991]. These findings are similar to those of other workers studying patients after both cardiac [Fiaccadori 1989] and major abdominal surgery [Waxman 1982]. Increased plasma lactate

Table 3. Influence of High Lactate Levels (>2 mmol/L) on Outcome

	Odds Ratio	95% Confidence Interval	P
Use of red blood cells	1.6	1.1-2.4	.002
Intensive care unit stay >24 h	3.4	1.7-6.7	.0001
Use of intraaortic balloon pump	5.9	1.6-22.6	.006
Mortality	5.6	1.1-28.6	.04

levels reflect the onset of anaerobic metabolism secondary to inadequate cellular oxygen uptake. However, it is surprising that a progressive rise in plasma lactate concentration has been shown to occur after CPB despite a rise in cardiac index and oxygen uptake [Ariza 1991]. The possible explanations for this observation are, first, the hypermetabolic response after cardiac surgery, which may increase oxygen demand over and above what appears to be an adequate O<sub>2</sub> delivery (DO<sub>2</sub>). Furthermore, an increase in oxygen extraction ratio in these circumstances may also reflect the inability of the myocardium to respond rapidly to the increased demands of the immediate postoperative period. Second, a fall in DO<sub>2</sub> could result in rise in lactate in parallel with a rise in cardiac index, provided that hemoglobin levels fall sufficiently. Third, a delay in the tissue washout of lactate, such that plasma levels increased only after rewarming, with a consequent increase in tissue perfusion, could have occurred. Fourth, systemic microvascular control may become disordered in CPB, resulting in peripheral arteriovenous shunting and a rise in tissue lactate levels despite an apparently adequate cardiac output. Impaired cellular use of oxygen due to similar mechanisms has been proposed to occur after major abdominal surgery [Waxman 1982]. Finally, the elevation in lactate could be due to impaired clearance. Siegel and coworkers have demonstrated in pediatric patients a strong correlation between the initial post-CPB serum lactate levels and capillary leakage (maximal weight gain), duration of intravenous inotropic support, duration of ventilatory support, and length of hospital stay [Siegel 1996]. They have also shown that serum lactate level was the best predictor of mortality, and a rule predicting mortality at a serum lactate level of >4.2 mmol/L had a positive predictive value of 100% and a negative predictive value of 97%.

Maillet and colleagues have demonstrated that nonelective surgery, prolonged CPB, and intraoperative use of vasopressors were independent risk factors for immediate hyperlactatemia after cardiac surgery and also have shown that immediate hyperlactatemia more accurately predicted ICU mortality than late hyperlactatemia [Maillet 2003]. Our study has demonstrated that increased cross-clamp and CPB times and highly positive fluid balance at the end of the operation are associated with an early rise in postoperative lactate levels, which is associated with increases in need for IABP support, length of ICU stay, need for red blood cell transfusion, length of hospital stay, and mortality rates. Increase in the blood lactate level is associated with adverse outcome during and after cardiac surgery, so monitoring blood lactate level seems to be a valuable tool in identifying the patients who have the potential to deteriorate.

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