Intensive Care Med (2003) 29:1279–1285
DOI 10.1007/s00134-003-1860-6

ORIGINAL

Iqbal Mustafa
Hubert Roth
Asikin Hanafiah
Tarmizi Hakim
Maizul Anwar
Erwin Siregar
Xavier M. Leverve

Effect of cardiopulmonary bypass on lactate metabolism

Received: 12 November 2002
Accepted: 15 May 2003
Published online: 5 July 2003

I. Mustafa
Intensive Care Unit,
Harapan Kita National Cardiovascular Center, Jakarta, Indonesia

H. Roth · X. M. Leverve (✉)
INSERM-E0221 Bioénergétique Fondamentale et Appliquée,
Université Joseph Fourier et Département de Médecine Aiguë Spécialisée,
Centre Hospitalier Universitaire de Grenoble,
BP 53 X, 38041 Grenoble, France
e-mail: Xavier.Leverve@ujf-grenoble.fr
Tel.: +33-4-76514386
Fax: +33-4-76514218

A. Hanafiah
Department of Cardiology,
Harapan Kita National Cardiovascular Center, Jakarta, Indonesia

T. Hakim · M. Anwar
Department of Cardiothoracic Surgery,
Harapan Kita National Cardiovascular Center, Jakarta, Indonesia

E. Siregar
Department of Anesthesiology,
Harapan Kita National Cardiovascular Center, Jakarta, Indonesia

Abstract *Objective:* We have investigated the role of cardiopulmonary bypass on lactate metabolism in patients undergoing uncomplicated surgery for elective coronary artery bypass grafting (CABG). *Design:* Prospective non-randomized observational study. *Settings:* National Cardiovascular Center. *Patients:* Three independent groups were studied: preoperative (n=20), postoperative with bypass (CPB, n=20) and postoperative without bypass (NO-CPB, n=20). *Interventions:* Lactate metabolism was investigated with the use of an exogenous lactate challenge test (2.5 mmol Na-lactate/kg body weight in 15 min). Blood lactate was sequentially determined after the end of infusion. Lactate clearance and endogenous production were estimated from the area under the curve, and a bi-exponential fitting permitted modeling the lactate-decay into two compartments. *Measurements and main results:* Lactate metabolism parameters (basal lactate, clearance, endogenous production and half-lives [HL] I and II) were not different between the NO-CPB and preoperative groups. In the CPB group, as compared to the other two groups, basal lactate and endogenous production were not significantly affected while lactate clearance (CPB: 6.02±0.97 versus preoperative: 9.41±0.93 and NO-CPB: 9.6±0.8 ml/kg per min) and HL-I (CPB: 10.6±1.4 versus preoperative: 17.2±2.3 and NO-CPB: 18.8±2.5 min) were decreased (p<0.001) and HL-II was increased (CPB: 171±41versus preoperative: 73±12 and NO-CPB: 48±2.9 min, p<0.01). *Conclusion:* While surgery and anesthesia per se do not seem to alter lactate metabolism, CPB significantly decreased lactate clearance, this effect being possibly related to a mild liver dysfunction even in uncomplicated elective surgery.

Keywords Lactate endogenous production · Lactate clearance · Liver function · Modeling · Beating heart surgery

Introduction

Hyperlactatemia after cardiac surgery with cardiopulmonary bypass (CPB) has long been recognized [1, 2, 3, 4, 5, 6] as a consequence of probable inadequate tissue perfusion [2, 7, 8, 9, 10, 11]. Indeed, despite some technical advances [2, 12, 13], insufficient tissue perfusion during CPB remains a concern [1, 2, 10, 11]. Recent reports suggest that elective coronary artery bypass grafting (CABG) with beating heart improves the tolerance [14, 15].

Blood lactate correlates with illness severity [16, 17], but it does not allow differentiation between excessive production and decreased consumption [9, 18]. The lactate turnover rate is increased in many pathological conditions, including cardiogenic shock [19], but decreased

lactate clearance may also increase lactate concentration [20, 21]. Therefore, assessment of lactate metabolism from blood lactate concentration alone is ambiguous.

The infusion of an exogenous load of lactate makes it possible to evaluate lactate clearance and endogenous production [20]. This tool was used in the present study to investigate lactate metabolism after elective CABG.

Material and methods

Patients

Three groups of patients suffering from coronary heart disease and requiring CABG were investigated for lactate metabolism in a non-randomized prospective observational study. Exclusion criteria were: age under 19 or over 75 years, ejection fraction below 35%, renal failure (creatinine above 15 mg/l), liver failure (see Table 1), non-insulin and insulin-dependent diabetes, or patients requiring epinephrine or more than one inotropic drug or more than 10 μg/kg per min dobutamine or dopamine (see Table 2). One group was studied before surgery (preoperative, *n*=20) and two others 14–16 h after surgery, one with cardiopulmonary bypass (CPB, *n*=20) and one with beating heart (NO-CPB, *n*=20). All patients presented uneventful surgical procedures and the postoperative period was uncomplicated. The ethic committee of the National Cardiovascular Center, Harapan-Kita-Hospital, Jakarta Indonesia, approved the study protocol and informed written consent was obtained from every patient. The CABG procedures were performed with CPB or with the beating heart technique, depending on the surgeon's preference.

Table 1 Patient and surgery characteristics. (*Preoperative* before surgery (*n*=20), *CPB* postoperative after bypass (*n*=20), *NO-CPB* postoperative after surgery with beating heart (*n*=20)). Values are means ± SEM. Age, weight, height and body mass index (*BMI*) were not different within the three groups, ejection fraction [%, (end-diastolic volume end-systolic volume)×100/end-diastolic volume] was significantly lower in CPB patients as compared to both the preoperative group and NO-CPB (ANOVA and post-hoc Fischer's test [1]$p<0.01$), the number of grafts between CPB and NO-CPB was compared by a chi-square test, [2]$p<0.05$

	Preoperative	CPB	NO-CPB
Age (years)	53±2	57±2	53±1
Weight (kg)	67±2	69±3	69±2
Height (cm)	165±2	166±2	164±2
BMI (kg/cm^2)	24.3±0.7	24.6±0.7	25.6±0.7
Ejection fraction (%)	55±2	45±3[1]	54±3
SGOT (IU/l)	19.5±0.8	20.3±1.5	24.0±2.6
SGPT (IU/l)	21.2±1.3	22.2±2.0	27.2±3.0
Temperature during surgery (°C)		31.2±0.2	
Temperature at the admission (°C)		35.6±0.5	35.3±1.1
Bypass time (min)		100±4.9	
Number of grafts		4	2[2]
Aortic cross-clamping time (min)		68±4	
Length of anesthesia (min)		315±12	357±16[1]

Surgical procedure and peri/postoperative care

Anesthesia was standardized: after premedication with 2.5–5 mg of midazolam i.v., induction was performed with propofol (3–5 mg/kg) and 1–2 μg/kg sufentanil before intubation with 0.1–0.2 mg/kg pancuronium bromide. Anesthesia was maintained with a continuous infusion of propofol, and i.v. bolus of sufentanil was administered when there was evidence of poor analgesia and/or when blood pressure or heart rate increased more than 30%. Nitroglycerin was continuously infused and the rate was modulated according to blood pressure: it was increased when blood pressure increased more than 30%.

For CPB, the extracorporeal circuit consisted of a roller pump (Sarns 8000) and a membrane oxygenator (Capiox Sx). The pump flow was 2.4 l/min per m^2. During CPB, patients were cooled to 31–32°C and they received intermittent antegrade normothermic blood cardioplegia, which was a mixture of 400–600 ml of oxygenated blood with graduated doses of potassium-magnesium solution. Standard systemic heparinization (3 mg/kg) was performed and an activated clotting time of greater than 480 s was maintained during CPB; heparin was neutralized with protamine sulfate on discontinuation.

For the beating heart technique, traction sutures were applied to the pericardial edges, displacing the heart anteriorly. For exposure of the left anterior descending coronary artery or its diagonal branches, additional pericardial traction sutures were inserted anterior to the left phrenic nerve to rotate the heart and a moist sponge was placed behind its laterodorsal aspect, bringing the coronary artery into the operative field. For exposure of obtuse marginal or right coronary branches, two wet cotton tapes were passed through the transverse sinus with their right ends secured to surgical drapes. The two loose lengths of tape were then used to lift and rotate the heart toward the surgeon, as well as to stabilize the coronary artery. Patients were heparinized (1.5 mg/kg) and two 5-0 Prolene (Ethicon, Sommerville, NJ) sutures were used to occlude the coronary artery on either side of the anastomosis site temporarily. Heparin was neutralized with protamine sulfate after all anastomoses were completed.

Table 2 Postoperative use of inotropes and/or vasoactive agents. (*CPB* postoperative after bypass (*n*=20), *NO-CPB* postoperative after surgery with beating heart (*n*=20))

	Inotrope/vasodilating treatment, number of patients				
	No treatment	Dobutamine 5–10 μg/kg per min	Dobutamine 5–10 μg/kg per min + Milrinone 0.5 μg/kg per min	Dobutamine 5–10 μg/kg per min + Norepinephrine 0.05–0.1 μg/kg per min	Milrinone 0.5 μg/kg per min
NO-CPB	12	4	0	1	3
CPB	8	4	5	0	3

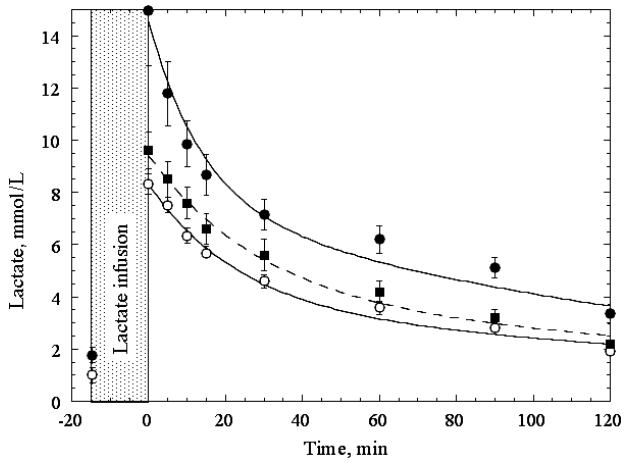

Fig. 1 Exogenous Lactate Challenge Test in three groups of patients before or after CABG surgery with or without cardiopulmonary bypass. Three groups of patients: preoperative patients (*open circles*, *n*=20) and postoperative patients (14–16 h after surgery) with cardiopulmonary bypass (CPB, *closed circles*, *n*=20) or without bypass (NO-CPB, *closed squares*, *n*=20) were challenged with an exogenous load of sodium lactate continuously infused from −15 min to 0. Curves represent the best fits of bi-exponential modeling (see Materials and Methods) of the decay of the plasma lactate from T0 up to 120 min

Postoperative care was also standardized: (1) when the cardiac index was below 2.5 l/min per m^2 despite sufficient volume expansion (pulmonary capillary wedge pressure 12–16 mmHg), dobutamine was infused; (2) the mean arterial pressure was maintained between 60 and 90 mmHg with norepinephrine and nitroglycerine; (3) hemoglobin concentration was maintained around 100 g/l. Patients were weaned from mechanical ventilation as soon as they had been rewarmed and were hemodynamically stable. All patients were extubated before the study, meaning that all were hemodynamically stable.

Exogenous lactate challenge test (ELCT)

Lactate metabolism was investigated at 8 a.m. after an overnight fast in preoperative patients or 14–16 h after surgery in the two postoperative groups, also under fasting conditions (Fig. 1). The total duration of the study was 180 min. In preoperative patients, one venous cannula was inserted into a wrist vein of an arm for the collection of blood samples. This hand was placed in a thermostabilized box heated at 50°C to achieve partial arterialization of venous blood [20]. Another venous cannula was inserted into an antecubital vein of the contralateral arm for lactate infusion. In postoperative patients lactate was infused through a central venous line, while blood samples were collected from a radial artery catheter. After a first blood sample was taken for basal lactate determination (T–15), 2.5 mmol/kg body weight sodium lactate was infused over a 15-min period. At the end of the infusion (T0) and after 5, 10, 15, 30, 60, 90 and 120 min, blood samples were collected for immediate bedside whole blood lactate determination (Analogs-LM-5 lactate analyzer, Analox Instruments, Hammersmith, London, UK), which was calibrated before each investigation. The response was linear between 0 and 20 mM, the coefficient of variation was1.6% and the identity curve comparing this method and the standard enzymatic procedure was y=1.01x0.09, *r*=0.998, *n*=56.

Calculations

The clearance of exogenous lactate (ml/kg per min) was the ratio of the lactate load (mmol/kg) to the area under the lactate concentration curve (µmol/min per ml). Areas were calculated graphically from the unadjusted experimental points by using Kaleidagraph (Abelbeck Software, Reading, PA, USA) as described in [20]. The endogenous lactate production (µmol/kg per min) was calculated as the product of basal lactate concentration and lactate clearance rate. There is no fitting of the data and the area under the curve (representing the part of exogenous lactate not cleared at any given time) is calculated graphically using the method of sum of trapezes. Therefore, estimation of endogenous lactate production by this method is relatively robust, depending only on two assumptions: (1) the dilution space of lactate was estimated to be 60% of body mass (a value widely used) and (2) exogenous lactate infusion does not significantly affect endogenous lactate production. Data from the literature supports the latter fact [22].

The kinetics of exogenous plasma lactate disappearance could be assessed with either a mono-compartmental model [22, 23, 24, 25, 26] or a two-compartmental model [20, 26, 27, 28]. From a theoretical point of view, a two-compartmental modeling seems more appropriate since lactate utilization is related to two major processes, i.e. oxidation and transformation into glucose. We have compared the mathematical fitting resulting from either mono- or bi-compartmental pharmacokinetic modeling in healthy controls and in postoperative patients [20, 26, 27, 28]. Bi-exponential fitting resulted in a better description of the lactate decay, therefore this modeling was applied to describe the kinetics of plasma lactate decay over time from the end of exogenous lactate infusion (T0 = peak of lactate) to 120 min (T120). Experimental values were fitted by means of the least-square method, using commercial software (Kaleidagraph, Abelbeck Software, Reading, PA, USA). In each experiment, mathematical fitting of the experimental data of lactate decay permits the calculation of two different half-lives corresponding to the two exponential curves (HL-I and HL-II).

Statistical analysis

The results are presented as means ± SEM. When variables were normally distributed, statistical comparisons were made as indicated either by a paired Student *t*-test or by an unpaired Student *t*-test or, when three groups were compared, by an ANOVA followed by post-hoc analysis (Fisher's PLSD) if a significant difference ($p<0.05$) was found by ANOVA. In the case of non-normally distributed variables (HL-1 and HL-2), comparisons were first analyzed by a Kruskal-Wallis test. When Kruskal-Wallis analysis showed significant differences among the three groups a post-hoc comparison by a Mann-Whitney test was then performed. Non-parametric variables (number of grafts, use of inotropes) were compared by a chi-square analysis.

Results

The baseline characteristics of the participants and of the surgical procedure are listed in Table 1. The three groups were matched for age, height, weight and body mass index (BMI). Ejection fraction was similar between preoperative and NO-CPB, while it was lower in the CPB group ($p<0.05$). In the CPB group the bypass time was approximately 100 min, while the mean aortic cross-clamping time was 68 min. During this procedure, patients were placed in hypothermia (31°C), but body tem-

perature at the time of admission to the ICU was the same for CPB and NO-CPB. The number of grafts was significantly higher ($p<0.05$) in CPB, while the total length of anesthesia was shorter ($p<0.05$) as compared with NO-CPB. Table 2 shows the use of inotropes or vasoactive agents, which was not different for CPB and NO-CPB.

Hemodynamic parameters (Table 3) at the time of the lactate test were identical in the two postoperative groups. As shown in Table 4, basal lactate was not different in the three groups. At the end of lactate infusion, the peak value of blood lactate was steadily and significantly higher as compared to the basal value as a result of the lactate load. The peak value was significantly higher in the CPB group as compared to both preoperative and NO-CPB groups, while there was no significant difference between the latter two groups. After 120 min blood lactate returned to the basal value in both preoperative and NO-CPB groups, while it remained significantly higher in the CPB group. Hence, as compared to preoperative patients, equivalent lactate load resulted in higher peak and T-120 blood lactate values in the CPB group.

Table 3 Hemodynamics parameters. (*CPB* postoperative after bypass (n=20), *NO-CPB* postoperative after surgery with beating heart (n=20), VO_2 oxygen consumption, DO_2 oxygen delivery, *MAP* mean arterial pressure, *lowest MAP* lowest mean arterial pressure observed during the 12 h following surgery) Values are means ± SEM, no significant difference (unpaired Student's *t*-test) was observed between the two groups except for cardiac index, *$p<0.05$

	CPB	NO-CPB
Cardiac index (l/min per m^2)	3.3±0.1	2.9±0.1*
VO_2 (ml/min per m^2)	120±6	122±6
DO_2 (ml/min per m^2)	454±23	443±20
Systolic pressure (mmHg)	131±5.4	135±5.2
Diastolic pressure (mmHg)	66±2.7	66±2.4
MAP (mmHg)	86±3.3	87±3.2
Heart rate (beat/min)	93±5	96±3
Lowest MAP (mmHg)	73.9±2.2	72.2±2.4

The evolution of blood lactate was different between CPB and both preoperative and NO-CPB groups (Table 4). The lactate clearance was significantly lower in the CPB group as compared to both preoperative and NO-CPB groups, but there was no difference between the latter two groups. Endogenous lactate production among the three groups was not significantly different. Fitting of mathematical modeling was assessed by correlation coefficients (r), which were similar in the three groups: 0.98±0.003, 0.99±0.002 and 0.98±0.002 for preoperative, CPB and NO-CPB, respectively. Bi-exponential fitting allowed the calculation of two distinct half-lives (HL-1 and HL-2), which were similar in preoperative and NO-CPB groups, while both parameters were significantly different in the CPB group. As compared with preoperative and NO-CPB, HL-I was lower in the CPB group, whereas HL-II was higher. This indicated that total lactate clearance and the balance between the two different states were affected in the CPB group.

Discussion

The data indicate that 14–16 h after surgery, patients undergoing a CPB for CABG exhibit altered lactate metabolism as compared with patients undergoing CABG without bypass or with preoperative patients. Although the selection of patients between CPB and NO-CPB groups was not based on randomization, strict identical criteria of inclusion have been used regarding patient selection as well as perioperative and postoperative management. In fact, the surgeon's choice between NO-CPB or CPB was based on the anticipation of the surgical difficulty of the procedure, as judged from preoperative angiography, and not from the severity of the disease. Due to lack of randomization and the limited number of patients in each group (20 patients), a difference in ejection fraction was found between NO-CPB and both preoperative and CPB groups. However, though lower by 10% in the CPB group (45% as compared with the other groups' 55%), this value of ejection fraction was clearly higher

Table 4 Parameters of lactate metabolism. (*Lactate (T15)* blood lactate before lactate infusion, *lactate (T0)* peak of blood lactate at the end of lactate infusion, *lactate (T120)* blood lactate 120 min after the end of lactate infusion.) Groups were the same as in Table 1. Values are means ± SEM, for non-normal distributed parameters (HL-1 and HL-2) minimal and maximal values were added in parentheses (min-max).

	Preoperative	CPB	NO-CPB
Lactate (T−15) (mmol/l)	1.5±0.1	1.8±0.2	2.1±0.3
Lactate (T0) (mmol/l)	8.6±0.3[1]	14.8±2.1[1,2]	9.6±0.7[1,3]
Lactate (T120) (mmol/l)	1.9±0.1	3.4±0.4[1,2]	2.2±0.3[2]
Clearance, (ml/kg per min)	9.41±0.93	6.02±0.97[2]	9.6±0.8[3]
End product, (µmol/kg per min)	14.9±1.8	12.1±2.9	19.3±2.2
Half-life I (min)	17.2±2.3 (5–46)	10.6±1.4 (2.2–26)[2]	18.8±2.5 (4.2–42)[3]
Half-life II (min)	73±12 (19–210)	171±41 (34–848)[2]	48±2.9 (30–77)[3]

[1] significant difference versus before lactate infusion T−15 ($p<0.01$)
[2] significant difference ($p<0.05$) versus preoperative
[3] significant difference ($p<0.05$) versus CPB
The effect of exogenous lactate infusion (comparison between T−15 and T0) was made using a paired Student's *t*-test

than 35%, a value recognized as a threshold for postoperative complications. Cardiac index before the test was lower in the NO-CPB group as compared to the CPB group, indicating that if the preoperative ejection fraction was higher in NO-CPB as compared to CPB, the cardiac function before the test was not better. In addition, there was no significant difference between the two postoperative groups concerning the use of inotropes (Table 2) and hemodynamic data (Table 3).

The alteration in lactate metabolism is minor since neither basal lactate nor endogenous lactate production differed much among the three groups and the alteration was only revealed by the exogenous lactate infusion. Interestingly, lactate turnover is lower in all three groups of the present study as compared to data from the current literature, including our own previous study [20]. We have recently investigated Indonesian healthy controls and we found much lower values than those currently found in a healthy European population (unpublished). Hence basal lactate turnover appears to be lower in an Asian population living in Indonesia as compared to a Caucasian one living in Europe.

Lactate clearance and metabolism (HL-1 and HL-2) were affected in the CPB group, and the difference persisted when adjusted for the number of independent parameters of lactate metabolism. Considered all together, these results are very coherent since all five parameters investigating lactate metabolism: (1) maximal lactate concentration, (2) lactate recovery after 120 min, (3) lactate clearance, (4) HL-1 and (5) HL-2, significantly differed between the CPB and both preoperative and NO-CPB groups, while none of them differed between the preoperative and NO-CPB groups (Table 4). Hence, the CPB group was, indeed, different from the other two regarding lactate metabolism. The decrease in lactate clearance was most probably responsible for the increase in both peak and residual value after 120 min in the CPB group. A decrease in the volume distribution of lactate might contribute to increase the lactate peak. However, the peak was approximately 50% higher in the CPB group as compared to the other two and it is unlikely that such a difference between CPB and NO-CPB patients is related to hypovolemia in view of the similar hemodynamic data (Table 3).

The minor alteration in clearance after bypass was insignificant in these uncomplicated postoperative patients, unless lactate production increased, as is mimicked here by the exogenous lactate infusion. Hence, any rise in lactate production, e.g. in shock, hypoxia, epinephrine administration, etc., would increase blood lactate, an effect amplified by the moderate decrease in the clearance. Therefore, in these conditions of cardiac surgery, increased blood lactate probably suggests an increased lactate production. The lack of effect of beating heart surgery (NO-CPB) is another important finding. In this group, lactate metabolism was very similar to preoperative patients.

The recycling level of lactate depends on liver function, and the significant increase in the HL-II observed in CBP patients could be interpreted as decreased lactate metabolism through gluconeogenesis as was proposed after hepatectomy [20]. Accordingly, the significant decrease in HL-I in these CPB patients may indicate a higher probability of lactate being oxidized. Hence, the balance between oxidation and recycling is probably slightly modified in CPB patients: lactate oxidation is favored while lactate recycling is impaired. Again, these changes have been observed only when lactate metabolism was driven to an extremely high value by the exogenous lactate infusion. The understanding of the consequences of increased lactate oxidation by various tissues needs to be considered in the frame of the complex metabolic network of the whole body, i.e. inter-organ substrate cycles.

On the basis of several considerations [9, 29], it can be proposed that increased lactate turnover (i.e. production by some tissues and simultaneous consumption by others) represents a metabolic way of sharing substrate oxidation (respiration) among different tissues or cells. Indeed, when a net flux of lactate is released by some cells, this implies a net efflux of reducing equivalents (i.e. a non-complete oxidation), whereas a net uptake of lactate by others means a net import of exogenous-reducing equivalents, which are then oxidized. This could be viewed as an adaptive mechanism: some cells supplying others with regards to oxidative metabolism. Conversely, when the rise in lactate is mainly the consequence of a decreased lactate clearance, this is probably a negative event since it indicates a reduction of lactate clearance at the level of the body as a whole, i.e. a decrease in the oxidative capacity. This was shown recently in critically ill patients, where a decreased lactate clearance was associated with poor outcome [30].

Liver hypoperfusion and hypothermia during surgery may participate in the liver alteration. It was recently shown that hypothermia during CPB was responsible for metabolic disturbances [32]. In this report, increased blood lactate was found during and after surgery in hypothermic conditions associated with a reduction of acetoacetate/3-hydroxybutyrate ratio indicating a potential liver dysfunction [32]. Interestingly, hepatic blood flow was not affected by temperature while liver oxygen extraction was decreased in the hypothermic group, suggesting a metabolic effect. Although hypothermia decreases the liver respiratory rate and metabolic activity, it is not yet clear how these effects can persist 1 or 2 days after the end of the hypothermic period.

An inflammatory response could also explain the deleterious consequence of CPB on liver metabolism. Decreased splanchnic flow could cause endotoxin or bacterial translocations and endotoxins are present in the inferior vena cava during CPB [33, 34]. Endotoxin exerts some metabolic effects on liver cells [35], but the use of

steroid pretreatment reduces their release [36]. Extracorporeal circulation exposes blood to artificial membranes and to mechanical damage of the circulating cells responsible for activation of complement [37, 38] and platelet decrease. By increasing the regional generation of free oxygen radicals, CPB has been associated with some postoperative dysfunctions [39, 40]. Activated granulocytes and free radicals were shown to be drained from the inferior vena cava [40]. Nevertheless, the surgical procedure per se could also be responsible for the inflammatory response and, indeed, some authors did not find any difference according to the surgical procedure with or without CPB [41, 42].

In conclusion, the CPB procedure for CABG alters lactate metabolism by decreasing its clearance, this effect being possibly located in the liver, but the exact mechanism of such a deleterious effect is not clear. In uneventful elective surgery this alteration is minor since exogenous lactate infusion is necessary to substantiate lactate concentration abnormality. This could indicate that a lactate production increase is probably responsible for a high lactate concentration after cardiac surgery. The lack of consequence on lactate metabolism of the beating heart procedure could also be emphasized.

Acknowledgement The authors are indebted to Professor Bambang Sutrisna from the Department of Epidemiology, Faculty of Public Health, University of Indonesia, Jakarta, Indonesia, for helpful discussions regarding the statistical evaluation of this work. Dr Christiane Keriel is acknowledged for help in correcting this manuscript.

References

1. Landow L (1993) Splanchnic lactate production in cardiac surgery patients. Crit Care Med 21:S84–S91
2. Takala J, Uusaro A, Parviainen I, Ruokonen E (1996) Lactate metabolism and regional lactate exchange after cardiac surgery. New Horiz 4:483–492
3. Hayhoe M, Bellomo R, Liu G, Kellum JA, McNicol L, Buxton B (1999) Role of the splanchnic circulation in acid-base balance during cardiopulmonary bypass. Crit Care Med 27:2671–2677
4. Sandstrom K, Nilsson K, Andreasson S, Larsson LE (1999) Open heart surgery; pump prime effects and cerebral arteriovenous differences in glucose, lactate and ketones. Paediatr Anaesth 9:53–59
5. Munoz R, Laussen PC, Palacio G, Zienko L, Piercey G, Wessel DL (2000) 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 119:155–162
6. Thoren A, Elam M, Ricksten SE (2001) Jejunal mucosal perfusion is well maintained during mild hypothermic cardiopulmonary bypass in humans. Anesth Analg 92:5–11
7. Hotchkiss RS, Karl IE (1992) Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 267:1503–1510
8. Leverve X (1998) Metabolic and nutritional consequences of chronic hypoxia. Clin Nutr 17:241–251
9. Leverve XM (1999) Energy metabolism in critically ill patients: lactate is a major oxidizable substrate. Curr Opin Clin Nutr Metab Care 2:165–169
10. Jacob W, Ruokonen E, Takala J (2000) Assessment of the adequacy of systemic and regional perfusion after cardiac surgery. Br J Anaesth 84:571–577
11. Pölönen P, Ruokonen E, Hippelainen M, Pöyhönen M, Takala J (2000) A prospective randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059
12. Swan H, Sanchez M, Tyndall M, Koch C (1990) Quality control of perfusion: monitoring venous blood oxygen tension to prevent hypoxic acidosis. J Thorac Cardiovasc Surg 99:868–872
13. Vedrinne C, Tronc F, Martinot S, Robin J, Allevard AM, Vincent M, Lehot JJ, Franck M, Champsaur G (2000) Better preservation of endothelial function and decreased activation of the fetal renin-angiotensin pathway with the use of pulsatile flow during experimental fetal bypass. J Thorac Cardiovasc Surg 120:770–777
14. Koh TW, Carr-White GS, DeSouza AC, Ferdinand FD, Hooper J, Kemp M, Gibson DG, Pepper JR (1999) Intraoperative cardiac troponin T release and lactate metabolism during coronary artery surgery: comparison of beating heart with conventional coronary artery surgery with cardiopulmonary bypass. Heart 81:495–500
15. Mathieu P, Dupuis J, Carrier M, Cermacek P, Pellerin M, Perrault LP, Cartier R, Taillerfer J, Conrad Pelletier L (2001) Pulmonary metabolism of endothelin1 during on-pump and beating heart. J Thorac Cardiovasc Surg 121:1137–1142
16. Vincent JL (1996) End-points of resuscitation: arterial blood pressure, oxygen delivery, blood lactate, or...? Intensive Care Med 22:3–5
17. Marecaux G, Pinsky M, Dupont E, Kahn R, Vincent J (1996) Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. Intensive Care Med 22:404–408
18. Leverve XM (1999) Lactic acidosis. A new insight? Minerva Anestesiol 65:205–209
19. Chiolero RL, Revelly JP, Leverve X, Gersbach P, Cayeux MC, Berger MM, Tappy L (2000) Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. Crit Care Med 28:3784–3791
20. Chiolero R, Tappy L, Gillet M, Revelly JP, Roth H, Cayeux C, Schneiter P, Leverve X (1999) Effect of major hepatectomy on glucose and lactate metabolism. Ann Surg 229:505–513
21. Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, Grimaud D (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157:1021–1026
22. Jenssen T, Nurjhan N, Consoli A, Gerich JE (1993) Dose-response effects of lactate infusions on gluconeogenesis from lactate in normal man. Eur J Clin Invest 23:448–454
23. Kreisberg RA, Pennington LF, Boshell BR (1970) Lactate turnover and gluconeogenesis in normal and obese humans. Effect of starvation. Diabetes 19:53–63
24. Searle GL, Cavalieri RR (1972) Determination of lactate kinetics in the human analysis of data from single injection vs continuous infusion methods. Proc Soc Exp Biol Med 139:1002–1006

25. Woll P, Record C (1979) Lactate elimination in man: effects of lactate concentration and hepatic dysfunction. Eur J Clin Invest 9:397–404
26. Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D (1997) Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. Crit Care Med 25:58–62
27. Connor H, Woods H, Ledingham J, Murray J (1982) A model of L(+)-lactate metabolism in normal man. Ann Nutr Metab 26:254–263
28. Record CO, Chase RA, Williams R, Appleton D (1981) Disturbances of lactate metabolism in patients with liver damage due to paracetamol overdose. Metabolism 30:638–643
29. Leverve X, Mustafa I, Péronnet F. Pivotal role of lactate in aerobic metabolism (1998) In:Vincent J (ed) Yearbook of intensive care and emergency medicine. Springer, Berlin, pp 588–596
30. Levraut J, Ichai C, Petit I, Ciebiera JP, Perus O, Grimaud D (2003) Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. Crit Care Med 31:705–710
31. Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Hansen EJ (1993) Regional blood flow and oxygen transport in septic shock. Crit Care Med 21:1296–1303
32. Hashimoto K, Sasaki T, Hashiya T, Onogashi K, Takakura H, Oshiumi M, Takeuchi S (2001) Superior hepatic mitochondrial oxidation-reduction state in normothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 121:1179–1186
33. Ohri SK, Bowles CW, Mathie RT, Lawrence DR, Keogh BE, Taylor KM (1997) Effect of cardiopulmonary bypass perfusion protocols on gut tissue oxygenation and blood flow. Ann Thorac Surg 64:163–170
34. Wan S, LeClerc JL, Schmartz D, Barvais L, Huynh CH, Deviere J, DeSmet JM, Vincent JL (1997) Hepatic release of interleukin-10 during cardiopulmonary bypass in steroid-pretreated patients. Am Heart J 133:335–339
35. Leclercq P, Filippi C, Sibille B, Hamant S, Keriel C, Leverve X (1997) Inhibition of glycerol metabolism in hepatocytes isolated from endotoxic rats. Biochem J 325:519–525
36. Wan S, LeClerc JL, Huynh CH, Schmartz D, DeSmet JM, Yim AP, Vincent JL (1999) Does steroid pretreatment increase endotoxin release during clinical cardiopulmonary bypass? J Thorac Cardiovasc Surg 117:1004–1008
37. Bagge L, Lilienberg G, Nystrom SO, Tyden H (1986) Coagulation, fibrinolysis and bleeding after open-heart surgery. Scand J Thorac Cardiovasc Surg 20:151–160
38. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW (1981) Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 304:497–503
39. Menasche P, Piwnica A (1989) Free radicals and myocardial protection: a surgical viewpoint. Ann Thorac Surg 47:939–945
40. Pesonen EJ, Korpela R, Leijala M, Sairanen H, Pitkanen OM, Raivio KO, Venge P, Andersson S (1996) Prolonged granulocyte activation, as well as hypoxanthine and free radical production after open heart surgery in children. Intensive Care Med 22:500–506
41. Cox CM, Ascione R, Cohen AM, Davies IM, Ryder IG, Angelini GD (2000) Effect of cardiopulmonary bypass on pulmonary gas exchange: a prospective randomized study. Ann Thorac Surg 69:140–145
42. Fransen E, Maessen J, Dentener M, Senden N, Geskes G, Buurman W (1998) Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. Chest 113:1290–1295