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Coronary Sinus Lactate as Marker of Myocardial Ischemia in Cardiac Surgery: Correlation with Morbidity and Mortality after Cardiac Surgery

Lactatul din sinusul coronarian - marker al ischemiei miocardice în chirurgia cardiacă: corelații cu morbiditatea și mortalitatea postoperatorie

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Abstract

Introduction. Perioperative myocardial injuries are one of the most frequent causes of morbidity and mortality after cardiac surgery, the most common etiology being the poor myocardial protection during aortic crossclamp. During aortic crossclamp progressive accumulation of lactate and intracellular acidosis are well-known phenomena, and are associated with alteration of myocardial contractile function. Our objective was to study the coronary sinus lactate levels as a predictor of postoperative hemodynamic outcome in open-heart surgical patients.

Material and methods. We performed a prospective clinical trial, including 142 adult patients with elective cardiac surgery. Anterograde cardioplegia was administered in 82 patients, retrograde cardioplegia in 60 (in 30 patients it was administered intermittently and in 30 continuously). Blood was collected simultaneously from the aortic cardioplegic line (inflow) and from coronary sinus or the aortic root (outflow) before aortic crossclamp, after crossclamp at every 10 minutes and after crossclamp removal at 0 and 10 minutes. All patients were operated on cardiopulmonary bypass with cardiac arrest, using warm-blood cardioplegia for cardioprotection.

Results. Lactate levels showed increasing values during aortic crossclamp, and a rapid decline after crossclamp removal. The incidence of low cardiac output was significantly higher in patients with lactate levels that exceeded 4 mmol/L. In patients who died in the postoperative period, lactate level was even higher (5 mmol/L), with only a modest recovery after crossclamp removal.

Conclusion. Monitoring lactate level in coronary sinus blood is a reliable method and has a good prognostic value regarding postoperative morbidity and mortality in open heart surgery.

Keywords: cardiac surgery; myocardial injuries; coronary sinus; lactate levels

Rezumat

Introducere. Leziunile miocardice perioperatorii sunt cauza cea mai frecventă a morbidității și mortalității după intervenții chirurgicale cardiace, cauzele cele mai frecvente fiind protecția miocardică deficitară din timpul

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clampajului aortic. În timpul ischemiei miocardice acumularea progresivă de lactat și acidoza celulară sunt fenomene bine-cunoscute, fiind asociate cu alterarea funcției contractile miocardice. Scopul lucrării noastre a fost de a studia eficiența monitorizării nivelului de lactat din sinusul coronarian, ca factor predictiv al evoluției hemodinamice postoperatorii la pacientul operat pe cord deschis.

Materiale și metode. Am efectuat un studiu clinic prospectiv, incluzând 142 pacienți programați pentru intervenție chirurgicală pe cord deschis. Cardioplegia anterogradă a fost administrată la 82 pacienți, pe cale retrogradă la 60 (din care la 30 pacienți a fost administrat intermitent, la 30 în mod continuu). Toți pacienții au fost operați în bypass cardiopulmonar total cu oprire cardiacă, folosind cardioplegie caldă. Am recoltat sânge simultan din linia de cardioplegie (inflow) și sinusul coronarian sau rădăcina aortei (outflow) înainte de clamparea aortei, imediat după clampare, apoi din 10 în 10 minute, respectiv imediat după declampare și la 10 minute după aceasta.

Rezultate: Nivelul lactatului a crescut progresiv în timpul clampajului aortic, cu scădere rapidă după declampare. Incidența sindromului de debit cardiac scăzut a fost mai mare la pacienții cu lactat peste 4 mmol/L. La pacienții care au decedat în perioada postoperatorie, nivelul de lactat a fost peste 5 mmol/L, cu scădere ușoară după declampare.

Concluzii. Monitorizarea nivelului de lactat din sinusul coronarian este o metodă fiabilă, având o valoare prognostică bună în ceea ce privește morbiditatea și mortalitatea postoperatorie în chirurgia cardiacă.

Cuvinte cheie: chirurgie cardiacă, leziuni miocardice, sinus coronarian, nivelul lactatului

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Myocardial ischemia is a metabolic phenomenon that occurs in patients undergoing open heart surgery and it is caused by the interruption of coronary blood flow during aortic cross-clamping followed by reperfusion after aortic clamp removal and by the stress imposed during cardiopulmonary bypass (CPB). The injuries caused by myocardial ischemia / reperfusion clinically manifest as hemodynamic instability, arrhythmias, increased need for vasoactive agents, intra-aortic balloon pump (IABP) or ventricular assist devices (VAD), difficulty of weaning from CPB. The severity of these injuries will result in increased postoperative morbidity and mortality (1).

In cardiac surgery it is absolutely crucial to prevent these injuries that lead to myocardial stunning or necrosis. Myocardial stunning is characterized clinically by an increased need for postoperative inotropic support despite a technically successful surgical intervention. In high-risk patients with limited cardiac reserve this is associated with a 5 fold increase in mortality (2). The incidence of postoperative myocardial

necrosis is lower and its consequences may not be evident in the immediate postoperative period. Although in recent years we understand much better the underlying molecular mechanisms of myocardial stunning and infarction, we have no effective way to efficiently prevent these complications.

Myocardial protection aims to prevent cardiac dysfunction occurring as a consequence of myocardial ischemia / reperfusion. Although mortality in cardiac surgery was significantly reduced in the last decade, myocardial injury, evidenced by elevated creatine kinase-MB (CK-MB) and troponin, is relatively common. This is attributed to suboptimal myocardial protection during aortic crossclamping, requiring further studies for developing effective cardioprotective strategies (3).

During aortic crossclamping, progressive accumulation of lactate and intracellular acidosis are well-known phenomena, despite intermittent administration of different cardioplegic solutions (4). Lactate production induced by prolonged ischemia is associated with depletion

of adenosine triphosphate (ATP), leading to alterations of the myocardial contractile function (5, 6). Monitoring the acid-base balance of blood obtained from coronary sinus (CS) during aortic crossclamping would allow assessment of the quality of myocardial protection.

Our objective was to study the coronary sinus lactate levels as a predictor of postoperative outcome in open heart surgical patients.

Material and methods

To monitor metabolic changes during myocardial ischemia, we performed a prospective clinical trial, including 142 adult patients with elective cardiac surgery. The study was approved by the Ethical Committee of the Institute of Cardiovascular Surgery and Transplantation, Tirgu Mures and all the patients gave informed written consents.

We excluded patients with coronary diseases because of the possibility of non-uniform spreading of cardioplegic solution leading to incomplete protection and those with ejection fraction under 35%. In 82 patients cardioplegia was administered antegrade, in 60 retrograde (in 30 patients was administrated intermittently and in 30 continuously). There were no statistical differences among groups for clinical and technical characteristics (Table I). All patients were operated on cardiopulmonary bypass with cardiac arrest at normothermia or mild hypother-

mia (33°C), using warm-blood cardioplegia, described by Calafiore (7).

To determine lactate levels, blood was collected simultaneously from the aortic cardioplegic line (inflow) and coronary sinus (outflow) in antegrade cardioplegia cases, and from coronary sinus (inflow) and aortic root (outflow) in patients with retrograde administration, before aortic crossclamp (preclp), immediately after crossclamp (clp 0) and at 10 (clp 10), 20 (clp 20), 30 (clp 30) 40 (clp 40), 60 (clp 60), 80 (clp 80) minutes, then immediately after the removal of aortic crossclamp (declp 0) and 10 minutes later (declp 10). In order to draw venous blood or to give cardioplegic solution, direct approach of coronary sinus was required in total cardiopulmonary bypass, with direct cannulation of superior and inferior vena cava and their complete occlusion with a tourniquet. Right oblique atriotomy allowed access to the coronary sinus and also the surgical intervention.

Statistical analysis were performed using GraphPad Prism, version 5.0. Data were tested for normality and distribution with Kolmogorov-Smirnov test and were described by mean and standard deviation. We used two-tailed paired t-test and one-way ANOVA test with Bonferroni's correction to compare quantitative variables. Fisher's exact test was also used to compare groups. We considered the differences statistically significant when p-value was less than 0.05.

Table I. Patients characteristics (VR – valvular replacement, CG – correction of congenital heart disease)

	Intermittent anterograde administration N=82 pts	Intermittent retrograde administration N=30 pts	Continuous retrograde administration N=30 pts	ANOVA p
Mean age (years)	59.1 ± 9.8	60.17±8.8	57.77±10.3	NS
Male/female (No)	54/28	23/7	20/10	NS
VR/CG (No)	79/3	30/0	28/2	NS
Crossclamp time (minutes)	47.48±19.5	48.3±18.7	46.33±20.3	NS
Cardiopulmonary bypass time (minutes)	72.18±25.9	74.23±24.9	70.03±26.1	NS

Results

Lactate levels in samples simultaneously collected from blood cardioplegia (inflow) and coronary sinus in antegrade cardioplegia or aortic root in retrograde administration (outflow) showed increasing values during aortic cross-clamping with a higher increase in blood samples drawn at outflow and a rapid decline after removal of the crossclamp (Table II). Lactate levels increased less in patients who had received continuous retrograde cardioplegia.

According to gender, age or type of surgery, we did not notice statistically significant differ-

ences in lactate levels at different times of intervention.

The most frequent postoperative complications were respiratory distress syndrome (4 patients), renal dysfunction/ failure (19 patients) and neurological disorders (9 patients). The number and severity of postoperative complications were lower in patients who received continuous retrograde cardioplegia, whereas in the other two groups were nearly identical, but the differences were not statistically significant (Table III).

In 24 patients who developed low cardiac output (demonstrated by transpulmonary cathe-

Tabel II. Mean lactate level variations (mmol/L) in the studied groups

	Antegrade Administration (82)		Intermittent retrograde administration (30)		Continuous retrograde administration (30)		ANOVA test
*	In	Out	In	Out	In	Out	P out
Preclp	1.18	1.62	1.21	1.65	1.16	1.58	NS
Clp 0	1.64	2.56	1.81	2.88	1.6	2.13	0.0005
Clp 10	1.85	2.95	1.99	2.96	1.8	2.69	0.0004
Clp 20	1.89	3.78	1.98	3.85	1.81	3.23	0.0178
Clp 30	1.89	4.53	2.08	4.66	1.8	3.9	0.0033
Clp 40	2.10	5.47	2.18	5.53	2.1	4.28	0.0116
Clp 60	2.34	6.37	2.29	6.31	2.2	4.58	0.0142
Clp 80	2.84	6.37	2.66	6.73	2.5	4.95	0.0102
Declp 0	2.52	4.97	2.8	5.2	2.4	4	0.0024
Declp 10	1.78	1.78	1.95	2.59	1.8	2.31	NS

*Before aortic crossclamp (Preclp), immediately after crossclamp (Clp 0) and at 10 (Clp 10), 20 (Clp 20), 30 (Clp 30) 40 (Clp 40), 60 (Clp 60), 80 (Clp 80) minutes, then immediately after the removal of aortic crossclamp (Declp 0) and 10 minutes later (Declp 10).

Table III. Postoperative complications in the studied groups

	Intermittent antegrade administration N=82 pts	Intermittent retrograde administration N=30 pts	Continuous retrograde administration N=30 pts	Fisher's exact test p
Low Cardiac Output	15	5	3	NS
Acute Respiratory Distress Syndrome	3	1	0	NS
Renal dysfunction/ failure	6/ 6	3/1	2/1	NS
Neurological disorders	6	2	1	NS
Death	4	1	1	NS

ter or echocardiography) we noticed that lactate levels were increased for a longer period (30-80 minutes), whereas in patients with normal cardiac output levels were normal or elevated for a shorter period of time (10 minutes) (fig. 1). The difference in lactate levels immediately after crossclamp removal was statistically significant ($p < 0.0001$; two-tailed paired t-test) between patients with normal and low cardiac output. No patient with lactate less than 2.2 mmol/L has developed low cardiac output syndrome, 42.5% with lactate between 2.2 to 4 mmol/L had hemodynamic instability and 69.6% of patients with lactate higher than 4 mmol/L developed postoperatively low cardiac output syndrome.

The same correlation can be observed comparing lactate levels and postoperative mortality. In those patients who died in the postoperative period, lactate levels were higher ($p = 0.0004$) with only a modest recovery (to 5 mmol/L) af-

ter removal of crossclamp; the increase in lactate levels in the survivors was shorter, with a return to normal in 10 minutes after removal of the aortic crossclamp (fig. 2).

Discussions

Improved myocardium preservation techniques during aortic crossclamping significantly contributed to the development of cardiac surgery, however, there is still controversy regarding the ideal composition of cardioplegia (blood or crystalloid solutions), the method of delivery (antegrade or retrograde), temperature (cold or warm) or the type of administration (intermittent or continuous). In inappropriate myocardial protection, contraction band necrosis and dystrophic calcifications were observed on the myocardium, leading to an increase in early and late postoperative complications, decreased cardiac

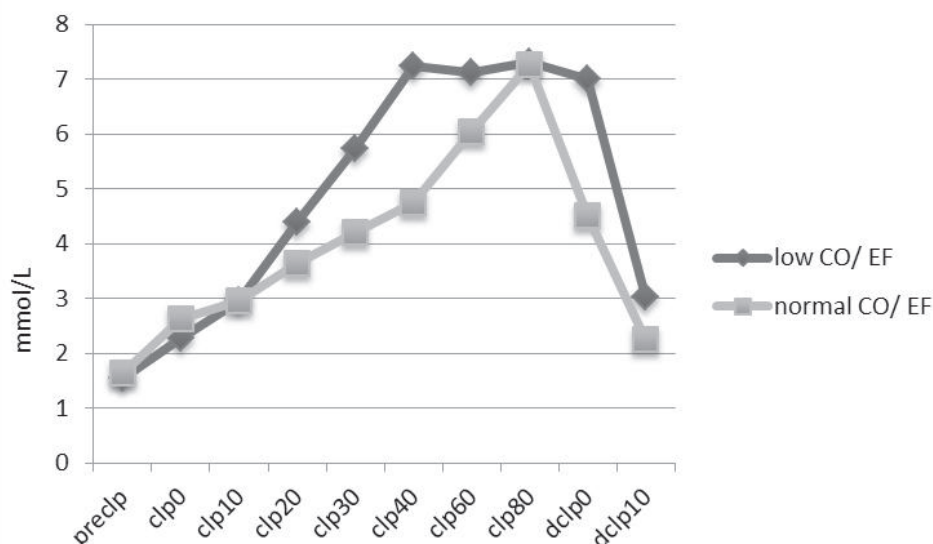


Figure 1. Lactate levels (mmol/L) at different moments of surgery in patients with normal and low cardiac output syndrome (CO=cardiac output measured by transpulmonary catheter; EF=ejection fraction, measured by echocardiography) *Before aortic crossclamp (preclp), immediately after crossclamp (clp 0) and at 10 (clp 10), 20 (clp 20), 30 (clp 30) 40 (clp 40), 60 (clp 60), 80 (clp 80) minutes, then immediately after the removal of aortic crossclamp (declp 0) and 10 minutes later (declp 10).

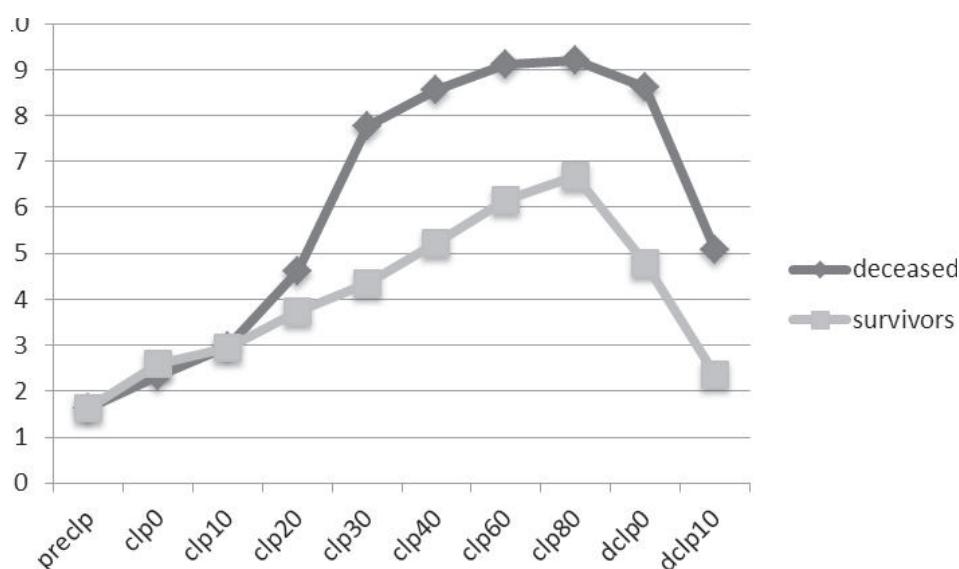


Figure 2. Lactate levels (mmol/L) in different stages of surgery in survivors and deceased patients.

*Before aortic crossclamp (preclp), immediately after crossclamp (clp 0) and at 10 (clp 10), 20 (clp 20), 30 (clp 30) 40 (clp 40), 60 (clp 60), 80 (clp 80) minutes, then immediately after the removal of aortic crossclamp (dclp 0) and 10 minutes later (dclp 10).

performance and impaired quality of life (8). Hypoperfusion of organs and tissues due to low cardiac output syndrome leads to metabolic acidosis, development of severe organ dysfunctions and accumulation of endogenous toxins, which ultimately contribute to the development of multiple organ dysfunction.

In recent years, most studies support the efficacy of blood cardioplegia administered at normothermia or mild hypothermia (30-33°C) with antegrade or retrograde, intermittent or continuous administration. Blood gives to the cardioplegic solution tonicity, rheological and buffer capacity and it has antioxidant properties, thereby protecting the myocardium against ischemic injuries (9). Nevertheless, there are still severe postoperative complications after heart surgery, probably because the development of low cardiac output syndrome can also be caused by other mechanisms, such as preoperative ventricular dysfunction, ventriculotomy, acid-base disorders, triggered and amplified by the inflamma-

tory syndrome during extracorporeal circulation, but the major mechanism remains myocardial ischemia / reperfusion injury. Myocardial recovery is dependent on myocardial protection, therefore it is imperative to monitor its effectiveness. One of the most sensitive markers of myocardial ischemia is lactate measured directly in the coronary sinus blood because it can accurately reflect changes in the myocardial metabolic level (10). Other biomarkers such as myocardial enzymes (CK-MB, troponin I or T), serum lactate, ischemia modified albumin, natriuretic peptide, unbound fatty acids were also studied, but none of these was able to demonstrate a link between the obtained values and patient's prognosis (1, 11-13). The earliest alteration caused by inadequate myocardial protection is the development of anaerobic metabolism, myocardial tissue acidosis and lactate production, while myocardial necrosis with release of myocardial enzymes, such as Troponine, occurring later (14). Recent studies reported that troponin I, as a marker of

intraoperative myocardial damage has a high specificity and sensitivity, with a predictive value for the development of postoperative hemodynamic complications, but lactate levels in the coronary sinus could be an earlier sign, making it possible to improve myocardial protection in order to prevent severe injury (9). By monitoring the metabolic changes during surgery (coronary sinus metabolites namely the myocardial tissue pH) Khabbaz et al. have demonstrated that measurement of lactate in the coronary sinus blood 10 minutes before removal of the aortic crossclamp is the best predictor of postoperative cardiac dysfunction (15). Since the cardioplegic solution is administered immediately after aortic clamping and is reinfused every 20 minutes, in our study we determined the coronary sinus lactate throughout myocardial ischemia to immediately detect any alteration in the cardiac metabolism.

Intraoperative alterations in lactate metabolism were described by Khuri et al., who demonstrated that there is a direct correlation between the severity of myocardial acidosis during myocardial ischemia and the patients' outcome and showed that prevention of intraoperative acidosis might improve the patients' prognosis after open-heart surgery (16). Onorati et al. also found that higher lactate levels during reperfusion correlate with severe hemodynamic complications (9). We noticed that there was a slight increase in lactate levels in the cardioplegic line (inflow). This was probably due to lactate production not only in the ischemic myocardium but also in hypoperfused tissues during extracorporeal circulation. Due to this increase, in the later stages of the surgical intervention, the myocardium is perfused with blood cardioplegia carrying increased lactate levels. The increase in lactate levels was more pronounced at outflow, reaching pathological values at 20 minutes of ischemia. Differences between mean values measured at the entrance and exit of myocardial circulation were

statistically significant on all measurements, the largest being after 60 and 80 minutes of aortic crossclamping and especially in patients who died. Lactate levels showed a rapid decline immediately after removal of the aortic crossclamp, in most cases returning to normal in 10 minutes of reperfusion. Increasing lactate levels during myocardial ischemia suggest that despite properly infused cardioplegic solution, minor myocardial injuries occur leading to myocardial apoptosis or necrosis if aortic crossclamping lasts longer (17). Metabolic acidosis occurs due to the anaerobic metabolism during ischemia and may induce an inflammatory response following reperfusion, which may contribute to the development of hemodynamic disorders in the postoperative period. Acidosis itself decreases myocardial contractility and cardiac response to exogenous catecholamines and is a risk factor for arrhythmia development (18-20).

Comparing antegrade and retrograde groups, we found that lactate levels were higher in those who received antegrade and intermittent retrograde cardioplegia. From a theoretical perspective, retrograde cardioplegia has many advantages, its use being particularly recommended in patients with severe proximal coronary stenosis and low left ventricular contractility, but its use implies a correct insertion of the catheter into the coronary sinus to infuse the entire myocardium and to maintain a perfusion pressure of 40 mmHg during administration, in order to prevent perivascular hemorrhage and edema (17, 21). The disadvantage of this method is the direct shunting of blood in atrial and ventricular cavities due to arterial-sinusoidal and thebesian vessels, therefore delivery of the cardioplegic solution with a flow of 100 ml/min being necessary, in order to compensate for physiological shunting and decrease the lactate production (22). With all these drawbacks, retrograde cardioplegia is frequently used in patients with coronary and valvular heart disease. In recent years it has been

recommended to use a combined cardioplegia to improve myocardial protection. This means delivering an antegrade cardioplegia followed by retrograde myocardial perfusion. The "Patch" study demonstrated the efficiency of this combined administration, in patients with severe pre-operative left ventricular dysfunction (23).

Conclusions

Lactate levels were significantly higher in patients with low cardiac output and other post-operative dysfunctions. We noticed a statistically significant correlation between lactate levels and postoperative morbidity and mortality, therefore we can affirm that monitoring lactate levels in the coronary sinus is a reliable method and has a good prognostic value regarding postoperative morbidity and mortality in open heart surgical patients. Continuous retrograde administration of cardioplegia seems to be a safe method of myocardial protection, if this technique is correctly used.

Abbreviations

ATP - adenosine triphosphate
CG - correction of congenital heart disease
Clp - clamp (aortic crossscamp)
CK-MB - creatine kinase-MB
CPB - cardiopulmonary bypass
CS - coronary sinus
IABP - intra-aortic balloon pump
VAD - ventricular assist devices
VR - valvular replacement

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