Am J Physiol Endocrinol Metab 284: E788–E794, 2003.
First published August 20, 2002; 10.1152/ajpendo.00522.2001.

Myocardial interstitial glucose and lactate before, during, and after cardioplegic heart arrest

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Submitted 21 November 2001; accepted in final form 31 July 2002

Kennergren, Charles, Vittorio Mantovani, Lena Strindberg, Eva Berglin, Anders Hamberger, and Peter Lönnroth. Myocardial interstitial glucose and lactate before, during, and after cardioplegic heart arrest. *Am J Physiol Endocrinol Metab* 284: E788–E794, 2003. First published August 20, 2002; 10.1152/ajpendo.00522.2001.—The interstitial fluid of the human myocardium was monitored in 13 patients undergoing aortic valve and/or bypass surgery before, during, and after hypothermic potassium cardioplegia. The regulation of glucose and lactate was studied after sampling with microdialysis. The following questions were addressed. *1*) Is the rate of transcapillary diffusion the limiting step for myocardial uptake of glucose before or after cardioplegia? *2*) Does cold potassium cardioplegia induce a critical deprivation of glucose and/or accumulation of lactate in the myocardium? Before cardioplegia, interstitial glucose was ~50% of the plasma level ($P < 0.001$). Interstitial glucose decreased significantly immediately after induction of cardioplegia and remained low (1.25 ± 0.25 mM) throughout cardioplegia. It was restored to precardioplegic levels 1 h after release of the aortic clamp. Interstitial glucose then decreased again at 25 and 35 h postoperatively to the levels observed during cardioplegia. Interstitial lactate decreased immediately after induction of cardioplegia but returned to basal level during the clamping period. At 25 and 35 h, interstitial lactate was significantly lower than before and during cardioplegia. Glucose transport over the capillary endothelium is considered rate limiting for its uptake in the working heart but not during cold potassium cardioplegia despite the glucose deprivation following perfusion of glucose-free cardioplegic solution. Lactate accumulated during cardioplegia but never reached exceedingly high interstitial levels. We conclude that microdialysis provides information that may be relevant for myocardial protection during open-heart surgery.

myocardium; ischemia; microdialysis; surgery

A BETTER UNDERSTANDING of the regulation of delivery and uptake of nutrients in the heart is required to optimize myocardial metabolic balance during cardioplegia. Research in this area has focused mainly on the pre- and immediately postoperative situations, and various studies on plasma sampling techniques have been published (1, 5, 17), including single- and multiple-isotope balance studies (24, 38, 44). Some (5, 36, 37, 39), but not all (31), investigators have demonstrated decreased cardiac uptake and oxidation of glucose and lactate in the initial postoperative period.

However, a more detailed knowledge is required of how the concentration of nutrients is regulated in the myocardium, where interstitial fluid shifts are brought about by perfusion of cardioplegic solutions. A key issue is the monitoring of the myocardial metabolism during the cardioplegic period during which relevant plasma sampling cannot be carried out. Sampling of the interstitial fluid of the myocardium by means of microdialysis before, during, and after open-heart surgery is now used also in the clinical situation (18, 19). When properly calibrated, the approach offers high-precision data from the myocardial interstitium (26). The technique has previously been used for metabolic balance measurements in other organs (14, 15, 29). Myocardial microdialysis has been performed in experimental setups of both the calibrated (25) and the noncalibrated type (20). Noncalibrated microdialysis sampling of the human heart during cardioplegia was recently reported from two different centers (9, 18, 19).

In the present study, we used internal reference calibration for measurement of interstitial glucose and lactate in the myocardium. Glucose and lactate were chosen as both being important nutrients for the myocardium during normal conditions. Increased lactate production serves as a marker for ischemia in the heart. Thirteen patients were monitored before, during, and after open-heart surgery, including hypothermic cardiopulmonary bypass and cold potassium cardioplegia, in an attempt to establish whether *1*) the transcapillary diffusion is a rate-limiting step for myocardial glucose uptake before or after cardioplegia; and *2*) glucose is lowered and/or lactate increased to a critical extent during cold cardioplegia.

PATIENTS, MATERIALS, AND METHODS

Patients. Thirteen patients of Caucasian origin, 3 females and 10 males, mean age 62 yr (range 33–77 yr; Table 1) gave

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their informed consent to participate in the study, which was approved by the local ethics committee. No high-risk patients (i.e., patients with cerebral lesions, renal insufficiency, or recent myocardial infarction) were included in the study. The ejection fraction (EF) was evaluated with echocardiography and/or angiography, and patients with an EF of <35% were excluded from the study, as were known cases of diabetes mellitus. Four patients (all males) underwent coronary artery bypass surgery (CABG), including one to four distal anastomoses. Three of these received a left internal mammary artery graft to the left anterior descending coronary artery. One of the CABG patients also underwent aortic valve replacement. In another patient, the CABG was an elective reoperation. Nine patients (3 females, 6 males) received valve prosthesis because of aortic valve disease. Acetylsalicylic acid, warfarin, and digoxin medications were discontinued preoperatively. In the patients from the CABG group, the dose of selective β-blockers was reduced by 50% postoperatively, and antiangina medication was discontinued. In the valve group, diuretics were reduced or discontinued postoperatively.

Protocol. Food and fluid intake was discontinued no later than at 12:00 midnight on the day preceding surgery. No intravenous infusions (including glucose substitution) were given preoperatively. Before surgery, the patients were sedated with 10 mg of morphine hydrochloride and 0.4 mg of hyoscine hydrobromide (morphine-scopolamine, Pharmacia) and 1 mg of flunitrazepam (Rohypnol, Roche). One or more indwelling catheters were established in the radial and/or femoral arteries for blood pressure measurements and blood sampling. Central and peripheral venous indwelling catheters were established. Anesthesia was induced with thiopental sodium (Pentothal, Abbott), fentanyl (Fentanyl, Dumex-Alpharma) and pancuronium bromide (Pavulon, Organon Teknika) and maintained with fentanyl, droperidol (Dridol, Janssen-Cilag), halothane (Fluothane, Zeneca), or enflurane (Efrane, Abbott) and midazolam (Dormicum, Roche). Before sternotomy, a sinus coronary catheter (Wilton-Webster, Baldwin Park, CA) was introduced through the right external jugular vein and placed with its tip in the great cardiac vein with fluoroscopic guidance.

The microdialysis probes were inserted into the region between the left anterior descending artery and the second diagonal artery immediately after a full median sternotomy (18–20). Care was taken to avoid vessels and to place the probes at equal depth (i.e., 2–3 mm). The patients were heparinized (300 U/kg body wt + 7,500 U heparin) before bypass was instituted. Anticoagulation was reversed with protamine (1 mg/100 U heparin) when patients had been weaned from bypass. The hearts were cannulated, either with a two-stage venous cannula in the right atrium (CABG group) or via bicaval cannulation (valve group). After aortic cross-clamping, the hearts were arrested with cold (2–4°C), crystalloid, glucose-free cardioplegic solution (Plegisol; Abbott). The electrolyte composition was (in meq) 110 Na^+, 160 Cl^-, 16 K^+, 2.4 Ca^{2+}, and 32 Mg^{2+}, including 10 ml of 8.4% $NaHCO_3$ for a pH of 7.8, at room temperature. The solution was administered in the coronary arteries in an antegrade fashion. The cardioplegia was repeated at intervals ranging from 10 to 60 min. In one patient (*patient 8*), both antegrade and retrograde infusion of cardioplegic solution was used. A mean of 1,600 ml (range 1,000–2,800) of cardioplegic solution was administered. Ice slush was routinely used for topical cooling. The mean for the lowest body core temperature was 32°C (range 30–34°C). The mean cardiac arrest time was 65 min (range 33–93 min). After aortic declamping, internal defibrillation was applied if sinus rhythm did not develop spontaneously. One patient (*patient 9*) needed seven defibrillations to convert to sinus rhythm. After declamping, a mean reperfusion period of 23 min (range 12–39 min) was allowed before patients were weaned from the bypass. Weaning off bypass was routinely done at a core temperature of 36°C if reperfusion was considered sufficient; otherwise longer reperfusion was allowed. Glucose (5%) solutions were used for the administration of parenteral drugs peroperatively and for up to 9 h after surgery. Postoperatively, the patients were monitored according to clinical routine, including continuous electrocardiogram, arterial and central venous pressures, and P_{O_2} measurements. The patients were extubated within 4 h postoperatively. In case of extended drainage from the chest tubes, as with *patient 1*, the tracheal tube remained in place for longer. This patient underwent resurgery on the first postoperative day due to diffuse bleeding unrelated to the microdialysis probe. Coronary sinus catheters were removed no later than the morning after surgery. In *patient 13*, the coronary sinus catheter was extracted a few hours postoperatively due to ventricular fibrillation cured by defibrillation. However, because arrhythmia persisted after its removal, the catheter was thought not to be the cause.

The microdialysis probes were extracted percutaneously (18, 19) no later than 48 h after surgery. With few exceptions, the patients could start intake of fluids and some food on the first postoperative day. Three patients had short spells of atrial fibrillation postoperatively; *patient 1* had persistent

Table 1. *Clinical characteristics*

Patient No.	Sex	Age, yr	BMI	Diagnosis	Surgery	Clamping Time, min	EF, %
1	M	42	22.8	AS	AVR	83	60n
2	M	66	27.7	AS	AVR	65	40n
3	M	33	22.7	AS	AVR	74	55n
4	M	48	28.1	AS	AVR	51	60n
5	F	70	24.1	AS	AVR	71	72n
6	M	74	27.0	AP+AS	CABG × 1,AVR	93	55n
7	M	72	24.7	AP	CABG × 4	46	60a
8	F	67	31.5	AS	AVR	89	60n
9	M	69	23.4	AP	CABG × 4	41	70a
10	M	53	24.2	AP	CABG × 3	33	40a, 50n
11	M	61	29.6	AS	AVR	52	65n
12	M	63	27.4	AS	AVR	87	55n
13	F	77	24.0	AS	AVR	62	77n

BMI, body mass index; EF, ejection factor; AP, angina pectoris; AS, aortic valve stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; a, measured by angiography; n, measured by noninvasive ultracardiography

atrial fibrillation during admission. *Patients 1* and *7* showed transient ST segment alterations postoperatively. However, plasma markers for myocardial ischemia, such as aspartate aminotransferase and creatine kinase MB were insignificantly elevated, and no case of myocardial infarction was diagnosed.

Microdialysis. The microdialysis probes were developed and manufactured in our laboratory (18–20). Two types of probe were used, identical except for the length of the outflow tubing. The length of probes used for perioperative measurements was 30 mm to minimize the dead space. Sampling periods were 10 min. Probes for postoperative measurements had an outflow tubing of 470 mm. This permitted tunneling of the probes under the lower left rib for collection of extrathoracic samples. Sampling periods were 60 min. A vial adapter for sample collection was connected to the outlet tubing, and the inlet tubing was connected to an infusion pump (CMA 100; CMA, Stockholm, Sweden). The inlet tubing was ~2,000 mm long, allowing the pump to be placed outside the sterile field.

The permeable membrane (0.6 mm OD, 0.1-μm pores; CPC/PE; Gambro, Lund, Sweden) allowed passage of molecules exceeding the size of the markers used. The probes were perfused with sterile, isotonic NaCl solution at room temperature at 2.5 μl/min. Priming of the probes to evacuate the air began not later than 20 min before implantation. Sampling was done before cardioplegia, at 10-min intervals during cardioplegia and reperfusion, and thereafter at 60-min intervals. Samples were stored at −80°C until analysis.

In situ calibration was performed with an internal reference technique (27). Before and during cardioplegia and in 3-h pulses at 25 and 35 h postoperatively, 5 μCi/ml [^{14}C]lactate and 5 μCi/ml [^{3}H]glucose (Amersham, Buckinghamshire, UK) were added to the perfusate. In this way, recalibration data were achieved during the fluid shifts and temperature changes expected during the period. The loss of radioactivity over the microdialysis membrane was used to calculate relative recovery. Continuous perfusion with internal reference markers was avoided to prevent accumulation of the label in ambience of the catheter (27). Data were corrected for the delay caused by passing the dead space. Due to the variation in duration of the cardioplegia, data are presented as mean interstitial glucose and lactate concentrations in samples collected during the first 10 min after the onset of cardioplegia as well as in samples representing the middle of the whole cardioplegic period and just before release of the aortic clamp.

Blood samples. Arterial blood was drawn from the radial or femoral artery and venous blood from the coronary sinus, both in the middle of microdialysis sampling periods (corrected for dead-space delay). The blood samples were centrifuged, and the plasma was decanted and stored at −80°C.

Analyses. Glucose and lactate concentrations in plasma and dialysates were determined enzymatically using 10-μl samples for simultaneous analysis of glucose and lactate (YSI 2700 select biochemical analyzer; Yellow Springs Instruments, Yellow Springs, OH). Radioactivity was counted in a liquid scintillation counter with a quench-corrected (external standards) double-isotope program (1900 CA, TRI-CARB; Packard Instruments, Meriden, CT).

Statistics. The results are expressed as means ± SE. Significance of differences was tested with ANOVA and, when appropriate, Student's *t*-test for paired and unpaired observations. A difference of $P < 0.05$ was considered statistically significant.

RESULTS

There were no infections, infarctions, local bleeding, or other complications related to the study. The microdialysis probes were implanted and extracted without inducing arrhythmias or other side effects. Blood glucose increased ~1 h after surgery, since infusions containing glucose were given perioperatively (Fig. 1*A*). Glucose infusions were also given postoperatively. Consequently, the high blood glucose levels at 25 and 35 h postoperatively were postprandial, in contrast to the levels recorded before cardioplegia (Fig. 1*A*).

The relative recovery (dialysate concentration/interstitial concentration) of interstitial glucose and lactate before induction of cardioplegia was 28 ± 7 and 31 ±

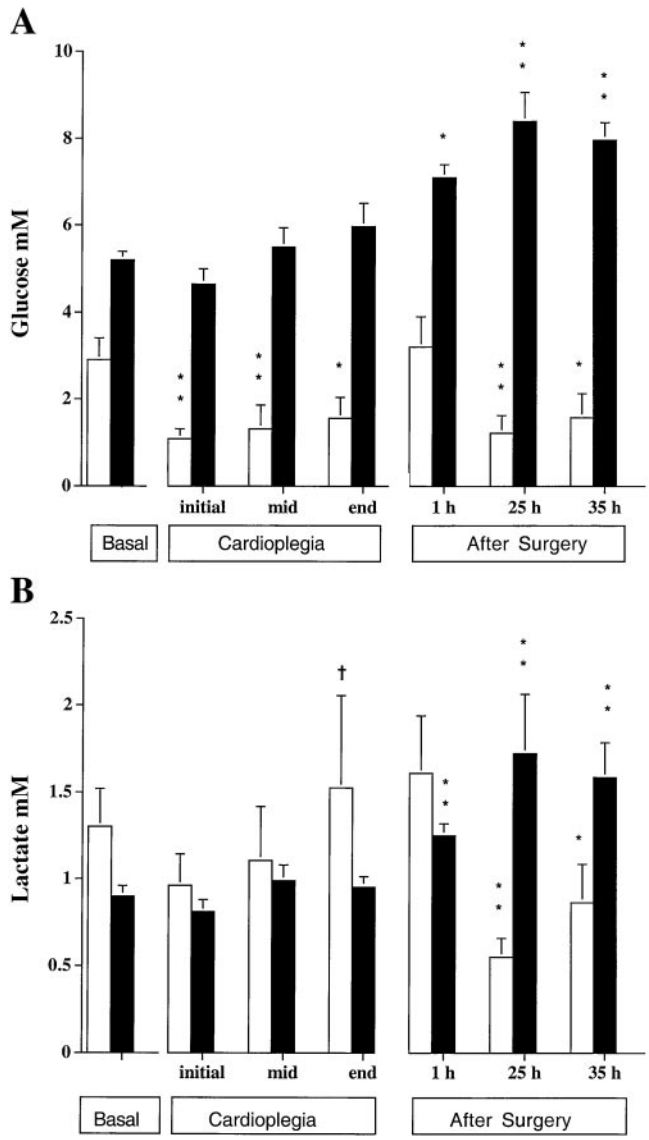

Fig. 1. Glucose concentrations (*A*) and lactate concentrations (*B*) in interstitial fluid (open bars) and arterial blood (filled bars) before, during, and after cardioplegia. Data are depicted as means ± SE; n = 7–11 patients. Statistical significance for comparisons of concentrations with the basal level in the respective compartment: $^{*}P < 0.01$, $^{**}P < 0.005$. Statistically significant difference of interstitial lactate concentration during cardioplegia: $\dagger P < 0.05$.

7%, respectively. The recovery declined during cardioplegia to 20 ± 2 and 16 ± 6%, respectively, but increased 25 h postoperatively to 43 ± 7 and 45 ± 6%, respectively.

Interstitial glucose decreased immediately and significantly after coronary instillation of glucose-free cardioplegic solution and remained low throughout cardioplegia (Fig. 1*A*). It was then restored to precardioplegic levels at 1 h after release of the aortic clamp. Interstitial glucose decreased again, at 25 and 35 h after surgery, to levels similar to those recorded during cardioplegia (Fig. 1*A*).

Plasma lactate increased slightly postoperatively (Fig. 1*B*). A statistically nonsignificant decrease in interstitial lactate was registered immediately at induction of cardioplegia, followed by a significant increase throughout the clamping period (Fig. 1*B*). The lowest levels of interstitial lactate were recorded 25 and 35 h after surgery.

The uptake and release of glucose and lactate in the myocardium were calculated from the differences between the arterial-coronary sinus (a-v) and arterial-interstitial (a-i) concentrations. There was a significant uptake of glucose before cardioplegia (Table 2). Both the a-v and the a-i concentration differences for glucose increased significantly postoperatively. Throughout the recording period, interstitial glucose was lower than both arterial and venous blood glucose (Fig. 1*A*); therefore, the a-i concentration differences of glucose exceeded the corresponding a-v differences (Table 2).

Before cardioplegia, a small, but statistically significant, a-v difference was recorded for lactate, indicating a myocardial uptake (Table 2). This switched to a significant negative lactate balance 1 h after cardioplegia. The a-i difference for lactate increased significantly 25 h after surgery, indicating a significant rate of lactate utilization by the myocardium.

Table 2. *Concentration differences of glucose and lactate immediately before and 1 or 25 h after cardioplegia*

	Concentration, mmol/l	*P* Value
Glucose		
a-v		
Before	0.20 ± 0.07	<0.001
1 h	0.40 ± 0.08*	<0.05
a-i		
Before	2.21 ± 0.63	<0.001
1 h	3.76 ± 0.85*	<0.001
25 h	7.5 ± 0.7†	<0.001
Lactate		
a-v		
Before	0.16 ± 0.05	<0.01
1 h	−0.26 ± 0.07†	<0.001
a-i		
Before	−0.50 ± 0.23	NS
1 h	−0.35 ± 0.31	NS
25 h	1.18 ± 0.38†	<0.001

Data are means ± SE, n = 7–11 patients. a-v, Concentration difference between arterial and sinus coronarious samples; a-i, arterial-interstitial concentration difference; NS, not significant. Statistical significance for differences compared with cardioplegia is indicated: *$P < 0.01$; †$P < 0.005$.

DISCUSSION

To our knowledge, this is the first study in which calibrated microdialysis has been used for direct measurement of nutrient concentrations in the interstitium of the human heart. The results show that *1*) there are significant differences in a-i concentration for both glucose and lactate in the beating heart, indicating that transcapillary diffusion is a rate-limiting step for both the uptake and the release of glucose and lactate; and *2*) interstitial glucose and lactate levels change during cardioplegia but never reach nonphysiological concentrations.

Before cardioplegia. Interstitial glucose in the myocardium was only ~50% of that in arterial plasma, indicating that the entry of glucose into the interstitial fluid does not balance its rate of elimination. Consequently, transcapillary diffusion of glucose in addition to the myocellular glucose transporter is a rate-limiting step for myocardial glucose uptake. This is in agreement with findings in skeletal muscle in resting subjects, in which the glucose uptake rate correlates negatively with interstitial glucose concentration (12, 13). In working skeletal muscle, blood flow and capillary permeability increase to reduce the concentration difference between arterial and interstitial glucose. The interstitial glucose concentration was surprisingly low, since the blood flow in the myocardium is much higher than in skeletal muscle, which, in turn, indicates that the cellular uptake of glucose in the myocardium is extremely efficient (5, 10, 41).

Small hydrophilic molecules exchange via passive diffusion through intercellular clefts in continuous capillaries (4). Thus the extraction fraction (ExF) for glucose and lactate can be calculated according to the formula: $ExF = (A - I) \times (I - e^{-PS/Q})$, where A is the arterial concentration, I is the interstitial concentration, PS is the permeability surface-area product, and Q is the flow of plasma (4). In our study, the a-v difference of glucose was 0.2 mmol/l and, hence, the resulting apparent PS/Q ratio in the myocardium could be approximated to 0.1 ml·100 g^{-1}·min^{-1}. With the assumption of a plasma flow of 60 ml·100 g^{-1}·min^{-1} (40), the apparent PS for glucose approximates 6 ml·100 g^{-1}·min^{-1} and the glucose uptake 20 μmol·100 g^{-1}·min^{-1}. This PS value is considerably lower than that previously reported for perfused animal heart preparations (4) and may indicate a reduced nutritional myocardial blood flow in our patients. Interestingly, despite normal coronary blood flow, myocardial glucose uptake is reduced to 40 μmol·100 g^{-1}·min^{-1} in patients with coronary heart disease (30). It is noteworthy that the present results were obtained in 13 patients, four of whom had coronary heart disease, and that the glucose balance was estimated during non-insulin-stimulated conditions. Hence, the low PS/Q ratio demonstrated in the present study

indicates that capillary permeability was low in the patients currently investigated.

Our results suggest that coronary heart disease may be characterized not only by myocardial hypoxia due to reduced blood flow but also by restricted availability of nutrients and consequently reduced ATP levels, in agreement with previous studies (21, 35). The subject group presently investigated was small; consequently, subgrouping of the subjects could not lead to any firm conclusion as to the nutrient availability in the four patients with coronary artery disease subjected to coronary bypass surgery, since they did not show lower interstitial glucose levels than the rest of the patients (data not shown). In a previous and larger study (18, 19), we were able to compare data from patients with ischemic and nonischemic heart disease. As expected, the patients with ischemic heart disease had more marked relative changes in the appearance of ischemic markers in the interstitial fluid perioperatively compared with the subjects with nonischemic heart disease. It was noteworthy, however, that the concentration of substrates like nutritive amino acids did not differ between the groups. It may thus be concluded that, even if small differences exist between different patients in this regard, larger study groups are needed to give further evidence.

Interstitial lactate did not differ from plasma lactate, even though lactate was lower in venous plasma than in arterial plasma. However, lactate metabolism is not reflected by interstitial concentration measurements only (16). An interstitial concentration of lactate higher than that in plasma does not rule out ongoing lactate uptake and oxidation, since a net myocardial release of lactate may prevail simultaneously with lactate uptake and oxidation (6, 24, 42, 43). Furthermore, there are regional variations of lactate oxidation within the myocardium when the left ventricle wall releases lactate more efficiently than do the other regions (6, 7). Therefore, we found no a-i concentration difference for lactate in the wall of the left ventricle, whereas the a-v concentration difference indicated myocardial uptake and oxidation of lactate.

During cardioplegia. It is notable that mean interstitial glucose, which was low throughout the cardioplegic period, was never lower than 1 mmol/l, despite repeated administration of glucose-free cardioplegic solution. Apparently, glucose was not totally depleted despite low or abolished glucose uptake under low temperature. Interstitial lactate also decreased initially and accumulated slowly during heart arrest, despite the intermittent perfusion with cardioplegic solution. The mean interstitial lactate levels did not exceed the precardioplegia levels during this period. Because the glucose uptake was very low, we conclude that the interstitial lactate is probably derived more from glycogen breakdown. Clearly, in our study this did not lead to exceedingly high interstitial levels of lactate (Fig. 1*B*).

Finally, it should be noted that, because diffusion over the microdialysis membrane was reduced at lower temperatures, subsequent recalibrations were performed.

After cardioplegia. Interstitial glucose increased significantly immediately after release of the aortic cross-clamp, whereas interstitial lactate remained high. Both a-i and a-v differences for glucose increased significantly, indicating enhanced glucose consumption. In contrast, lactate a-i was negative as a result of net myocardial release of lactate. The elimination and oxidation of glucose, as well as of lactate, were low during the early postoperative phase, as reported previously (36). Very high interstitial lactate concentrations were registered in two (*patients 6* and *9*) of the four patients with coronary heart disease immediately after release of the cross-clamp (4 and 12 mmol/l, respectively; data not shown). This may be due to a previous upregulation of the glycolytic capacity.

At 25 and 35 h after release of the cross-clamp, all patients displayed very low interstitial glucose and lactate, indicating high elimination and oxidation rates. This is in agreement with previous studies at 4 h (5) and 8 h (39) after surgery. In this late phase, patients with coronary heart disease had equally low interstitial glucose and lactate levels, as did the other patients. It should be noted that the 25- and 35-h samples were collected postprandially; hence, blood glucose as well as plasma lactate were high (Fig. 1). The low interstitial levels therefore indicate a rapid elimination of glucose and lactate from the interstitial fluid into the myocardial cells.

Markers for ischemia accumulate in the interstitial fluid early during cardioplegia (9, 19) and are steadily released during reperfusion (9). The present data do not indicate that the poor delivery of glucose or the lactate accumulation in the myocardium potentiates the trauma of cold cardioplegia (8). Accordingly, the addition of glucose and/or lactate to cardioplegic solutions has no convincing cardioprotective effect (2, 11, 33, 34). Protection by other compounds such as α-ketoglutarate (22) and cocarboxylase (23) or by ischemic preconditioning (3) may be more efficient. The addition of adenosine to the cardioplegic solution or for pretreatment has not given conclusive effects so far (28, 32, 40).

In summary, microdialysis may constitute a useful tool in the evaluation of cardioprotective measures during open-heart surgery. The results show that capillary delivery of glucose is a rate-limiting step for myocardial glucose uptake in the beating heart but not during cold cardioplegia. Furthermore, during cardioplegia, lactate has been found to accumulate in the interstitium but not at exceedingly high levels.

We are grateful to the surgeons who skillfully and patiently helped implant the microdialysis probes and to Dr. Klaus Kirnö for expertly inserting the coronary sinus probes. We also thank Gudrun Jonson for skillful secretarial aid.

This study was supported by grants from the Swedish Research Council (Project nos. 10864, 11330, and 12206), the Swedish Diabetes Association, Novo Nordisk Foundation, the Magn. Bergvalls Foundation, and the Inga-Britt and Arne Lundberg Foundation.

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