Changes in metabolism and blood flow in peripheral tissue (skeletal muscle) during cardiac surgery with cardiopulmonary bypass: the biochemical microdialysis study

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The aim of this study was to monitor the metabolism and blood flow in the interstitium of the skeletal muscle during cardiac surgery with cardiopulmonary bypass (CPB) and in the early postoperative period by means of microdialysis and to compare metabolic changes during CPB at normothermia (NT) and hypothermia (HT).

Surgical revascularization using CPB was performed in 50 patients, 25 patients (group HT) were operated using hypothermic CPB, 25 (group NT) using normothermic CPB. Intersitial microdialysis was performed by two CMA 60 probes (CMA Microdialysis AB, Solna, Sweden) inserted into the patient’s deltoid muscle. Constituents analyzed in the obtained dialysates, collected at intervals, were glucose, urea, glycerol and lactate. Tissue blood flow was monitored by dynamic microdialysis with gentamicin as a marker.

In both groups, NT versus HT, similar dynamics of concentrations were found. Low initial concentrations were followed by gradual increases during CPB and in the following phase of the operation. Concentrations were higher in the NT group. Immediately after the operation, the decrease in values continued, with a gradual increase in the succeeding postoperative period in both groups. Similar dynamic changes in the lactate concentration were found in both groups. The gentamicin concentrations were lower in the NT group (versus the HT group).

The results showed dynamic changes in the interstitial concentrations of glucose, urea, glycerol and lactate, which depend on the phase of the surgery in the CPB and early postoperative phase in the both groups of patients. Higher tissue perfusion of the skeletal muscle was noted in those patients operated on in normothermia. The dynamics of the concentration changes of these substances in the interstitium of the skeletal muscle has been proven to be caused by both the metabolic activity of the tissue and by the blood flow through the interstitium of the muscle. Perfusion (2004) 19, 53–63.

Introduction

Surgical revascularization of myocardium during cardiopulmonary bypass (CPB), extracorporeal circulation, ranks among contemporary routine treatment methods of ischaemic heart disease. The operated patients, however, run a certain risk due to both complications of the surgery and their general condition, resulting either from the primary disease or from the accompanying secondary diseases.

One of the precipitating causes of the complications can be the systemic and organ changes, which develop due to the changes of blood circulation during surgery. At the operation, but mainly during the CPB, blood flow in the peripheral and splanchnic circulation is redistributed. Hypoperfusion of peripheral tissues and splanchnic organs caused by vasoconstriction, centralization of the circulation, and possibly by hypothermia, can lead to severe complications. The decrease of blood pressure with constant cardiac output, controlled haemodilution, and, first of all, the total (body) hypothermia decreases energy demands of the cells, but, at the same time, leads to the activation of the adrenergic system with consequent deterioration of the vasoconstriction of the peripheral and splanchnic vessels. These changes may lead to severe renal, gastrointestinal or hepatopancreatic complications, or to ischaemia of extremities, mainly if the arteries are affected prior to surgery.

It is difficult to assess local changes of blood circulation in these areas, or to describe the metabolic changes. Direct measurement of the flow through the splanchnic or skeletal muscles during
routine cardiac surgery is both technically and ethically impracticable. The evaluation of the standard biochemical and haemodynamic parameters (blood pressure, heart rate, O$_2$ saturation in the capillary bed, temperature, diuresis, peripheral vessel resistance, etc.) yields general results, but does not give information on regional changes or changes in the interstitial space.

One of the methods enabling biochemical monitoring of metabolic changes and blood flow in the interstitial space of organs and tissues is microdialysis.

This minimally invasive method makes it possible to follow the kinetics of chosen analytes in the otherwise inaccessible sites. The substances in the interstitium go through the semipermeable membrane of the inserted microdialysis probe (Figure 1). This microdialysis probe is a flexible polyamide catheter (30 mm in length) designed for microdialysis in subcutaneous adipose tissue and resting skeletal muscle (Figure 2). The inlet tubing of the probe is connected to the pump with an appropriate solution (Ringer solution in this study) and continuously perfused. The outlet tubing ends in a plastic test tube that collects the dialysis sample (Figures 2 and 4).

This solution, in the form of a dialysate, is then analysed biochemically. The concentration changes of a particular metabolite in the interstitium are given by the local production of the substance and the change in the blood flow.$^{3-6}$

Monitoring of the concentration changes in low molecular weight metabolites (glucose, lactate, glycerol and urea) by microdialysis reflects the actual metabolism of the peripheral tissue.$^{6,7}$ In our study, the skeletal muscle. Monitoring by means of microdialysis with the use of gentamicin as a flow marker gives information on the actual blood flow through the interstitium.

The aim of this study was to monitor the metabolism and blood flow in the interstitium of the peripheral tissue (skeletal muscle) during surgery with cardiopulmonary bypass and during the early postoperative period by means of microdialysis; also, the comparison of metabolic changes during CPB at normothermia and hypothermia.
Patients

Fifty randomly chosen patients with ischaemic heart disease, on whom cardiac surgery – surgical revascularization of the myocardium with CPB – was performed at the Department of Cardiac Surgery in the Charles University Hospital in Hradec Králové, Czech Republic. There were 41 men and nine women with ages ranging from 51 to 79 years in this population.

The patients were randomized into two groups:

Group one – NT – consisted of 25 patients, on whom the revascularization of the heart was performed with standard CPB and normothermia (36°C).

Group two – HT – consisted of 25 patients, on whom the surgery was performed with standard CPB and hypothermia (32°C).

The differences between the two groups (age, duration of CPB, accompanying diseases) were not statistically significant (Table 1). All routine therapeutic and monitoring steps commonly used with this diagnosis and method of treatment were performed. In all the patients, surgery was elective; patients operated on as emergencies were excluded from the study. Before the start of the investigation, a detailed description of the study was given to the patients, who gave their informed consent.

Methods

The anaesthetic managements, CPB and surgical procedures were standardized in both groups. Anaesthesia was induced with sufentanil and midazolam, muscle relaxation with pipecuronium bromide. The extracorporeal circuit consisted of a membrane oxygenator (Dideco D 704, Dideco S.p.A., Mirandola, Italy or Macchi Oxi Ultra, Edwards Lifesciences Macchi Ltd., Sao Paulo, Brazil) and Polystan roller pumps (Polystan A/S, Værløse, Denmark). The pumps were operated in a continuous flow manner. Oxygenators and tubing were primed with Hartmann’s solution, low molecular weight dextran, 10% mannitol solution, gelatin solution, 8.4% sodium bicarbonate, magnesium sulphate, methylprednisolone, heparin 2500 u and aprotinin (Gordox, Gedeon Richter, Hungary) 500 000 KIU. Patients were heparinized before CPB (2.5 mg/kg). Additional doses of heparin were given when the ACT was shorter than 400 seconds. After CPB, heparin was neutralized with protamine sulphate at a 1:1 ratio (controlled by ACT). A standard aortic and a two-stage venous cannula were used. Moderate hypothermia (32°C) and calculated blood flow of 2.4 L/min/m² during CPB, cold crystalloid potassium cardioplegia (St. Thomas’s Hospital Solution) and topical cooling for myocardial protection were employed in the HT group. Normothermia (36°C), calculated blood flow of 2.8–3.0 L/min/m² and warm blood cardioplegia (St.Thomas’s Solution 4:1) were employed in the NT group.

The microdialysis described in this study was performed by two CMA 60 microdialysis probes (CMA Microdialysis AB, Solna, Sweden) (Figure 2) inserted into the deltoid muscle (musculus deltoideus) of the operated patient in the operating theatre after introduction of anaesthesia (Figures 3–5). The probes were perfused using Ringer’s solution at the constant flow rate of 0.3 mL/hour.

<table>
<thead>
<tr>
<th>Table 1 Groups of patients, NT versus HT</th>
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<tbody>
<tr>
<td><strong>NT (n = 25)</strong></td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>CPB time</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Dyslipidaemia</td>
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<td>Obesity</td>
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Figure 4 Test tubes in special holder.
Dialysates were taken at the following intervals: at the beginning of surgery, at the beginning of CPB, at the end of CPB, at the end of the surgery and every two hours in the postoperative period. Samples were taken into special tubes and transported into a biochemical laboratory. The amounts of dialysates in the single samples were recorded as well. The blood flow through the interstitium was monitored by means of dynamic microdialysis of gentamicin as the flow marker in the dialysates taken from the second probe. A known amount of gentamicin (Gentamicin, Lek, Slovenia), 80 mg/1000 mL of Ringer’s solution (167.2 μmol/L) was added into the dialysis solution of the second probe, and, at the outlet of the microdialysis probe, the changes in its concentration were monitored biochemically. Blood flow through the interstitium of the skeletal muscle is directly proportional to the decrease in gentamicin at the outlet of the probe.

We excluded possible changes of concentration of the analytes resulting from the dilution of the dialysates during CPB by means of simultaneous microdialysis using the dialysation solution with the addition of dextran (Ringer’s solution with dextran in the ratio of 1:1). The concentrations of analytes found were the same as in the dialysates, where only the Ringer’s solution had been used. There was practically no difference found in the amount of dialysate, therefore, the method with the solution enriched by dextran has been discontinued.

The analyses of glucose, urea and lactate levels were assessed by a Hitachi 917 analyser (Roche Diagnostics GmbH, Mannheim, Germany), glycerol concentration by a colourimetric method (Randox) on a Cobas MIRA Plus analyser (Roche Diagnostics GmbH, Mannheim, Germany). Gentamicin in the microdialysate was determined by the AxSYM analyser (Abbott Laboratories, Abbott Park, USA) using the Fluorescence Polarization ImmunoAssay (FPIA) method.3

After evaluation of the results of microdialysis, these were statistically processed using the SIGMA STAT software (Jandel Scientific Corporation, San Raphael, USA). The unpaired t-test, ANOVA, linear regression and Pearson’s correlation were used. Data processing was done in co-operation with the Department of Computer Systems and the Centre of Medical Informatics of the University Hospital in Hradec Králové. The analysis results of the dialysates of both groups were evaluated, statistically compared and arranged into graphs.

There was no case of a local complication at any cannula insertion site, and there were no signs of general infection or catheter sepsis.

The study was approved by the Ethical Committee of the University Hospital and Medical Faculty of Charles University, Hradec Králové.
Results

In both groups, similar dynamics of interstitial concentration of the measured substances during the operation and in the early postoperative period were found (Tables 2–4, Figures 6–8). Low initial concentrations were followed by a gradual increase during CPB and in the following phase of the operation. The concentrations of the measured analytes were higher in the NT group of patients, which was shown by normal metabolic activity of the cells during normothermia (in comparison with the lower values at hypothermia). Immediately after the operation, the decrease in the measured values continued, with a gradual increase in the subsequent postoperative period in both groups. A significant difference could be seen in the concentration increase in all the measured analytes in the HT group compared with the NT group, due to the increase in metabolic activity of the cells in the HT group (Figures 6–10).

The trend in the dynamic changes of the measured analytes, i.e., the substances showing the metabolic activity of the skeletal muscle, showed the lower metabolic cell activity during hypothermia and its evident growth (as compared with the NT group) following rewarming of the tissue.

Using analysis, statistics and graphic processing of the lactate concentration (Table 5, Figure 9) as a substance indicating the anaerobic metabolism of the skeletal muscle, similar dynamic changes were found in both groups, both during the operation and in the postoperative phase.

The analysis of gentamicin concentration (Table 6, Figure 9) as a flow marker showed lower values of gentamicin concentration in the dialysate during the operation and early postoperative periods in the normothermia group of patients (versus the HT group), which is evidence of higher flow through the tissue in the skeletal muscle compared with the group of patients operated with hypothermia.

Discussion

Microdialysis has been known since 1974. The first human application (microdialysis of the cerebral tissue) was performed or described as late as in the year 1990. The pioneers of this method were, in particular, Swedish scientists; Myerson et al.

Table 2 Concentrations of glucose in samples (mean ± SD)

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<tr>
<td>Normothermia</td>
<td>0.37 ± 0.1</td>
<td>1.21 ± 0.5</td>
<td>2.72 ± 1.6</td>
<td>4.40 ± 2.5</td>
<td>2.08 ± 1.6</td>
<td>1.89 ± 1.3</td>
<td>1.92 ± 1.7</td>
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<tr>
<td>Hypothermia</td>
<td>0.46 ± 0.4</td>
<td>1.39 ± 0.8</td>
<td>2.23 ± 1.4</td>
<td>3.18 ± 1.7</td>
<td>2.31 ± 1.5</td>
<td>2.19 ± 1.7</td>
<td>2.52 ± 2.0</td>
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Table 3 Concentrations of urea in samples (mean ± SD)

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<tr>
<td>Normothermia</td>
<td>0.49 ± 0.2</td>
<td>1.71 ± 0.8</td>
<td>2.39 ± 1.3</td>
<td>3.14 ± 1.5</td>
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<td>1.57 ± 0.8</td>
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<tr>
<td>Hypothermia</td>
<td>0.67 ± 0.4</td>
<td>1.69 ± 0.8</td>
<td>2.14 ± 1.2</td>
<td>2.62 ± 1.2</td>
<td>2.05 ± 0.8</td>
<td>1.87 ± 1.1</td>
<td>1.89 ± 1.3</td>
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Table 4 Concentrations of glycerol in samples (mean ± SD)

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<tbody>
<tr>
<td>Normothermia</td>
<td>27.9 ± 28.3</td>
<td>40.9 ± 23.7</td>
<td>64.0 ± 20.6</td>
<td>63.5 ± 32.6</td>
<td>31.1 ± 19.6</td>
<td>32.5 ± 25.4</td>
<td>38.4 ± 30.5</td>
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<tr>
<td>Hypothermia</td>
<td>25.0 ± 20.9</td>
<td>30.9 ± 7.1</td>
<td>50.2 ± 27.9</td>
<td>59.4 ± 45.0</td>
<td>43.8 ± 24.7</td>
<td>49.9 ± 45.2</td>
<td>46.0 ± 36.5</td>
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Table 5 Concentrations of lactate in samples (mean ± SD)

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<tbody>
<tr>
<td>Normothermia</td>
<td>0.18 ± 0.1</td>
<td>0.56 ± 0.2</td>
<td>1.19 ± 0.9</td>
<td>1.25 ± 0.4</td>
<td>1.11 ± 1.0</td>
<td>1.44 ± 0.8</td>
<td>1.25 ± 1.0</td>
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<tr>
<td>Hypothermia</td>
<td>0.26 ± 0.2</td>
<td>0.69 ± 0.3</td>
<td>1.08 ± 0.3</td>
<td>1.40 ± 0.5</td>
<td>1.17 ± 0.4</td>
<td>1.36 ± 0.9</td>
<td>1.41 ± 1.1</td>
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gersted of the Karolinska University in Stockholm, Hillered at the University of Uppsala, or at the same time Lonnroth et al. in Göteborg. At present, this minimally invasive method is being used both in experiments on animals and in the human clinical practice. The experimental studies are directed mainly at the microdialysis of liver and cerebral tissue of laboratory animals and the study of the influence of single substances on their metabolism. In clinical practice, microdialysis analyses are used

Figure 6 Concentrations of glucose in intervals – hypothermia versus normothermia.

Figure 7 Concentrations of urea in intervals – hypothermia versus normothermia.
in terminally ill patients, e.g., after cerebral traumas.\textsuperscript{8-14}

Microdialysis has been used, only rarely, in cardiac surgery. Langemann et al.,\textsuperscript{15} and Habicht\textsuperscript{16} have analysed the stage of myocardial ischaemia at cardiac arrest during cardiac surgery by means of microdialysis probes inserted into the ventricular septum. They analysed identical substances during

Figure 8 Concentrations of glycerol in intervals – hypothermia versus normothermia.

Figure 9 Concentrations of lactate in intervals – hypothermia versus normothermia.
the study of cerebral ischaemia (glutathione, ascorbic acid, cysteine, uric acid, glucose, lactate, etc.). Kennergen et al., as well as Mantovani and colleagues, followed the T-troponin and aspartate aminotransferase levels in the myocardial interstitium of the left chamber prior to and after the operation. Wilkstrom et al., as well as Hudspeth et al., Walker et al. and Zemgulis et al., in their experiments on animals, have similarly followed the influence of ischaemia and administered drugs on the metabolism of cardiac muscle, the influence of acute ischaemia, the extent of the resulting injury on the myocardium, and the grade of irreversibility. The studies of Baumgartner et al., Brock et al. and Conroy et al. deal with the analysis of the grade of damage of the cerebral tissue in animals during extracorporeal circulation (CPB) or during the cardiac arrest by using microdialysis. The influence of CPB on metabolism and local blood flow in skeletal muscle during cardiac surgery and in the early postoperative period has not been published in the world literature so far.

Microdialysis is a safe process. Changes in concentration of certain metabolites in the interstitium are given by three main factors: local production of the substance, local increase or decrease given by the functions of the cells and by changes of blood flow. Equilibrium of a substance between the interstitium and the dialysate is produced by the concentration gradients, the velocity of the flow of the dialysis solution, the membrane properties, the hydrostatic pressure and the special ion conditions that develop on the internal and external sides of membrane.

Table 6 Concentrations of gentamicin in samples (mean ± SD)

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<tbody>
<tr>
<td>Normothermia</td>
<td>146.3 ± 13.0</td>
<td>141.4 ± 32.4</td>
<td>138.9 ± 19.9</td>
<td>133.4 ± 20.3</td>
<td>144.7 ± 16.1</td>
<td>147.7 ± 22.1</td>
<td>137.7 ± 21.1</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>189.2 ± 50.5</td>
<td>191.8 ± 58.5</td>
<td>203.4 ± 64.3</td>
<td>191.8 ± 57.5</td>
<td>199.4 ± 71.8</td>
<td>207.7 ± 91.2</td>
<td>191.1 ± 84.6</td>
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Figure 10 Concentrations of gentamicin in intervals – hypothermia versus normothermia.
this reason, we have focused on microdialysis of the skeletal muscle as a typical peripheral tissue. The changes in the flow and metabolism, thus, represent the ‘whole periphery’.

In our study, we have selected the analysis of the flow and metabolism of the deltoid muscle. This typical skeletal muscle is easily accessible (for handling by the samplers) throughout the course of the cardiac surgery (Figure 5).

In this study, the concentration changes of the single analytes in the skeletal muscle were studied during the operation and in the early postoperative period. The absolute values, i.e., the real concentrations of the studied substances in the interstitium, can partially differ from the values we have analysed. The fast dynamics of cardiac surgery produce intervals too short for standard microdialysis (the flow rate 0.01–0.1 mL/hour). The amount of dialysate is usually so small in the single phases that it may be insufficient for analysis by standard methods. Microdialysis must be performed at higher flow rates of the dialysis solution (flow rate in this study 0.3 mL/hour) or 100% recovery might not be reached (equilibrium between the interstitium of the tissue and the dialysate on the semipermeable membrane). A smaller volume of single dialysis sample can also be caused by loss of the dialysis solution due to the changes of interstitium osmolality. Adding dextran, as a high molecular weight substance to prevent this transfer of the solution (1:1 with the Ringer’s solution), as recommended by Rosdahl et al., did not improve the situation in our study. The amount of the dialysate in the samples, and its possible decrease, remained practically the same. Concentrations of the single analytes remained the same as well (Ringer’s solution with dextran versus without dextran). The CMA 600 microdialysis analyser, which enables the analysis of a smaller volume in separate samples (circa 0.5 μL), was not at our disposal at the time of the study.

Although it is obviously impossible to work with real concentrations of the analytes, the trends of the measured substances during the particular phases of surgery, CPB and the postoperative period can be assessed accurately, and the different conditions of CPB (NT versus HT) can be compared.

In both groups (NT versus HT), similar dynamics of the interstitial concentrations of the measured substances has been found. Low initial concentrations gradually rose during CPB. Further increases in the levels could be seen after termination of CPB, in the postsurgery phase. Immediately after surgery, the levels decreased then increased gradually again in the next postoperative phase in both groups.

These changes, as mentioned above, are given not only by the metabolism of the cells of interstitial tissues, but also by changes in local blood flow through the tissues.

To determine blood flow in our study, we have chosen the method of microdialysis of the so-called flow marker. It is a substance added in a specific concentration to the microdialysis solution (in our study, the Ringer’s solution) and its concentration is determined at the outlet of the probe. It is held that the lower its concentration at the outlet is, the higher is the blood flow in the interstitium, and vice versa. The flow marker must meet some essential criteria. It must be sterile, nontoxic, nonvolatile and easily determinable in a laboratory. Its molecules must be of significantly smaller size than the pores of the microdialysis membranes, and, at the same time, they must not bind to this membrane. It must not be liable to any active transport processes in the interstitium and the adjacent cell membranes and its clearance must not depend on the presence of a physiological carrier.

We have chosen gentamicin as the flow marker. This original choice has come from the fact that the biochemical determination of other frequently used substances, such as ethanol or lithium, is more difficult and financially too demanding. During the study, gentamicin has proven to be an appropriate substance for microdialysis of tissue flow. In certain circumstances (e.g., hyperosmolality of the interstitium in the region of the inserted MD probe or a considerably higher hydrostatic pressure in the probe than in its surroundings), a perfusion solution leaves the probe much more easily than gentamicin and it can paradoxically increase its concentration at the outlet of the probe.

Nevertheless, it is necessary to emphasize that we assessed only the trends in blood flow changes. The real values in blood flow, related to, for example, surface or the mass of the tissue, cannot be determined by any known means.

From the evaluated results of our study, it is possible to state that the higher concentrations of the analytes in the NT group (versus HT) during the operation and CPB are given by higher blood flow through the tissue and normal metabolic activity of the cells. On the contrary, the lower concentrations in the HT group are given, not only by lower blood flow, but by lower metabolic activity as well, which is the result of controlled hypothermia. The rising concentrations in this group in the early postoperative phase (versus NT) are, thus, given by increased metabolic activity of the tissue after reaching normal temperature, because the tissue blood flow stays on the same level (Figure 10).
Dynamic changes in lactate concentrations as a marker of anaerobic metabolism of the skeletal muscle were practically identical in both the groups. Interpreting the results, we are so far not able to determine what plays the more important role in influencing the concentration of the substances in the study period; namely, if it is the blood flow, change in production and release of the analytes into the interstitium (ureagenesis, glucogenesis, glycolysis, lipolysis) or the change in utilization of the particular substance by the cells. Further research in this field, e.g., microdialysis with the addition of special substrates is, therefore, necessary.

Conclusion

The results of the microdialysis study showed dynamic changes in the interstitial concentrations of the substances studied (glucose, urea, glycerol and lactate) that depend on the stage of surgery with CPB and in the early postoperative course. These changes were practically identical in both groups of patients, normothermia and hypothermia. Higher tissue perfusion of the skeletal muscle was noted in the patients operated on at normothermia. The dynamics of the concentration changes of the measured substances in the interstitium of the skeletal muscle has been proven to be caused both by the metabolic activity of the tissue and by the blood flow through the interstitium of the muscle.

Acknowledgements

This study was supported by Grant No. 6547-3 of IGA Czech Ministry of Health.

References


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