Skeletal Muscle Reperfusion Injury: Reversal by Controlled Limb Reperfusion

A Case Report

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Despite successful surgical revascularization of ischemic limbs, a local and systemic reperfusion injury may occur after normal blood reperfusion. Recent experimental and clinical application of controlled limb reperfusion in Europe has demonstrated superior results, with lower morbidity and mortality. This new surgical technique includes modification of the reperfusate (calcium, pH, substrates, osmolality, free radical scavenger) and the circumstances of initial reperfusion (time, temperature, pressure). This report describes the first application of controlled limb reperfusion after reperfusion injury.

A 16-year-old boy underwent femoral access cardiopulmonary bypass for repeat cardiac repair with an ischemic time of 245 minutes. Postoperatively, severe ischemia/reperfusion syndrome developed with muscle contracture, immobility, and anesthesia of the right leg with a second ischemic time of about 6 hours. The systemic creatine phosphokinase level was 88,000 U/L; myoglobin was 27,000 ng/mL. He underwent controlled limb reperfusion by withdrawing blood from the aorta and mixing it with a crystalloid solution (calcium-reduced, hyperosmolar, hyperglycemic, alkalotic, glutamate- and aspartate-enriched, and containing a free radical scavenger) under controlled conditions (blood:crystalloid solution 6:1, for 30 minutes, reperfusion pressure <50 mm Hg, and normothermia) before establishing normal blood reperfusion.

Metabolic data from the central and femoral vein demonstrated a significant reduction of all previous elevated enzyme levels, avoidance of hyperkalemia, normalization of acidosis, and avoidance of systemic reperfusion injury with no multiorgan failure. Limb salvage was accomplished and functional recovery almost complete.

To the authors' knowledge, this is the first application of controlled limb reperfusion reported in North America. With this surgical technique we were able to prevent metabolic local and systemic reperfusion changes after prolonged ischemia and also reduced previous reperfusion changes. This report confirms former experimental data, and further clinical studies are warranted.
Introduction

Morbidity and mortality rates after revascularization of acutely ischemic limbs have changed little in the past 30 years. Amputation rates vary between 12% and 22%, and mortality after simple embolectomy may be as high as 52%.\textsuperscript{1,2} Recently it has become more obvious that revascularization and uncontrolled reperfusion with normal blood at systemic pressure may lead to an oxygen-free-radical-induced skeletal muscle reperfusion injury followed by severe local and systemic complications.\textsuperscript{3,4} In this case, severe reperfusion changes were evident from pronounced biochemical and functional changes after only 4 hours of limb ischemia during cardiopulmonary bypass. Previous studies have shown that interventions during the initial reperfusion phase (controlled reperfusion) after prolonged limb ischemia can limit reperfusion injury and may reduce the severity of local and systemic complications.\textsuperscript{5,7} Furthermore, the superiority of controlled limb reperfusion over clinical standard was demonstrated in an adult in vivo pig model subjected to prolonged ischemia\textsuperscript{6,8} and for the first time in clinical studies in patients with prolonged total limb ischemia.\textsuperscript{5,7} A recent published European multicenter study supports this concept.\textsuperscript{7} This report describes the application of controlled limb reperfusion after reperfusion injury. In the same individual, evidence is presented for the development of skeletal muscle reperfusion injury after uncontrolled normal blood reperfusion, and reduction of reperfusion changes with use of controlled limb reperfusion.

Materials and Methods

Patient

The patient is a 16-year-old male, in whom Tetralogy of Fallot was diagnosed at birth. He underwent several intracardiac repair procedures and presented with tricuspid valve regurgitation, combined pulmonary artery stenosis and regurgitation, and right heart failure. He underwent homograft placement of the right ventricular outflow tract. Cardiopulmonary bypass was instituted emergently, when a graft from the main pulmonary artery to the right pulmonary artery anterior to the aorta was inadvertently entered during sternotomy. The right femoral artery and vein were cannulated. Total bypass time was 222 minutes and total cannulation time (first ischemic time) was 245 minutes. The right common femoral arteriotomy was repaired primarily with interrupted prolene sutures. Distal pulses were palpable postoperatively. The patient was brought to the intensive care unit intubated, ventilated, and with minimal inotropic support.

During the postoperative course, the patient lost palpable pulses and Doppler signals of the right leg. Leg swelling developed, with anesthe-

<table>
<thead>
<tr>
<th>Table I. Composition of the reperfusate solution.</th>
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<tr>
<td>Content</td>
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<tr>
<td>Glucose 10%</td>
</tr>
<tr>
<td>CPD</td>
</tr>
<tr>
<td>Glutamate/aspartate</td>
</tr>
<tr>
<td>THAM</td>
</tr>
<tr>
<td>Allopurinol</td>
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CPD: citrate-phosphate-dextrose; THAM: tromethamol.
sia of the foot and parts of the lower leg, as well as severe contracture with active and passive immobility in the ankle joint and reduced mobility in the knee joint. The motor function of the whole leg was lost. The heart rate was 114 beats per minute, the blood pressure was 75/56 mm Hg and the patient received 5 μg/kg/min dopamine. The systemic creatine phosphokinase (CPK) levels were 88,350 IU/L, myoglobin 27,000 ng/mL, potassium 4.8 mEq/L, pH 7.32, and oxygen saturation 100%. With severe local and beginning systemic reperfusion injury, he was brought to surgery. Controlled limb reperfusion was performed as described. The (second) total ischemic time was about 6 hours. Controlled limb reperfusion and blood sampling were approved by the local ethics committee. Informed consent was obtained from the parents before the procedure.

Operative Technique

After induction of adequate anesthesia, the patient was prepped and draped in a routine sterile fashion. The right groin was explored and the common, superficial, and deep femoral arteries exposed, isolated, and encircled with vessel loops. There was no stenosis at the previous arteriotomy site and upon opening of the common femoral artery and distal exploration with a Fogarty catheter there was no thrombotic material. The musculature was edematous and pale and did not contract upon mechanical stimulation. The femoral vein was cannulated with a 12 G IV line for blood sampling. Heparin (300 U/kg) was given systematically. A wire enforced 12F cannula was inserted into the iliac artery to aspirate autogenous blood for subsequent mixture with the crystalloid reperfusion solution (Table I). The cannula was connected to the tubing of the reperfusion set. A smaller tubing line (to ensure a 1:6 crystalloid:blood ratio) was used for the crystalloid solution. Both lines were inserted into the head of a roller pump. A Y-connector was used to connect both lines after the roller pump, thus delivering the final reperfusion solution in a 6:1 (blood:solution) ratio into the superficial femoral artery of the ischemic leg. Incorporated into this line was a heat exchanger to ensure normothermia and an arterial filter. The superficial femoral artery was cannulated with a 10F dual-lumen catheter with a self-inflating balloon (Research Medical Inc, Salt Lake City, UT) to allow for monitoring of perfusion pressure in the femoral artery.

Against usual practice, the deep femoral artery was not cannulated because of technical difficulty. Controlled reperfusion was thus only applied into the superficial femoral artery. Controlled limb reperfusion at normothermia and a flow rate between 150 and 170 mL/min was performed for 30 minutes. Care was taken to ensure a reperfusion pressure of less than 60 mm Hg at all times. After 30 minutes the line content was emptied into the patient, the arteries de-cannulated and the arteriotomy site repaired primarily. After releasing the clamp, the leg was reperfused with normal blood at systemic pressure. At the end of the procedure, pulses were felt in all arteries and there was immediate capillary refill. The muscle was pink and viable. A four compartment fasciotomy was performed as a precaution. Systemic heparinization was continued and the patient brought to the intensive care unit in stable condition.

Measurements

Measurements of the listed parameters were performed with standard clinical laboratory equipment. Blood samples were obtained 2 hours before revascularization from the superior vena cava of the patient (central vein), and the femoral vein at the end of ischemia (just before initiating controlled reperfusion), at 10 and 25 minutes during the controlled reperfusion period, and 15 minutes after reestablishing normal blood flow (45 minutes). Further blood samples were taken from the central vein 2 hours (120 minutes) and 6 hours (360 minutes) after the procedure. Measured parameters included myoglobin, lactate, CPK, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), pH, PO2, and PCO2.

Results

Preoperative Data

Metabolic data are shown in Figures 1–4 and Table II. There were signs of severe local reperfusion injury with high levels of myoglobin and CPK (see Figures 1, 2). There was washout of lactate (see Figure 3) and mild hemodynamic compromise (mean arterial pressure [MAP] 65 mm Hg,
Table II. Metabolic data from central vein/femoral vein before OR, at the end of ischemia, and during and after controlled limb reperfusion.

<table>
<thead>
<tr>
<th></th>
<th>Before OR</th>
<th>End Ischemia</th>
<th>10 Minutes</th>
<th>25 Minutes</th>
<th>45 Minutes</th>
<th>120 Minutes</th>
<th>360 Minutes</th>
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<tbody>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.8/-</td>
<td>4.4/5.5</td>
<td>5.0/5.2</td>
<td>4.4/4.7</td>
<td>4.8/5.1</td>
<td>4.0/-</td>
<td>3.4/-</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.1/-</td>
<td>0.9/1.0</td>
<td>1.0/0.8</td>
<td>1.0/0.9</td>
<td>1.1/1.0</td>
<td>1.0/-</td>
<td>1.0/-</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>152/-</td>
<td>127/138</td>
<td>130/189</td>
<td>129/158</td>
<td>176/196</td>
<td>156/-</td>
<td>152/-</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1/-</td>
<td>1.0/1.0</td>
<td>0.8/0.9</td>
<td>0.7/0.9</td>
<td>0.8/1.0</td>
<td>0.9/-</td>
<td>0.8/-</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>14/-</td>
<td>12/15</td>
<td>13/14</td>
<td>11/14</td>
<td>14/15</td>
<td>14/-</td>
<td>9/-</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>4497/-</td>
<td>6659/7486</td>
<td>6945/7165</td>
<td>5123/5653</td>
<td>6283/6130</td>
<td>5733/-</td>
<td>5243/-</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td></td>
<td>186/206</td>
<td>188/199</td>
<td>145/171</td>
<td>165/184</td>
<td>254/-</td>
<td>368/-</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td></td>
<td>965/1592</td>
<td>964/1015</td>
<td>742/803</td>
<td>884/896</td>
<td>1397/-</td>
<td>2658/-</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td></td>
<td>44/34</td>
<td>40/39</td>
<td>42/41</td>
<td>39/37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td></td>
<td>41/52</td>
<td>47/54</td>
<td>44/46</td>
<td>59/68</td>
<td></td>
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</table>

heart rate 144 beats per minute, dopamine 5 μg/kg/min). The severely compromised limb status is documented in the method section. Metabolic data from the femoral vein at the end of ischemia (right before controlled reperfusion was started) indicate a severe local ischemic/reperfusion injury with compromised oxidative metabolism, acidosis, and cellular destruction.

Intraoperative Data

During the reperfusion phase, the inotropic support was continued, and the patient was in stable cardiopulmonary status (MAP between 65 and 80 mm Hg, heart rate 100–110 beats per minute). Application of diuretics or buffer was not necessary. Perfusion flow was between 150 and 170 mL/min, and perfusion pressure between 50 and 60 mm Hg. Calcium, glucose, and creatinine levels remained stable; normokalemia was maintained; pH increased to normal values; and myoglobin and CPK values were significantly reduced compared to prereperfusion values (both in central and femoral vein blood). Data are shown in Figures 1–4 and in Table II.

Postoperative Data

Values after 15 minutes of normal blood reperfusion (45 minutes) were slightly worse than at the end of controlled reperfusion, but still significantly better than before reperfusion. They normalized in the subsequent 2 hours (120 minutes). Values measured 2 and 6 hours after the procedure indicated normal values for electrolytes, lactate, and pH, as well as significantly reduced myoglobin and CPK levels (see Table II, Figures 1–4).

The patient was weaned of the ventilator 6 hours after surgery. He demonstrated normal cardiac (off inotropes), pulmonary, and renal function. Local wound care was performed on the fasciotomy site. His motor function of the leg in the hip and knee joint recovered com-
Myoglobin

![Myoglobin Graph](image)

**Figure 1.** Myoglobin measurements in central vein and femoral vein, 2 hours before controlled reperfusion (before OR), at the end of ischemia (right before controlled reperfusion), during (10 minutes and 25 minutes) controlled limb reperfusion, and after (45 minutes, 120 minutes, 360 minutes) controlled reperfusion during normal blood perfusion.

CPK

![CPK Graph](image)

**Figure 2.** CPK measurements in central vein and femoral vein, 2 hours before controlled reperfusion (before OR), at the end of ischemia (right before controlled reperfusion), during (10 minutes and 25 minutes) controlled limb reperfusion, and after (45 minutes, 120 minutes, 360 minutes) controlled reperfusion during normal blood perfusion.

Lactate

![Lactate Graph](image)

**Figure 3.** Lactate measurements in central vein and femoral vein, 2 hours before controlled reperfusion (before OR), at the end of ischemia (right before controlled reperfusion), during (10 minutes and 25 minutes) controlled limb reperfusion, and after (45 minutes, 120 minutes, 360 minutes) controlled reperfusion during normal blood perfusion.

pH

![pH Graph](image)

**Figure 4.** pH measurements in central vein and femoral vein, 2 hours before controlled reperfusion (before OR), at the end of ischemia (right before controlled reperfusion), during (10 minutes and 25 minutes) controlled limb reperfusion, and after (45 minutes, 120 minutes, 360 minutes) controlled reperfusion during normal blood perfusion.
pletely and that of the ankle joint partly. He was able to walk without personal or mechanical support. He regained complete sensory function. He was discharged from the hospital after 24 days. His fasciotomy site was grafted 1 month later without complications. Follow-up after 10 months revealed healed wounds, complete recovery of sensory function, but generalized muscle weakness and reduced motor function in the ankle joint, with normal function of the remainder of the leg. The patient requires a cane for longer walking distances. Leg perfusion was unremarkable.

Discussion

Only recently is there convincing evidence for the fact that the main injury to the ischemic muscle occurs with reperfusion rather than with the ischemic period. Furthermore, based on experimental and clinical studies it was proven that even after prolonged periods of ischemia previously thought to cause irreversible muscle damage, salvage is possible if careful control of the reperfusion and the circumstances of reperfusion is obtained. Even so, skeletal muscle is relatively resistant to ischemia—with the onset of normal blood reperfusion, damage occurs to the energy-depleted muscle cell. Despite the notion that reperfusion is necessary for the restoration of metabolic activity, it can also increase the extent of necrosis if it occurs under uncontrolled conditions. Cell swelling, acidosis, depletion of adenine nucleotide precursors, free radical production, and calcium overload contribute to the development of reperfusion injury. The concept of controlled limb reperfusion addresses each of these contributing factors. It incorporates modification of the reperfusionate (calcium, pH, substrates, osmolarity, free radical scavenger) and the circumstances of reperfusion (time, temperature, pressure) during the initial reperfusion period. The mechanisms responsible for the beneficial effect of controlled reperfusion are already discussed in detail elsewhere and are listed in Table I.

In this case, a severe local and initial systemic skeletal muscle reperfusion injury developed after 4 hours of complete limb ischemia during extracorporeal circulation followed by normal blood reperfusion after decannulation of the femoral artery. The damage was evident from metabolic studies of the central venous system and the femoral vein postoperatively and at the end of the second ischemic interval (before controlled reperfusion). Systemic CPK levels were > 88,000 U/L, LDH > 6,000 U/L, and myoglobin > 27,000 ng/mL. There was acidosis and elevated lactate levels. Femoral vein measurements revealed even higher values, suggesting a severe local skeletal muscle reperfusion injury as the source for the systemic changes. Secondary to this reperfusion injury a compartment syndrome developed and the distal pulses disappeared. In addition to biochemical changes, severe local reperfusion injury was evident from anesthesia of the leg, severe muscle contracture, complete active as well as passive immobility of the lower leg, and limb swelling. The severity of the local damage exceeded by far the damage previously reported from prolonged ischemic injury without reperfusion injury.

There are reports suggesting that avoiding the deleterious consequences of postreperfusion syndrome by primary amputation may lower mortality. Instead of primary amputation to avoid a second reperfusion injury, or just applying supportive therapy, controlled limb reperfusion was performed. Controlled reperfusion was (based on our experience) previously thought to be a contraindication and deemed unsuccessful after uncontrolled reperfusion already took place. However, with this approach not only was a second reperfusion injury avoided, but the established enormous reperfusion changes (CPK 88,000 U/L, myoglobin 28,000 ng/mL) were reversed, which was evident from the improved metabolic and functional status. Myoglobin, CPK, LDH, and potassium levels were significantly reduced, and signs of systemic reperfusion injury were omitted, which obviated ventilation, dialysis, and a prolonged ICU stay. Furthermore, we were able to preserve the viability of the patients leg and to demonstrate functional recovery. Besides reporting the first application of controlled limb reperfusion in the United States, this investigation suggests that, contrary to previous belief, controlled reperfusion may be beneficial even after reperfusion injury with subsequent muscle damage already established. This case is also unique since the development of skeletal muscle reperfusion injury after uncontrolled reperfusion and the beneficial effect of controlled limb reperfusion were demonstrated in the same patient. After a prolonged second ischemic period, controlled limb reperfusion successfully avoided new changes, and reduced previous reperfusion changes.
Experimentally, randomized studies have been conducted comparing metabolic changes during the initial reperfusion period with controlled versus uncontrolled limb reperfusion. Clinically, those studies are lacking; even so, controlled limb reperfusion has demonstrated promising results. Measurements from the femoral vein during the initial reperfusion period after uncontrolled reperfusion are nonexistent, even so, longer term systemic biochemical reperfusion changes are well known. It may be argued that fasciotomy has contributed to muscle recovery. There is no evidence that this can happen during the first hours of initial reperfusion, let alone reduce established reperfusion changes. In other words, usually even the best symptomatic treatment of reperfusion injury will take days to normalize biochemical abnormalities, whereas in this case reperfusion changes were reduced to normal within minutes of establishing controlled limb reperfusion.

Significantly reduced biochemical markers of cell injury during the controlled reperfusion period indicate a cessation of injury. In this case however, initially reduced levels rose again after normal blood flow was reestablished (reperfusion 45 minutes) until eventually falling again between 2 and 6 hours postoperatively. The authors explain this unique finding with washout from areas not perfused with controlled reperfusion (deep femoral artery). This is based on the fact that contrary to usual practice, the deep femoral artery was not cannulated and controlled limb reperfusion was applied only in the distribution of the superficial femoral artery. This technical detail of controlled limb reperfusion supported by metabolic data warrants further investigation.

Although this is new exciting clinical data, this is only a single case. Additional clinical applications of controlled limb reperfusion and randomized studies are necessary. Proof has to be submitted that controlled limb reperfusion is beneficial after reperfusion injury occurred.

REFERENCES


