Journal of Investigative Surgery, Volume 7, pp. 61–71
Printed in the UK.

0894-1939/94 $10.00 + .00

New Surgical Treatment for Severe Limb Ischemia

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Revascularization after prolonged complete limb ischemia may result in severe damage to skeletal muscle and systemic alterations (postischemic syndrome). Our previous experimental studies have shown that this injury can be reduced substantially by treating the jeopardized extremity by controlling the conditions of reperfusion and composition of the initial reperfusate. In the present study this concept of controlled limb reperfusion was applied in patients with prolonged severe limb ischemia. Controlled limb reperfusion was used in 14 patients after prolonged complete uni- or bilateral ischemia. The ischemic interval ranged from 5 to 21 h. Two patients were in cardiogenic shock, 11 had associated cardiac disease, and seven coexistent peripheral vascular disease. After systemic heparinization, standard thromboembolectomy was done using a Fogarty catheter. Cannulas were placed into the iliac, profunda, and superficial femoral arteries and were connected to a reperfusion set. Oxygenated blood was drawn from the iliac artery and mixed with an asanguineous solution (ratio 6:1). This controlled reperfusate was delivered into the profunda and superficial femoral arteries using a single rollerpump. The system allows control of the composition of the reperfusate (calcium, pH, osmolarity, glucose, substrate, pO_2, free radical scavengers) and the conditions of reperfusion (pressure, flow, temperature). After 30 min of controlled limb reperfusion, the cannulas were removed and normal blood reperfusion started. All 12 patients who were stable hemodynamically before the operation survived the revascularization. Eleven patients, including one with acute aortic occlusion for several hours, were discharged with functional recovery of their extremities. Despite the severe ischemic insult, controlled limb reperfusion avoided amputation and profound systemic complications. Two patients who were in cardiogenic shock preoperatively died from progressive cardiac failure. We conclude that controlled arterioarterial limb reperfusion may reduce the local manifestations of the postischemic syndrome after prolonged periods of ischemia, may salvage limbs thought previously to be damaged irreversibly by prolonged ischemia, and can be done easily in the operating room.

Keywords Reperfusion injury, limb ischemia, controlled limb reperfusion, revascularization syndrome, postischemic syndrome.

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Revascularization after prolonged complete limb ischemia results in a severe injury of skeletal muscle, which may lead eventually to amputation in 12 to 22% of cases.[1,2] The washout of myoglobin, potassium, lactate, and microthrombi from the damaged skeletal muscle cells into the systemic circulation may cause renal failure, arrhythmias, shock, and eventually death[1,3,4] and mortality rates vary from 7.5 to 41%.[1,3]

Skeletal muscle is relatively resistant to ischemia.[5,6] Even after prolonged periods of severe ischemia there is a remarkable cellular and structural integrity of skeletal muscle cells.[5,6] However, if normal reperfusion is instituted after prolonged periods of ischemia, additional damage (reperfusion injury) is superimposed on the injury already produced by the many hours of complete ischemia[5–27] and the combination of ischemic and reperfusion injury may lead to irreversible tissue loss. Intra- and extracellular swelling, tissue acidosis, free radical–mediated damage, loss of adenine nucleotide precursors, and intracellular calcium overload have been suggested to be the mechanisms responsible for reperfusion injury.[5–27]

Our experimental studies in isolated rat hindlimbs have shown that careful control of the composition of the reperfusate (hyperosmolarity, hyperglycemia, hypocalcemia, alcalosis, free radical scavengers, precursors of Krebs cycle intermediates) and the conditions of reperfusion (temperature, pressure, flow, duration) will reduce the additional damage imposed during normal reperfusion and might serve as a "treatment" for limbs damaged by ischemia.[6–12] Beneficial effects of modifications during the early reperfusion phase after extremity ischemia have also been reported by other authors, and include leukocyte depletion,[15] the addition of prostacyclin analogues,[16] mannitol,[26] macromolecules,[24] free radical scavengers,[12–14,17,19,20,22,23] lowering initial reperfusion flow,[23,25] and slow increase in oxygen content of the reperfusate.[23,27] After having established the principles of controlled limb reperfusion in an isolated rat hindlimb model,[6–12] we investigated the clinical applicability and the local as well as systemic effects of this new surgical strategy in an in vivo pig model after 6 h of acute infrarenal aortic occlusion.[22] The observations made during these experiments have indicated that the significant salvage of skeletal muscle and reduction in systemic alterations can be achieved with controlled limb reperfusion.[6–12,22]

In this clinical report, we detail our experience and describe the surgical technique for controlled arterioarterial limb reperfusion, document the functional recovery of limbs undergoing prolonged ischemia, and suggest that an aggressive treatment is necessary after prolonged ischemia to improve limb function and patient survival.

Patients and Methods

Patient Population

Controlled arterioarterial limb reperfusion was used in 14 patients (11 men, three women) with complete ischemic limbs. The design of the study was approved by the ethical committee of the Johann Wolfgang Goethe-University Frankfurt/Main.

The onset of acute limb ischemia was defined as the time of pain and/or inability to walk as reported by the patient or the referring physician. The diagnosis of acute lower limb ischemia was made by history and physical examination (pain, pulselessness, pallor, paralysis), and Doppler sonographic examination. Angiograms were not routinely employed preoperatively.

In all patients, initial signs and symptoms, length of time from sudden occlusion to start of reperfusion, severity of ischemia, associated disease, source and location of thrombi and emboli, type of surgical intervention, and outcome of surgery were registered.

Surgical Technique for Controlled Arterioarterial Limb Reperfusion

Fluid and electrolyte levels and cardiovascular abnormalities were corrected as much as possible before surgery. After the induction of general anesthesia, the patient received complete heparinization (300 mg/kg). A central venous catheter and a urinary catheter were introduced. Blood pressure, heart rate, and electrocardiogram were monitored continuously. In order to avoid fluid overload during controlled limb reperfusion, the anesthesiologists were restrictive in fluid replacement, and furosemide (10 mg) was given intravenously.

From a groin incision, the common femoral artery and the superficial and profunda femoral arteries were dissected and encircled with rubber bands. A longitudinal arteriotomy was performed just above the bifurcation and a Fogarty catheter was passed into the iliac, superficial, and profunda femoral arteries in order to remove all occluding material (thrombi and/or emboli). After all material had been successfully removed, no heparinized Ringer's solution or any other kind of irrigation of the vessels was performed. From the longitudinal arteriotomy a wire-enforced 22F cannula with a bullit tip was passed into the iliac artery in order to aspirate oxygenated blood. This cannula was connected to the blood line (Fig 1) of the reperfusion set (HP Medica, Augsburg, Germany). This blood line, together with the asanguineous solution line (Fig 1), was put in the head of a roller pump. The oxygenated blood from the iliac artery was mixed with the asanguineous solution (Table 1) at a ratio of 1:6 (1 part asanguineous solution:6 parts blood) in order to achieve the composition of a controlled reperfusate, ie, a hyperosmolar, hyperglycemic, alkalotic, substrate- and allopurinol-enriched, hypocalcemic reperfusate with a hemoglobin of 7–9 g/dL. The 1:6 ratio was automatically delivered by the 1:6 ratio of the inner diameters of the asanguineous solution and blood line; no manual mixing or measuring of the constituents was necessary. Both lines were connected with a Y-piece to form the delivery line (Fig 1). The modified blood was then passed through a heat exchanger and an arterial filter and at the end of the delivery line a Y-piece allowed the connection with two reperfusion cannulas. The reperfusion cannulas were placed into the superficial and profunda femoral arteries and consisted of a 9F catheter with self-inflating balloon and an additional pressure-monitoring line. The reperfusion set was primed with blood and crystalloid solution, and both reperfusion cannulas were carefully deaired and introduced into the superficial and profunda femoral arteries. The pressure-monitoring lines of the reperfusion cannulas were connected to a monitor and controlled limb reperfusion was started. The intra-arterial pressure did not exceed 40–50 mm Hg in either vessel (profunda or superficial femoral artery). If the pressure increased in one vascular bed, a tubing clamp was placed on the line in order to increase the resistance so that both vessels had approximately the same intra-arterial pressure. The flow of the controlled reperfusate, which could be adjusted with the roller pump, was approximately between 200 and 300 mL/min.

The duration of the controlled limb reperfusion was limited to the first 30 min. Thereafter, the cannulas were removed and the arteriotomy closed with a venous patch. Normal blood was then allowed to reperfuse the limb. During the first 24 h after the operation, the systemic systolic pressure did not exceed 120 mm Hg. Heparin therapy was continued postoperatively, but conversion to warfarin sodium was undertaken only in cases with documented sources of emboli (ie, cardiac).

Results

The patients ranged in age from 19 to 83 years (mean of 54 ± 20 years). Eleven patients (79%) had a history of accompanying cardiac disease, seven (50%) had coexistent periph-

During the 30 min of controlled arterioarterial limb reperfusion, no complications were noticed secondary to the infusion of the asanguineous solution necessary to modify the oxygenated blood. Normal blood reperfusion was allowed to occur after decannulation and closure of the arteriotomy with a venous patch. A prophylactic fasciotomy was done in 10 of 14 patients.

The overall survival rate in these severely compromised patients was 86%. The two patients who died were both in cardiogenic shock preoperatively when they developed sudden occlusion of the lower limbs. In both patients, insertion of an intra-aortic balloon pump was the cause of the thrombus formation. One of the patients had an acute thrombotic occlusion of the distal aorta and death was related to congestive failure and systemic complications after revascularization. The other patient with unilateral occlusion of the femoral artery had no severe systemic alterations secondary to reperfusion of the ischemic limb, but died in pump failure. The other 12 patients of our series were long-term survivors and experienced no episodes of severe systemic complications after revascularization of the ischemic limb. A patient with complete ischemia of both limbs for more than 18 h is also included in this group; he was treated by embolectomy and controlled bilateral limb reperfusion. Severe systemic alterations were avoided and he had a full recovery of both limbs at the time of discharge.

Eleven of the 12 surviving patients left the hospital with functional recovery of their extremities. One patient with incomplete revascularization after 16 h of severe ischemia did not regain motor control of the limb.

Discussion

In this clinical report, control of the initial reperfusion period is undertaken to treat skeletal muscle cells damaged by the preceding ischemia, and to reduce reperfusion injury caused by normal reperfusion of ischemic skeletal muscle. The principles of this new operative procedure are based on experimental studies in isolated rat hindlimbs[6-12] and more recently in the in vivo pig model.[22] Data from these studies have shown that a significant improvement in the metabolism, structure, and function of the limb can be obtained after severe ischemia, if control of the composition of the reperfusate and the conditions of reperfusion are done carefully. Consequently, this controlled limb reperfusion strategy was applied in humans.

Table 1
Composition of the Controlled Limb Reperfusate

Principle	Method	Concentration
Provide oxygen	Blood	Hb 7.8–8.9 g/dL
Avoid edema	Hyperosmolarity	340–350 mosmol/L
Provide substrate	Glutamate	13mM/L
	Aspartate	13mM/L
	Glucose	330–340 mg%
Reverse acidosis	THAM	pH 7.5–7.6
Avoid Ca^{++} overload	Ca^{++} reduction (CPD)	total Ca^{++} 1.5 mM/L
Prevent free radicals	Allopurinol	100 mg total dose

Note. THAM, tromethamol; CPD, citrate-phosphate-dextrose.

The reperfusate composition was modified to allow incorporation of the following principles:

(1) *Limitation of calcium influx* by adding citrate-phosphate-dextrose (CPD), which reduces the calcium concentration, to the blood. Skeletal muscle cells do not accumulate large amounts of calcium during ischemia,[6,11,35] but significant calcium uptake occurs during reperfusion[35,48–50] either because of defects in the membrane itself or alterations in membrane calcium channels.[50] The overloading of cellular and mitochondrial calcium during reperfusion may impair mitochondrial function and mediate cell death, and thereby contribute to injury, impaired recovery, and ongoing muscle destruction.[14,51,52] Therefore, lowering the calcium concentration in the initial reperfusate is thought to decrease intracellular calcium during reperfusion. Previous studies have demonstrated the beneficial role of lowering calcium concentration in ischemic myocardium[39,49] and skeletal muscle.[7,11] However, these beneficial effects are dose-dependent[11] and data suggest that there might be a calcium paradox in skeletal muscle, similar to myocardium, if the ischemic tissue is initially reperfused with a calcium-free or very low calcium reperfusate.[11]

(2) *Hyperosmolarity* (ie, glucose) to minimize postischemic edema and to allow cell volume regulation to occur more gradually when flow is restored, because a major part of reperfusion injury is massive tissue edema, endothelial swelling, and further capillary block that lead to tissue hypoxia and the no- or low-reflow phenomenon.[30]

(3) *Prevention of the production of oxygen free radicals* with xanthine-oxidase inhibitor (ie, allopurinol) to limit the cytotoxic effects of these compounds. Studies during reperfusion of human extremities have shown that there were immediate increases in plasma levels of xanthine-oxidase activity, uric acid, and histamine upon reperfusion after tourniquet ischemia.[18] Skeletal muscle is unique among tissues in that its xanthine-dehydrogenase is not converted to xanthine-oxidase during ischemia,[20] which might serve as one explanation for the observation that skeletal muscle is more resistant to ischemic injury than other tissues.[5,6] Xanthine-oxidase was found to be the primary source of active oxygen metabolites.[20] However, during reperfusion an increased concentration of cytosolic calcium leads to the proteolytic conversion of xanthine-dehydrogenase to xanthine-oxidase.[14] The rate of this conversion and the production of superoxide radicals are maximal early in the process of reperfusion, once sufficient oxygen is reintroduced in the presence of hypoxanthine to drive the reaction.[23]

(4) *Increase in glucose* concentrations to enhance osmotic effects and perhaps initiate anaerobic energy production at the start of reperfusion.[22] Furthermore, glucose uptake in skeletal muscle was found to be dependent on arterial glucose concentration during exercise,[53] and we found an increased glucose uptake during controlled reperfusion after ischemia in the in vivo pig model.[22]

(5) *Replenishment of amino acid precursors of Krebs cycle intermediates* (ie, glutamate and aspartate) needed to ensure more effective oxidative metabolism to produce energy for cell repair and subsequent mechanical function. Recently, Svedjeholm et al.[53] reported a significantly increased uptake of several amino acids, including aspartate and glutamate, by skeletal muscle after a period of reduced flow (ie, extracorporal circulation). Furthermore, glutamate uptake by skeletal muscle was related to arterial plasma levels, which may imply that substrate availability was rate-limiting.[54]

(6) *Reversal of tissue acidosis* with a buffer (ie, tromethamine) to provide an optimal intracellular milieu for effective resumption of metabolic function. Harken[55] reported that oxygen uptake of skeletal muscle is related to the pH of perfusing blood, in that acidosis decreases and alkalosis stimulates oxygen uptake. This relationship appears linear throughout the entire physiologic pH range (7.0–7.6),[55] and provides the basis for our approach to buffer tissue acidosis.

The composition of the asanguineous solution to be mixed with blood in order to achieve the controlled reperfusate was chosen to give maximal protection to skeletal muscle and to avoid any undesirable side effects due to the systemic application of the reperfusate. The relatively small amount of CPD (50 mL) added to the blood was chosen so that it did not reduce the ionized calcium in the systemic circulation. The addition of tromethamine as a buffer could not avoid completely the systemic acidosis in all of our patients, and occasionally, sodium bicarbonate had to be given in addition. Since volume overloading was not a problem in our patients, each received infusions with Ringer's solution upon arrival in the intensive care unit. There are reports showing the beneficial effects of the systemic application of amino acids in order to enhance myocardial function after acute coronary occlusion.[56] On the background of these and other studies[54] it seems favorable to give amino acids systemically in order to prevent acute cardiomyopathy. However, an overdose of glutamate and aspartate might result in neurotoxicity and reduced peripheral vascular resistance.[57] Persistent hyperglycemia did not occur in our patients.

The results of our previous studies[6–12] indicated that the beneficial effects of controlled limb reperfusion cannot be attributed to a single factor in this strategy. Rather, control of both the reperfusate *and* the conditions of reperfusion are necessary to avoid the deleterious effects of normal reperfusion.

A prerequisite of successful reversal of acute limb ischemia is the possibility for complete revascularization. Chronic distal occlusions in a patient with thrombotic occlusion based on severe arteriosclerosis may prevent complete revascularization and limb loss will be inevitable regardless of whether controlled limb reperfusion was used. In our patients complete revascularization could always be achieved with embolectomy or thrombectomy. In addition, one patient needed a thromboendarteriectomy of the iliac artery to improve inflow and in one patient the through-and-through bullet wound of the popliteal artery was reconstructed with a vein graft.

The controlled reperfusate is given at a flow of 200–300 mL/min in an adult patient. Since 6 parts blood are mixed with 1 part asanguineous solution, the patient will receive 860–1300 mL of extra fluid during this time period. In order to avoid fluid overload, the patients receive diuretics immediately upon arrival in the operating room and no infusions are given to the patient by the anesthesiologists. Nevertheless, careful control of the central venous pressure is done continuously and an increase in central venous pressure would be a reason to terminate the controlled reperfusion. This, however, was not necessary in our patients. On the contrary, we frequently observed a short (up to 10 min) hypovolemic phase with reduced blood pressure during priming of the reperfusion set with blood from the patient's iliac artery. This has led us to prime the set with banked blood in patients in cardiogenic shock.

Both patients who died were in cardiogenic shock preoperatively and both patients died in progressive congestive failure. The other 12 patients left the hospital and had only minor to moderate systemic signs of limb reperfusion. Hemodialysis for renal failure, arrhythmias, and hyperkalemia (>6 mEq/L) did not occur.

The described surgical approach to limit reperfusion injury in skeletal muscle can be used also to incorporate additional forms of treatment (eg, leukocyte depletion), incorporation of filters, or other modifications of the initial reperfusate that might evolve from future studies in this field. Furthermore, this clinical technique for reducing ischemic/reperfusion injury to skeletal muscle might also be used in replantation and transplantation of skeletal muscle being employed to treat fascial paralysis and Volkmann's ischemic contracture.

These preliminary clinical results may give the impetus for further studies comparing controlled and normal reperfusion after prolonged ischemia in a prospective, randomized manner. Hopefully, our studies will provide a basis for future studies to determine how further modifications of the conditions of reperfusion and the composition of the reperfusate may improve patients' conditions after revascularization for acute arterial occlusion.

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