Temporary Incomplete Ischemia of the Legs Caused by Aortic Clamping in Man

Improvement of Skeletal Muscle Metabolism by Low Molecular Dextran

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Temporary infrarenal clamping of the aorta during reconstructive surgery induces incomplete ischemia of the leg muscle. After release of the clamp, severe muscle metabolic derangement with loss of high-energy phosphate compounds has been observed, indicating a dysfunction or damage of the muscle cells. In six patients operated on for occlusive aortoiliac disease, low-molecular-weight dextran (LMWD) was peroperatively administered for optimal volume loading and prevention of clotting. No heparin was used. Before, during and after the clamping period the central hemodynamics were monitored, and glycogen, glucose, lactate, pyruvate, phosphocreatine (PCr), creatine (Cr), ATP, ADP and AMP content in the thigh muscle were analyzed using enzymatic fluorometric techniques. Even though ischemia developed during the occlusion, no decline in the adenylate (ATP + ADP + AMP) or creatine (PCr + Cr) pools occurred after the clamp was released, and the energy charge of the adenine nucleotides remained unchanged. It is suggested that LMDX prevents rheologic changes impairing the microcirculation during and after the ischemic period, and thereby improves oxygenation of the muscle tissue upon reperfusion.

TEMPORARY CROSS-CLAMPING of the aorta during aortic reconstructive surgery causes incomplete ischemia of the legs. This ischemia is moderate in patients who undergo operations for occlusive aortoiliac disease with a developed collateral circulation (OAD). Ischemia is more severe in patients who undergo operations for aortic abdominal aneurysms and have normal peripheral circulations (AAA). Only minor skeletal muscle metabolic changes occur during aortic clamping in the OAD patients. After the aorta is unclamped, when the blood flow to the legs is restored, a severe metabolic derangement with loss of high-energy phosphate compounds has been observed, indicating a dysfunction or damage of the muscle cells.[2,14]

The purpose of this study was to evaluate the effect of intraoperative administration of low-molecular-weight dextran on skeletal muscle metabolism during reconstructive surgery for occlusive arteriosclerotic disease of the aortic bifurcation.

Materials

Six patients (aged 55–67 years) undergoing reconstructive surgery because of occlusive aortoiliac disease were studied. All were operated on because of intermittent claudication of the legs, in three cases combined with pain at rest. No patient had any known metabolic or neuromuscular disease. All were, or had been, heavy smokers. Preoperatively, aortofemoral angiographic studies and a standardized walking test on a treadmill (speed 1.2 meters/second, inclination 5%) were performed, and the systolic blood pressure of the big toe (DTP) was measured. Mean DTP was 37 mmHg (range: 21–83 mmHg). The DTP is normally equal to or higher than the arterial blood pressure of the arm. The results are given in Table 1. The reconstruction in all patients was performed using a bifurcation graft; the distal anastomosis was made, bilaterally, at the level of the femoral bifurcation. All operations included temporary infrarenal aortic clamping, which lasted for 62–144 minutes (mean: 93 minutes) (Table 1).

The study was approved by the ethical committee of the University and informed consent was given by the patients.

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TABLE 1. *Patient Characteristics*

Age	Sex	Distal Toe Pressure of the Biopsied Leg (mmHg)	Walking Test, Meters	Duration of Aortic Clamping, (Minutes)	Concurrent Diseases
64	male	30 (170/95)	156	104	
60	male	83 (130/65)	204	144	High blood pressure
55	male	23 (165/90)	432	92	Hyperlipidemia
56	male	26 (140/75)	216	93	
56	male	21 (130/65)	102	62	Previous myocardial infarction, angina pectoris
67	male	40 (150/80)	90	62	High blood pressure

Numbers in parentheses indicate the blood pressure in the arm.

Anesthesia

Before operation an adrenergic block was administered, and was intended to last throughout the operation. For this purpose phenoxybenzamine and metoprolol were administered as previously described.[5] Morphine-scopolamine was administered to all patients 30 minutes before administration of the anesthesia (10–15 mg of droperidol and 2 mg/kg body weight of morphine, average: 150 mg). During the operation only 20–40 mg of morphine was used for supplementation. Muscle relaxation was achieved by the administration of pancuronium bromide. After the patients had tracheal tubes inserted they were connected to a volume-controlled ventilator (Siemens Elema 900) and ventilated with a N_2O/O_2 mixture (FI_{O_2} 0.35). Basic fluids were administered to achieve urine output of 1 ml/kg body weight/hour, (average: 400 ml 5.5% glucose solution/hour). Blood losses were assessed and replaced unit for unit. Ringer-acetate and 5% albumin solutions were administered to produce a larger circulating blood volume during the aortic clamping, and thereby a gradually increasing pulmonary capillary wedge pressure (PCW) to 10–15 mmHg immediately before unclamping the aorta. No diuretics or sodium bicarbonate solutions were administered to any patient. No heparin was administered. Instead, a maximal dose (1.5 g/kg body weight/24 hour) of low molecular-weight dextran (LMWD) was administered, starting after the administration of anesthesia (average: 1500 ml of LMWD). The administration was fractionated to administer 500 ml LMWD prior to clamping the aorta, 500 ml during the cross-clamping procedure, and the remaining part for four hours after unclamping the aorta. The amounts of fluids and blood transfusion, urine output, and the blood hematocrit are given in Table 2.

Procedures and Methods

After administration of anesthesia, a central venous catheter and a Swan-Ganz thermistor pulmonary artery catheter were introduced, and an arterial line was established from one radial artery. Cardiac output was determined (mean of five measurements) by means of a cardiac output computer (Edwards model 9520). Heart rate, arterial and pulmonary artery pressures, PCW, and central venous pressure (CVP) were monitored and registered. Measurements were made before and 30 minutes after clamping the aorta, and before as well as five and 30 minutes after unclamping the aorta. A baby-feeding catheter was inserted into the great saphenous vein and advanced into the iliac vein. Blood samples were collected, simultaneously, from the arterial, pulmonary artery and saphenous vein lines.

At the same time blood samples were taken, as well as at four and 16 hours after the aorta was unclamped, Radner forceps (No 13717, AB Stille-Werner, Stockholm, Sweden) were used to obtain biopsy specimens from the lateral vastus muscle of the leg, where the circulation was first restored. The arterial and venous blood samples

TABLE 2. *Blood Substitution, Fluid Therapy, Urine Output and Blood Hematocrit During the Day of Operation (24 hours) (mean ± SEM, n = 6)*

Fluids	
crystalloids, ml	7350 ± 722
albumin, ml	417 ± 154
dextran, ml	1333 ± 105
total fluids, ml	9183 ± 730
Blood, units	5.0 ± 1.0
Urine output, ml	3117 ± 234
Hematocrit, per cent	
before operation	44 ± 1
during operation	29 ± 1
after operation	29 ± 1

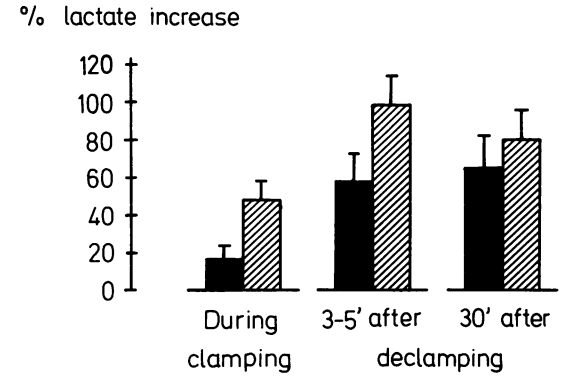

FIG. 1. Relative increase (per cent) of iliac venous lactate concentration during the aortic clamping as well as five and 30 minutes after unclamping the aorta in a control group (■, n = 12) and a dextran treated group of patients (▨, n = 6) (mean ± SEM).

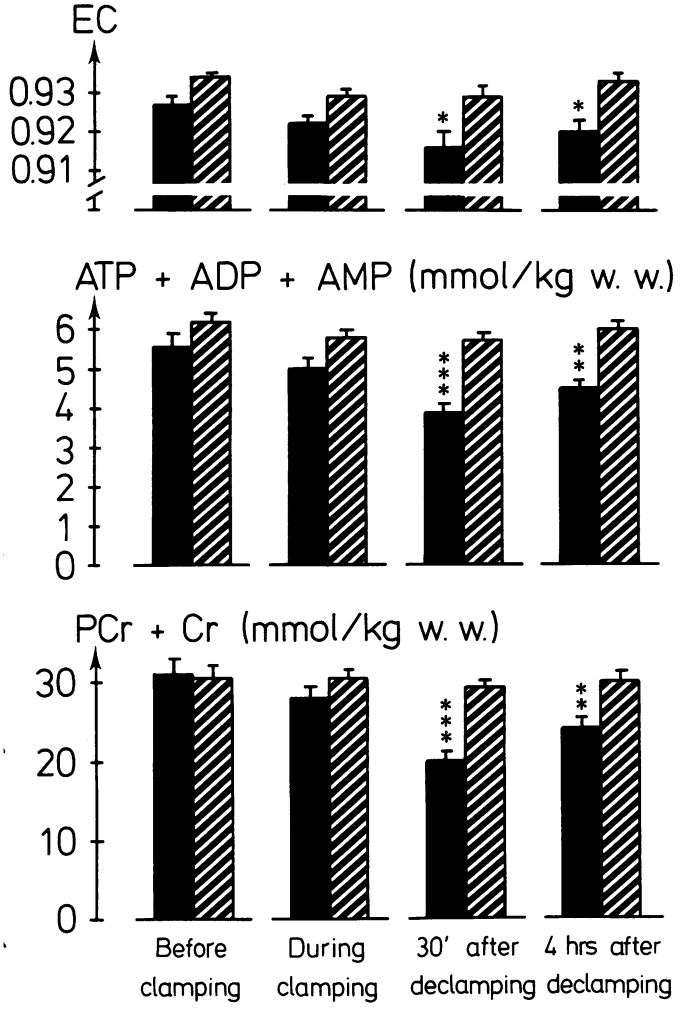

FIG. 2. Energy charge of the adenine nucleotides (EC), the adenylate (ATP + ADP + AMP, mmol/kg wet weight) and the creatine (PCr + Cr, mmol/kg wet weight) pool before as well as 30 minutes and four hours after declamping the aorta compared with values before clamping the aorta in a control group (■, n = 12) and a dextran treated group of patients (▨, n = 6) (mean ± SEM, *p < 0.05 **p < 0.01 ***p < 0.001).

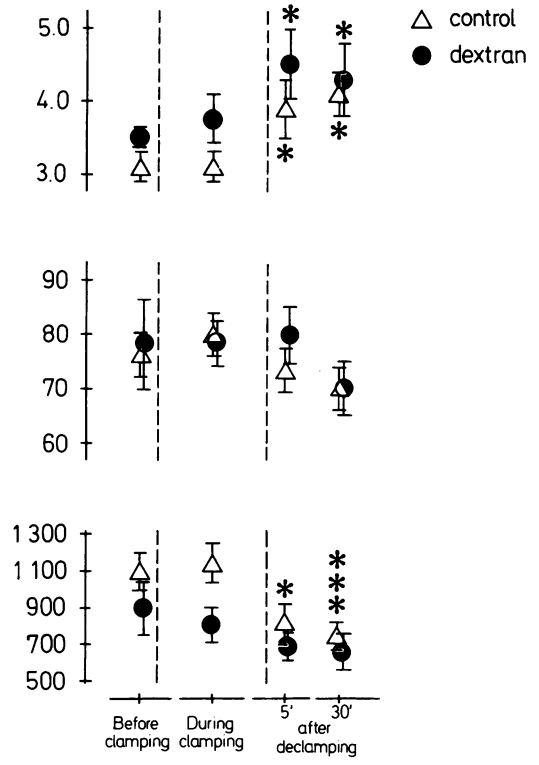

FIG. 3. (Top graph) cardiac index (l/min/m² BSA.), (center graph) mean arterial blood pressure (mmHg) and (bottom graph) systemic vascular resistance (dynes × sec × cm⁻⁵) before as well as five and 30 minutes after unclamping the aorta compared with values before clamping the aorta in a control group (△, n = 13) and a dextran treated group of patients (●, n = 6) (mean ± SEM, *p < 0.05, ***p < 0.001).

and the muscle tissue were frozen in liquid nitrogen and stored at −85 C for later analysis. Potassium, *p*H, P_{CO_2}, P_{O_2}, S_{O_2}, base excess (BE), hemoglobin, blood hematocrit, and activated partial prothrombin time (APTT: normal value < 35 seconds) were determined in arterial, mixed venous and iliac venous blood using standard clinical techniques. In addition, the dextran concentrations were determined in radial, arterial, and iliac venous blood. Glycogen, glucose, lactate, pyruvate, phosphocreatine (PCr), creatine (Cr), ATP, ADP, and AMP in muscle, as well as lactate and pyruvate in blood were analyzed using enzymatic fluorometric techniques.[2]

The data obtained were analyzed by means of Student's *t*-test for paired observations, and are given in the figures and text as mean values ± SEM. A probability value less than 0.05 was considered significant.

Results

The blood and skeletal muscle metabolic data as well as the central hemodynamic parameters are given

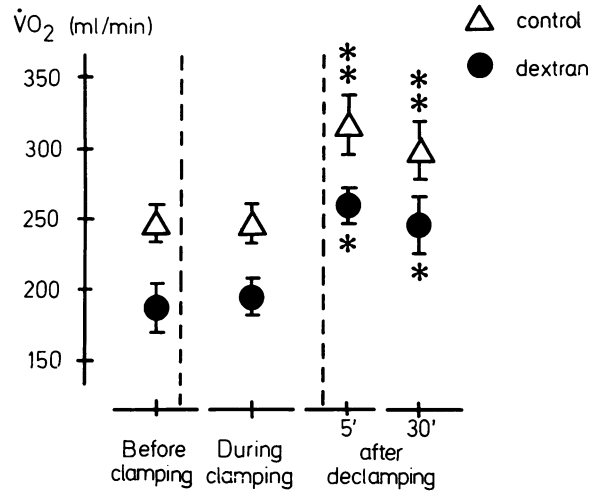

FIG. 4. Systemic oxygen consumption ($\dot{V}O_2$, ml/min) before as well as five and 30 minutes after unclamping the aorta compared with values before clamping the aorta in a control group (△, n = 13) and a dextran treated group of patients (●, n = 6) (mean ± SEM, *p < 0.05 **p < 0.01).

in Figures 1–4. These data are given with the results of a previous study carried out by our group,[5] where 5000 units of heparin chloride instead of LMWD were intravenously administered to 12 patients before clamping the aorta. After unclamping the aorta, the heparin was neutralized by the administration of protamine chloride if necessary. When the clotting time returned to normal, these patients received 500 ml of LMWD for four hours. In all other aspects these patients were treated as described above. Mean age of the subjects, duration of aortic clamping, total fluids infused and mean DTP were comparable to the present study.

Blood Metabolites

Arterial oxygen tension was 70 ± 8 mmHg (9.2 ± 1.0 kPa) before the aorta was clamped, and increased throughout the operation. After the aorta was unclamped the Pa_{CO_2} increased slightly, but the pH and BE decreased. No increase in the serum potassium level was observed after the release of the aortic clamp (Table 3).

The iliac venous and radial arterial blood content of lactate and pyruvate increased while the aorta was clamped and further rose five minutes after the aorta was unclamped. Relative lactate increase (per cent) of the iliac venous blood was significantly higher compared with the results in the heparin group. A significant increase occurred during the cross-clamping procedure (Fig. 1). The venous lactate/pyruvate (L/P) ratio was 17 ± 1 before clamping the aorta and unaffected by the clamping procedure.

Skeletal Muscle Metabolism

The mean metabolite contents in muscle before, during and after unclamping of the aorta are given in Table 4. Calculated adenylate energy charge and pool sizes for adenine nucleotides and phosphocreatine plus creatine are given in Figure 2. While the aorta was clamped, the muscle lactate content more than doubled, increasing the muscle L/P ratio from 21 ± 2 to 51 ± 9 (in the control group corresponding L/P ratio was 23 ± 1 and 40 ± 5). Glycogen and glucose contents were unchanged. Muscle PCr decreased, and muscle Cr increased significantly, but the creatine pool (PCr + Cr) was constant. The adenine nucleotides in muscle were unaffected (Table 4). Thirty minutes after unclamping the aorta muscle lactate was still high; PCr and Cr contents had, however, regained their preclamping values. The high-energy phosphate compounds were unchanged. The energy charge of the adenine nucleotides (EC = [ATP + 0.5 ADP]/[ATP + ADP + AMP])[4] was upheld during and after the cross-clamping procedure. When heparin was administered preoperatively instead of LMWD, a severe metabolic derangement after reperfusion was observed. Both EC and the adenylate and creatine pool sizes markedly

TABLE 3. *Mean Arterial Blood Gases (mmHg), Serum Potassium Concentration (mmol/l) and Plasma Activated Prothrombin Time (APTT, Normal Value < 35 Seconds Before, Five and 30 Minutes after Aortic Unclamping Compared with Values Before Aortic Clamping*

	Before Aortic Clamping	Before Aortic Unclamping	5 Minutes After Aortic Unclamping	30 Minutes After Aortic Unclamping
*p*H	7.44 ± 0.02	7.42 ± 0.03	7.36 ± 0.04†	7.39 ± 0.04*
P_{O_2}	70 ± 8	90 ± 14*	99 ± 15*	103 ± 13*
P_{CO_2}	30 ± 2	31 ± 2	34 ± 2*	32 ± 3
BE	−3.5 ± 1.0	−4.5 ± 0.5	−6.5 ± 1.0‡	−6.0 ± 1.5*
K^+	3.6 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	3.6 ± 0.1
APTT	43 ± 2	46 ± 2	51 ± 3	52 ± 4*

Mean ± SEM, n = 6. * p < 0.05. † p < 0.01. ‡ p < 0.001.

TABLE 4. *Mean Metabolite Concentration in Muscle (mmol/kg wet weight) Before and 30 Minutes, Four and 16 Hours After Aortic Unclamping Compared with Values Before Aortic Clamping*

	Before Aortic Clamping (n = 6)	Before Aortic Unclamping (n = 6)	30 Minutes After Aortic Unclamping (n = 6)	4 hours After Aortic Unclamping (n = 6)	16 hours After Aortic Unclamping (n = 4)
Glycogen	71.48 ± 7.06	69.45 ± 4.82	70.66 ± 4.46	66.75 ± 4.35	57.08 ± 7.24*
Glucose	1.96 ± 0.64	1.88 ± 0.21	2.58 ± 0.23	2.28 ± 0.32	1.31 ± 0.20
Lactate	1.78 ± 0.25	5.74 ± 1.52*	3.25 ± 0.82*	2.88 ± 0.57*	2.26 ± 0.40
Pyruvate	0.099 ± 0.027	0.089 ± 0.019	0.110 ± 0.025	0.170 ± 0.053	0.155 ± 0.020
PCr	17.27 ± 1.48	12.27 ± 1.81*	14.19 ± 0.81	16.35 ± 1.10	18.44 ± 0.75
Cr	13.27 ± 0.59	18.91 ± 2.30*	15.09 ± 0.79	13.86 ± 0.77	11.40 ± 1.28
ATP	5.43 ± 0.16	5.01 ± 0.14	4.93 ± 0.22	5.22 ± 0.22	5.25 ± 0.11
ADP	0.753 ± 0.029	0.766 ± 0.023	0.743 ± 0.016	0.747 ± 0.025	0.771 ± 0.054
AMP	0.031 ± 0.003	0.033 ± 0.005	0.031 ± 0.002	0.027 ± 0.001	0.028 ± 0.005

Mean ± SEM. * $p < 0.05$.

decreased, and had still not returned to their original levels four hours after the blood flow was restored (Fig. 2).

Central Hemodynamics

The central hemodynamic parameters are given in Figures 3 and 4. While the aorta was clamped, cardiac output, expressed as cardic index (CI: l/min/m^2 BSA), remained unchanged. After the aorta was unclamped, CI increased, due to a higher stroke index (SI: l/m^2 BSA; Fig. 3). The heart rate was constant during the entire operation. PCW was 15 ± 2 mmHg before the aorta was clamped, and did not change during the operation. Mean arterial blood pressure (MAP) was 78 ± 8 mmHg before the aorta was clamped, and was unaffected by both clamping and unclamping the aorta. Systemic vascular resistance (SVR: normal value 1000–1500 dynes × sec × cm^{-5}) was low at the start of the operation and remained unchanged throughout, though a slight decrease ($p < 0.01$) was observed after the release of the clamp. Left ventricular stroke work (LVSW: normal value 60–80 g) was 90 ± 14 g prior to the cross-clamping procedure, and not affected by the clamping procedure (Fig. 3). Oxygen consumption ($\dot{V}_{O_2}$: ml/min) increased after the aorta was unclamped (Fig. 4). Systemic oxygen transport (SO_2T: ml/min) was 1019 ± 105 ml/min, and did not change in the dextran group during the operation. In the control group, SO_2T increased from 890 ± 133 ml/min before the aorta was clamped to 1103 ± 306 after the aorta was unclamped. The systemic oxygen utilization coefficient was decreased (0.18 ± 0.01) in the dextran group, and increased by about 20% (to 0.24 ± 0.02) after the aorta was unclamped. In the control group, the coefficient was 0.29 ± 0.02 before the aorta was clamped and remained unchanged throughout the operation.

The intentional fluid treatment, including the administration of LMWD, resulted in a lowered hematocrit (29 ± 1%) during the operation (33 ± 1% in the control group) (Table 2). The blood dextran concentration was 9.9 ± 1.0 g/L before the cross-clamping procedure and did not change throughout the operation. The iliac vein blood levels were only sightly lower than the radial artery blood levels. APTT was less than 35 seconds before the administration of LMDX, but significantly rose to 43 ± 2 seconds before the aorta was clamped and to 52 ± 4 seconds at the end of operation.

Discussion

The effects of aortic clamping and unclamping on the central circulatory system have been shown to be modulated by vasodilatation and optimal volume loading, with 5% albumin and/or crystalloid solutions, prior to unclamping the aorta.[11,13,15] Despite an improved central circulation, a skeletal muscle metabolic derangement of the previously ischemic legs has been observed after unclamping the aorta. The muscle adenylate and creatine pools decreased, indicating injury to the muscle cells.[5,14] In these studies, heparin was used to prevent coagulation during the clamping period. In the present group of patients, LMWD was given both as an anticoagulant as well as a plasma volume expander. No loss of the high-energy phosphate pools, *i.e.* no muscle damage, was observed.

The metabolic effects from the administration of dextran, in conjunction with aortic clamping procedures, have, previously, only been studied in the blood. Mansberger et al.[10] found no P_{O_2} increase and lower excess lactate values of the femoral venous blood after the aorta was unclamped in patients who had intraoperative administration of dextran compared with patients receiving dextrose. These findings suggested that dextran enhanced capillary perfusion, both during the clamping period and following the release of the clamp. In dogs, on the other hand, the administration of dextran has had no effect

on acidosis or blood lactate production after the aorta was unclamped.[9,12] In the present study, femoral venous blood lactate increased more during the clamping procedure, but the acidosis was virtually the same as in the control patients. Previous studies have, however, shown that blood metabolic changes do not correctly reflect the muscle metabolic events.[2,5]

Since the relationship between incomplete ischemia and the muscle metabolic derangement following reperfusion is unknown, we can only speculate about why LMWD is beneficial in this situation. One explanation could be an increased blood flow through developed collaterals during the occlusion, as the cardiac output was slightly higher in the dextran group.[8] The increase of the iliac venous lactate concentration supported this, but also implied an improved capillary perfusion. The induced muscle tissue hypoxia, expressed as muscle L/P ratio, was, however, of the same size in both groups. This finding must indicate the presence of ischemia in spite of dextran administration, since the arterial oxygen tensions were normal and were equal in the two groups. The energy source of PCr was also tapped off in the dextran group. Even though systemic oxygen transport was higher in the dextran group before and after clamping the aorta, the systemic utilization of oxygen was lower, possibly indicating a *general* "luxury" perfusion. After the release of the clamp, cardiac output increased, and the systemic oxygen transport was the same in the two groups. The systemic utilization of oxygen increased only in the dextran group, now implying a more "efficient" microcirculation.

The impaired microcirculation with low perfusion pressure during ischemia has been explained by disturbed rheologic properties of the blood, *e.g.* aggregation of cells and increased viscosity. The administration of LMWD was shown to prevent these changes.[6,7] During prolonged graded arterial occlusion in dog experiments, capillary transport was observed to be flow-limited initially, but changed within one hour towards being diffusion-limited, probably secondary to an uneven flow distribution. If LMWD was administered, the disturbed transport returned to normal.[3]

Dextran has also been shown to improve capillary reperfusion after shock. This is due not only to a higher total blood flow, but also to a more diffuse distribution of flow.[1] In the present study LMWD might have prevented rheologic changes during the clamping period, enhancing capillary blood flow. Even if this were the case the tissue oxygenation would still not have improved (since L/P ratio in muscle increased), probably due to the decreased oxygen transport following the reduction of the blood flow to the legs. When the flow was restored after the clamp release the postulated improved capillary perfusion would permit better oxygenation of the muscle tissue preventing metabolic derangement. Hemodilution as such could also have this effect, but the blood hematocrits were practically the same in both groups of patients.

In conclusion, administration of LMWD for optimal volume loading and prevention of clotting during reconstructive aortic surgery for occlusive arteriosclerotic disease, improved the skeletal muscle metablism of the leg. No adverse effects such as excess bleeding or anaphylactoid reactions were observed.

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