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# SYMPATHETIC BLOCK SIGNIFICANTLY IMPROVES REPERFUSION IN SKELETAL MUSCLE FOLLOWING PROLONGED USE OF TOURNIQUET

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**The effects of guanethidine sympathetic nerve blocks on reperfusion of skeletal muscle was studied in rats. After 3 hours of ischaemia reperfusion was significantly better in animals that had received guanethidine.**

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Skeletal muscle does not tolerate long periods of ischaemia. The conventional method for extending the total ischaemic time is by intermittent reperfusion and reischemia (Anderson et al., 1990). This, however, often prolongs the overall time of surgery. It is therefore of interest to investigate other possible means of increasing the total ischaemic time that skeletal muscles can survive. The regulatory mechanisms of sympathetic nerves are well documented (Bolme et al., 1970) and potentially would be of benefit to the circulation in muscles following prolonged ischaemia. We have investigated the effect of sympathetic nerve block after long periods of muscle ischaemia in an animal experimental model as described for studies of reperfusion in skeletal muscles (Strock and Majno, 1969a; 1969b) which we have used previously (Gustafsson et al., 1998; Sirsjö et al., 1990; 1998).

## MATERIALS AND METHODS

The animal experiments described below were all approved by the local ethical committee of Linköping University, Linköping, Sweden.

### Animals, sympathetic blockade and anaesthesia

Male Sprague-Dawley rats (ALAB, Stockholm, Sweden) with body weight of about 300 g, were randomized into six groups. The animals were housed in Macrolon cages and fed laboratory chow. The sympathetic blockaded animals were injected 24 hours before the study with a 1.5% solution of guanethidine (Sigma Chemicals, St Louis, USA) in saline under the skin of the back (2.0 mg/100 g body weight). The rats were anaesthetized intraperitoneally with a mixture of ketamine 50 mg/kg body weight and xylazine 5 mg/kg body weight. During the experiment the animals were kept at room temperature thermostatically controlled at 22°C.

### Rat model for ischaemia

The tourniquet method used for the induction of ischaemia was similar to one we have previously

described (Gustafsson et al., 1998; Sirsjö et al., 1990; 1998). It was applied on the left thigh of the anaesthetized rat, and the rats were kept anaesthetized during the experiment. Eighteen rats had guanethidine injection; five of them had no ischaemia, six rats had a total of 3 hours of ischaemia interrupted after 1.5 hours by reperfusion for 20 minutes and seven rats had uninterrupted ischaemia for 3 hours. Sixteen rats were not given guanethidine; five of them had a total of 3 hours of ischaemia interrupted after 1.5 hours by reperfusion for 20 minutes and seven rats had uninterrupted ischaemia for 3 hours. A group of four rats served as non-ischemic controls.

### Laser Doppler imaging

For measurement of the microvascular perfusion rate, the surface of the anterior tibial muscle in the calf was sequentially scanned by a software controlled laser-Doppler imager after 20 minutes of reperfusion. Those animals with uninterrupted 3 hours ischaemia were also measured after 5 minutes of reperfusion. The area scanned consisted of 120 measurement points, covering an area of 15 mm × 5 mm. The back-scattered light from each measurement point was detected by a photodiode positioned 8 cm above the tissue surface and converted into an electrical signal. Each field scanning of the 120 points took about 30 seconds. The signal reflects the product of red cell velocity and red cell concentration as a measure of tissue perfusion at each point. After scanning was completed, a colour-coded image of the spatial tissue blood flow distribution was displayed on the computer monitor and data was stored on disk for off-line evaluation. The animals were killed after measurements while still under anaesthesia.

### Statistical analysis

For statistical analysis of the measurements, the Mann-Whitney test was used and a two-tailed *P*-value was calculated.

**Table 1—LDI-values (volts)**

Group	Normal	Guanethidine	Normal	Guanethidine	Normal	Guanethidine
Ischaemia (h)	0	0	1.5 × 2	1.5 × 2	3	3
Mean LDI (SD)						
5 min	—	—	—	—	7.3 (0.9)	4.4 (1.1)
20 min	6.3 (0.6)	7.6 (1)	4.6 (1.7)	4 (2.9)	1.9 (0.3)	3.2 (1.1)

## RESULTS

The results in each group are given in Table 1. The muscular perfusion after 3 hours of uninterrupted ischaemia was significantly higher ( $P=0.007$ ) in the guanethidine treated group than in the untreated group 20 minutes after removal of the tourniquet. Although the mean circulation was higher in the untreated group that had 20 minutes of reperfusion halfway through the 3 hours of ischaemia than the group that had guanethidine injection but no interrupted ischaemia, this difference was not statistically significant.

## DISCUSSION

Our results show that the post-ischaemic circulation in rat skeletal muscle can be significantly increased if the sympathetic nerves have been chemically blocked before tourniquet application to a limb for 3 hours. However, there was no difference between treated and non-treated animals that had reperfusion for 20 minutes after 1.5 hours of ischaemia and reapplication of the tourniquet for another 1.5 hours.

It is, therefore, interesting to speculate on the reason why a sympathetic nerve blockade has beneficial effect on the reperfusion following longer periods of ischaemia.

Restoration of the blood flow, after shorter periods of ischaemia, results in a period of reactive hyperaemia, i.e. a period of an increased basal microvascular blood flow (Haddy and Scott, 1978). With increasingly longer periods of ischaemia, the hyperaemia will progressively diminish and disappear (Gidlöf and Lewis, 1990). As seen from our results, 3 hours of ischaemia in untreated animals generated significantly higher blood flow after the first 5 minutes of reperfusion compared to the guanethidine treated animals. However, after 20 minutes of reperfusion, the perfusion was significantly below normal in both groups, indicating that the perfusion of the muscle was affected.

It therefore seems as if the immediate hyperaemia caused by the ischaemia may have a delayed negative effect on the final muscle reperfusion. These findings are supported by those of Anderson et al. (1990), who showed that a lowered reactive hyperaemia during the first minutes of reperfusion after prolonged ischaemia decreased the resulting muscle injury. The sympathetic nerves in the vessels of skeletal muscle have their endings

located in the adventitia and the outer muscle layers (Hudlicka, 1973). Noradrenalin is the main neurotransmitter and its release results in vasoconstriction via direct effect on the  $\alpha$ -receptors and by inhibiting vasodilating neuropeptides (Euler, 1946; Euler and Hillarp, 1956; Kawasaki et al., 1990). The sympathetic nerves influence, directly or indirectly, the initial reactive hyperaemia and the delayed reduction in the blood flow seen later during reperfusion after prolonged ischaemia.

By pre-treating the rats with guanethidine, the sympathetic nerves will not be activated after the 3 hours of ischaemia. This results in a reduced initial blood flow in the muscle compared with untreated rats, but leads to a later higher reperfusion than in untreated rats.

Our findings indicate that peripheral nerve blockade may be beneficial when ischaemia is used in clinical practice.

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