THE PROTECTIVE ROLE OF LOCAL HYPOTHERMIA IN TOURNIQUET-INDUCED ISCHAEMIA OF MUSCLE

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The protective effect of local hypothermia was studied in pig's limbs made ischaemic by long, repeated application of a pneumatic tourniquet. Twenty-one Landrace pigs were anaesthetised on two separate occasions six days apart and a pneumatic tourniquet at 500 mmHg pressure was applied to the same forelimb for three and two hours respectively. Ten of the pigs had local hypothermia from cold gel packs placed around the limb during the first tourniquet application; the other 11 had the ischaemic limb exposed to room temperature.

In comparison with the normothermic limbs, the hypothermic ischaemic limbs had significant slowing of metabolism. The hypothermic limbs also showed less inflammatory response and a faster rate of recovery, both immediately after removal of the tourniquet, and by the end of the experiment, 10 days after the first tourniquet. Local hypothermia produced by this technique was shown to be safe and effective, while appearing to protect muscles exposed to prolonged tourniquet-induced ischaemia.

Pneumatic tourniquets are used routinely to maintain bloodless fields during operations on limbs. It has been suggested that a tourniquet should be used only for a certain "safe" period, which has been variously reported to range from three hours (Klenerman 1962, 1980, 1982), two hours (Shaw Wilgis 1971; Flatt 1972; Santavirta, Kauste and Rindell 1978), and 75 minutes (Heppenstall, Balderston and Goodwin 1979; Rorabeck and Kennedy 1980) to the total avoidance of a tourniquet in athletes (Eriksson 1981; Dobner and Nitz 1982). With this uncertainty, it would seem logical that attempts should be made to reduce neuromuscular damage regardless of the time under tourniquet.

Local hypothermia is one such method (Seki 1980), but little information is available on the safety or efficiency of cooling during tourniquet application (Shehadi, Paletta and Cooper 1961; Paletta et al. 1962; Seki 1980). We have used an animal model to study the effect of hypothermia in reducing the damage to skeletal muscle made ischaemic by a tourniquet.

METHODS AND MATERIALS

Twenty-one Landrace pigs, weighing from 18 to 25 kg, were anaesthetised with Pentothal on two occasions six days apart. A pneumatic tourniquet at 500 mmHg pressure was applied to the same forelimb for three hours on the first occasion and two hours on the second. Ten of the 21 pigs were randomly selected for hypothermia. These pigs had local hypothermia during the first tourniquet application. This was produced by encasing the limb, including the area under the tourniquet cuff, with bags containing a cold polyglycol gel at −4 °C. The opposite forelimb, used as a control, was also rendered hypothermic by wrapping it with cold bags. Covers of insulating neoprene were placed over the limbs and bags to prolong the cold period. Hypothermia was not induced during the second tourniquet application, which was for a period of two hours, six days after the first period of ischaemia. Anaesthesia was maintained by further doses of intravenous Pentothal and by nitrous oxide. Halothane was not used because of the risk of malignant hyperthermia, to which this particular breed of pig is susceptible (Woolf et al. 1970).

At intervals from before the first application of a tourniquet and for 10 days after, blood samples were taken from indwelling catheters in the carotid artery and in a vein draining the ischaemic limb. Blood was analysed for serum lactate levels by the method of Gutmann and Wahlefeld (1974); serum potassium levels were measured using an Instrumental Laboratory Flame Photometer 543 with lithium as the standard reference. Serum pH was measured on a Radiometer M73 Copenhagen pH meter coupled with a BM5 Mk 2 Micro system standardised against pH 7.383 and pH 6.841. Nasal, skin and muscle temperature were monitored during and after the first application of a tourniquet (Ellab Instruments Type TE3 thermometers, Electrolaboratoriet, Copenhagen).

At both tourniquet applications, after iodine preparation of the skin, an open muscle biopsy was
performed on the limb under the area where the tourniquet was to be applied. The specimen was placed in Greiner tubes, stoppered and stored in liquid nitrogen. Ten minutes after removing the tourniquet another open biopsy of the same muscle was taken. A further biopsy was taken of the ischaemic limb muscle on the tenth day, just before the pig was killed by an overdose of Pentothal. Similar biopsies were taken from the control limb on days 6 and 10. The muscle biopsies were subsequently analysed for glycogen content and phosphofructokinase activity using the techniques described by Baldwin et al. (1973) and Passoneau and Lauderdale (1974). Statistical analysis of the raw data was performed using a two-way analysis of variance (ANOVAR), and the acceptance intervals of the means were used to calculate significance.

RESULTS

During tourniquet application
Blood from the central venous line showed no significant differences between hypothermic and normothermic groups in blood pH, serum potassium or lactate levels during the three hours of tourniquet application (Table I).

<table>
<thead>
<tr>
<th>Blood concentration</th>
<th>Hypothermic group</th>
<th>Normothermic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10) Mean SD</td>
<td>(n = 11) Mean SD</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>0.94 0.33</td>
<td>1.41 0.65</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.95 0.46</td>
<td>3.70 0.19</td>
</tr>
<tr>
<td>Hydrogen ion (pH)</td>
<td>7.52 0.08</td>
<td>7.57 0.07</td>
</tr>
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</table>

Temperatures. There was no significant difference between the nasal (central) temperature of the hypothermic and normothermic groups. Both groups showed a gradual rise in temperature from 37° to 38.6°C during the tourniquet period.

The mean muscle temperature of the normothermic ischaemic limb fell progressively during the first 90 minutes of tourniquet time and then levelled off (Fig. 1). The muscle temperature in the normothermic control limb remained constant during the experiment. In the hypothermic group, the muscle temperature of the ischaemic limb showed a rapid fall to very low levels (16°C) over the first 45 to 60 minutes and then levelled off for a further 30 minutes. Thereafter it rose gradually (Fig. 2). The muscle temperature of the hypothermic control limb fell almost as rapidly as that of the cooled ischaemic limb, reaching a minimum of about 30°C at 40 minutes. Thereafter, the muscle temperature rose, although after three hours it was still significantly (P < 0.01) lower than before the experiment began (Fig. 2).

The skin temperatures of both groups followed patterns similar to those of the respective muscle temperatures (Figs 3 and 4).

After tourniquet release
Lactate levels. Serum lactate levels in the veins draining the ischaemic limbs were significantly lower in the hypothermic group for the first 15 minutes, and again between two and three hours after tourniquet release (Fig. 5).

Potassium levels. There was a marked initial rise in serum potassium in the venous blood draining the ischaemic limbs of both the hypothermic and normothermic groups. However, the serum potassium levels in limbs which had been hypothermic returned to baseline levels within 10 minutes, whereas the serum levels in the normothermic limbs were still significantly raised 20 minutes after release of the tourniquet (Fig. 6).

Blood pH. Soon after releasing the tourniquet the pH of venous blood draining the ischaemic limbs of the hypothermic group was significantly higher than that in
Skin temperatures in the control and ischaemic limbs during and after application of the tourniquet. Note the different temperature scales. *P<0.05, **P<0.01. Figure 3—Normothermic group, results expressed as mean for 11 experiments with acceptance intervals of the mean. Note the progressive fall in temperature of the ischaemic limb during the period of the tourniquet and the significant elevation 45 to 90 minutes after release. Figure 4—Hypothermic group, mean for 11 experiments. Note the rapid fall in temperature of both ischaemic and control limbs, and the rapid rise after release of the tourniquet.

The normothermic group. Furthermore, the venous pH in the hypothermic group had returned to baseline levels within five minutes of tourniquet release; the venous pH of the normothermic group had not returned to baseline levels even after 15 minutes (Fig. 7). The arterial pH measured in the carotid artery remained stable during the tourniquet application and release.

Temperatures. Central (nasal) temperature. There was no significant difference in nasal temperature between the normothermic and hypothermic groups on release of the tourniquet.

Muscle and skin temperatures. The muscle and the skin temperatures of the ischaemic limb of both normothermic and hypothermic groups returned to control values within four minutes of release of the tourniquet (Figs 1 and 2). After this the temperatures of the ischaemic limb of both groups became higher than those of the control limb. In the normothermic group this rise in muscle temperature became significant between 30 and 120 minutes after tourniquet release (Fig. 1); the rise never became significant in the hypothermic group (Fig. 2). Similar changes were seen in the skin tempera-

Biochemical results for venous blood draining from hypothermic and normothermic limbs after release of the tourniquet. *P<0.05, **P<0.01. Figure 5—Lactate levels, mean of 10 experiments in each group with acceptance intervals of the mean. Note the significant elevation of lactate levels for 15 minutes after tourniquet release and again at 120 minutes and 180 minutes.

Figure 6—Serum potassium levels, mean for nine experiments in each group. Note the significant elevation in the normothermic group, which continued above the baseline even 20 minutes after release.

Figure 7—Venous pH, mean of eight experiments in each group. Note the significantly lower pH in the normothermic group soon after release and the slow return to baseline levels.
Table II. Glycogen content of muscle in mmol/kg wet weight, expressed as mean and SD for nine experiments in each group

<table>
<thead>
<tr>
<th></th>
<th>Tourniquet limb</th>
<th>Control</th>
<th>Tourniquet limb</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Day 1</td>
<td>25.4</td>
<td>23.5</td>
<td>25.4</td>
<td>23.5</td>
</tr>
<tr>
<td>Day 6</td>
<td>38.3</td>
<td>22.4*</td>
<td>28.9</td>
<td>15.7</td>
</tr>
<tr>
<td>Day 10</td>
<td>61.9</td>
<td>35.2</td>
<td>69.2</td>
<td>22.0</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01 with acceptance intervals of the mean measured from the result before tourniquet

atures of the normothermic group; they were significantly higher than the temperatures of the control limb for 30 to 90 minutes after release of the tourniquet (Fig. 3). No such difference was observed in the skin temperatures of the ischaemic and control limbs in the hypothermic group (Fig. 4).

Muscle glycogen. Interpretation of changes in muscle glycogen content during the different experimental procedures is confused by the finding of higher resting levels in the normothermic group (Table II). The reasons for this are not clear. Nevertheless, muscle glycogen levels in the hypothermic ischaemic limb exceeded those in the control limb on days 6 and 10, whereas levels in the normothermic ischaemic limb were below control limb values on both these days, but especially on day 6. Hypothermia also reduced the rate of muscle glycogen breakdown during the initial application of a tourniquet.

Muscle phosphofructokinase activity. There was no significant difference in phosphofructokinase (PFK) activity before or after the two tourniquet applications in either group (Table III). When the animals were killed on day 10, PFK activity in the ischaemic limb of the normothermic group was significantly lower than in the control limb and was also lower than that in the hypothermic ischaemic limb.

DISCUSSION

Method of hypothermia. The use of cold gel packs on the limb was found to be convenient and safe. Skin temperatures as low as 5°C (mean 9.3°C) and muscle temperatures as low as 11°C (mean 16°C) were produced by close application of cold packs covered by an insulating neoprene sleeve. No signs of ice burns, such as severe erythema or blistering, were seen in any of the 10 animals. During the period of tourniquet application, no significant differences were found between the hypothermic and normothermic groups as regards levels of serum lactate or serum potassium, nor in pH or nasal temperatures. This indicates that the ischaemic limb is effectively isolated from the rest of the body by the tourniquet, as was reported by Klenerman and Crawley (1977), so that the changes measured must be due to local hypothermia and not to cooling of the whole body.

Beneficial effects of hypothermia

Local muscle metabolism. Hypothermia produced a significant slowing of oxygen-independent metabolism, and in particular glycolysis, during tourniquet ischaemia. This was shown by the smaller fall in blood pH (Fig. 7) and muscle glycogen levels (Table II) during hypothermic ischaemia, and the smaller rise in serum lactate levels (Fig. 5) after tourniquet release. This slowing of metabolism is believed to have a protective role (Hagberg, Haljamae and Röckert 1970; Haljamae 1970; Seki 1980).

Muscle and skin temperatures. The rapid return of skin temperature to control levels after tourniquet release has been well documented (Déry et al. 1965; Sanders 1973; Harris et al. 1975; Modig, Kolstad and Wigrin 1978). The elevation of the skin temperature of the ischaemic limb above control values has also been reported by some, but not all, workers (Sanders 1973; Modig et al. 1978).

In this study the temperature of recently ischaemic muscle and skin in the normothermic group, but not in the hypothermic group, rose above that of the control

Table III. Phosphofructokinase activity in mol/min/g wet weight, expressed as mean and SD for nine experiments in each group
HYPOTHYROMIA IN TOURNIQUET-INDUCED ISCHAEMIA OF MUSCLE

Jennische Harris Gutmann Dobner

limb after release of the tourniquet. This indicates the possibility of an early inflammatory response activated by tissue damage; the absence of this response in hypothermic limbs suggests that hypothermia has protected against its development (Figs 1 to 4).

Local muscle damage. The lower levels of serum potassium in venous blood draining hypothermic limbs even 20 minutes after release of the tourniquet (Fig. 6) also suggest that hypothermia reduced the extent of muscle damage. Persistent elevation of potassium levels after the release of a tourniquet has been reported by many authors (Modig et al. 1978; Jennische, Amundson and Haljamäe 1979; Klenerman et al. 1980) and is thought to indicate continuing ischaemia of muscle.

The glycogen content of muscle and the activity of the glycolytic rate-limiting enzyme, phosphofructokinase, were used as additional indicators of muscle viability. At day 10, the glycogen content of the ischaemic limb muscle of the normothermic group was lower than its control whereas the glycogen content of the hypothermic ischaemic limb was elevated. Similarly, at day 10, PFK activity in the ischaemic limb muscle of the hypothermic group was elevated whereas in the normothermic group was decreased (Table III). This further suggests the relative reduction of damage in the muscle of the hypothermic limb.

Rate of recovery. The ischaemic limbs of both hypothermic and normothermic groups of animals developed reactive hyperaemia when the tourniquet was released. There was flushing of the skin, a rapid rise in skin and muscle temperature and a peak rise of serum potassium within the first minute. This maximum elevation of potassium levels in the blood draining the limb after tourniquet removal has been shown to correspond with the maximum blood flow into the limb (Jennische et al. 1979). In the hypothermic group there was a significantly faster return to normal levels of serum lactate, serum potassium and pH after the initial application of the tourniquet (Figs 5, 6 and 7). This indicates both less tissue damage and a more rapid rate of recovery.

CONCLUSION

The principal findings are that the described method of producing hypothermia is both effective and safe, and that it provides some protection to muscles exposed to tourniquet-induced ischaemia. Evidence of this protective role of hypothermia were the slowing of glycogenolysis and hydrogen ion production during ischaemia, reduced potassium efflux from muscle, a minimal inflammatory response on release of the tourniquet, and a faster rate of biochemical and metabolic recovery. All of these suggest a reduction of muscle damage. These studies provide strong evidence that local hypothermia could be a useful clinical method for the “safe” prolongation of time under a pneumatic tourniquet. Clinical trials should be undertaken to determine the role of hypothermia in surgical practice.

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REFERENCES


