DELAYED RECOVERY OF MUSCLE pH AFTER SHORT DURATION, HIGH INTENSITY EXERCISE IN MALIGNANT HYPERTERMIA SUSCEPTIBLE SUBJECTS

P. ALLSOP, L. JORFELDT, H. RUTBERG, C. LENNMARKEN AND G. M. HALL

SUMMARY

Six subjects susceptible to malignant hyperthermia (MHS) and seven control subjects exercised for 4 min at 120% of their calculated maximal oxygen uptake on a bicycle ergometer. Mean (SEM) muscle pH, measured with a needle-tipped electrode in the vastus lateralis muscle, decreased from a resting value of 7.16 (0.04) to 6.78 (0.04) after exercise in the control group, and from 7.15 (0.05) to 6.56 (0.05) in the MHS group (P < 0.01 compared with control group). A further decrease in muscle pH to 6.68 (0.06) by 5 min after exercise occurred in the control group, followed by incomplete recovery to 7.06 (0.04) 30 min after exercise. In the MHS group, however, muscle pH decreased to 6.45 (0.05) 5 min after exercise before recovering slowly to only 6.64 (0.07) after 30 min (P < 0.01 compared with control group). There was no difference in muscle temperature, venous pH or venous lactate concentrations between the two groups. The results show that there is abnormal recovery of muscle pH after short-duration, high-intensity exercise in MHS subjects.

KEY WORDS

Hyperthermia: exercise test, malignant. Metabolism: lactate, muscle pH.

Malignant hyperthermia is a rare condition in which susceptible individuals (MHS) develop a hypermetabolic response of skeletal muscle after challenge by certain triggering agents [1]. Although volatile anaesthetic agents and depolarizing neuromuscular blocking drugs are the most commonly implicated triggering agents in man, stress and severe exercise have also been proposed [2, 3]. There are conflicting reports of the effects of exercise in MHS subjects. Campbell and colleagues [4] and Stanec and Stefano [5] reported that there was increased sympathetic activity during exercise in MHS subjects, but this was not found by Rutberg and co-workers [6], who also failed to find any difference in muscle metabolites between MHS and normal subjects after exercise.

There is evidence from phosphorus-31 nuclear magnetic resonance spectroscopy ($^{31}$P-NMR), however, of decreased muscle pH immediately after high-intensity arm exercise in MHS subjects [7]. Another NMR study showed a decreased rate of recovery of the inorganic phosphate: phosphocreatine ratio after arm exercise in MHS individuals, suggesting continuing ATPase activity [8]. The purpose of the present study was to compare the recovery profiles of muscle pH and temperature in MHS and control subjects after high-intensity, short-duration exercise on a bicycle ergometer.

SUBJECTS AND METHODS

The study, performed in Linkoping, was approved by the local Ethics Committee and all subjects gave consent after a full explanation of the procedures and possible risks involved. We...
studied six MHS subjects who had been diagnosed by in vitro testing of muscle biopsies at the University of Lund according to the criteria of the European MH Group [9]. The control group comprised seven subjects recruited from the hospital staff. Characteristics of all subjects are shown in table I. The maximal oxygen uptake ($V_{O_{2}}$max) of each subject was calculated from a submaximal cycle test conducted on a previous occasion according to the method of Astrand and Ryhming [10]. All subjects undertook exercise only for recreational purposes and had similar levels of habitual activity.

After an overnight fast, each subject had an area of skin over the mid-part of the vastus lateralis muscle cleaned with alcohol and infiltrated with 2% lignocaine. The needle-tipped pH electrode (20-gauge, World Precision Instruments) and the NiCr/NiAl thermocouple (21-gauge, Comark) were inserted into the muscle 1 cm apart and resting values measured. Blood samples were collected from a cannula in a forearm vein for measurement of baseline pH, $P_{O_2}$, $P_{CO_2}$ and lactate concentrations. The ECG of each subject was displayed continuously throughout the study.

The pH electrode and thermocouple were removed and all subjects undertook the following exercise test: a 1-min warm up was undertaken at a work load equivalent to 60% $V_{O_{2}}$max, then after a 1-min rest, a further 4 min of exercise was performed at a work load equivalent to 120% $V_{O_{2}}$max. Most subjects needed considerable encouragement to complete this stage of the procedure. The exercise test was conducted with the subject in an upright posture on an electrically braked and compensated bicycle ergometer. On completion of the exercise, the subject was transferred rapidly to a couch and the pH and temperature probes reinserted into a second, prep repared site in the same muscle, at least 5 cm from the initial insertion. During the 30-min recovery period, muscle pH and temperature were measured continuously and blood samples were collected. The pH and temperature probes remained undisturbed during the recovery period.

The pH electrode was connected to a Corning M140 pH meter and, between subjects, was cleaned with acetone, sterilized in glutaraldehyde and washed liberally in sterile water. The electrode was calibrated before and after each insertion against standard pH buffers of 4.00, 7.00 and 10.00 (20 °C). The pH values obtained in the study were not corrected for temperature. The precautions necessary to ensure rapid response of the pH electrode (3 s) with good stability over a prolonged period of time were described in detail by Allsop and colleagues [11]. The thermocouple was linked to a Comark 2001 meter and the system calibrated against a mercury-in-glass reference thermometer. The thermocouple was cleaned and sterilized in the same manner as the pH electrode. Venous lactate concentrations were determined by standard enzymatic methods [12].

Results are presented as mean values (SEM). Data were analysed by two-way and one-way analysis of variance as appropriate.

### RESULTS

There was no significant difference between subject characteristics and power output of the MHS and control subjects except for a significantly decreased ($P < 0.05$) power to weight ratio in the MHS group (table I).

### TABLE I. Subject characteristics and power output data (mean (SEM)). *P < 0.05 between groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 7)</th>
<th>MHS (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6/1</td>
<td>6/0</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>36 (1)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.83 (0.02)</td>
<td>1.78 (0.03)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.6 (3.6)</td>
<td>77.2 (4.5)</td>
</tr>
<tr>
<td>Mean power (W)</td>
<td>327 (20)</td>
<td>290 (18)</td>
</tr>
<tr>
<td>Power/weight (W kg$^{-1}$)</td>
<td>4.3 (0.1) *</td>
<td>3.8 (0.2)</td>
</tr>
</tbody>
</table>

Muscle pH decreased significantly ($P < 0.01$) in response to exercise in both groups: from 7.16 (0.04) to 6.78 (0.04) in the control group, and from 7.15 (0.05) to 6.56 (0.05) in the MHS group (fig. 1). Muscle pH continued to decrease during the early part of the recovery period to a nadir of 6.68 (0.06) in the control group and 6.45 (0.05) in the MHS group after 5 min. Thereafter, pH recovered progressively in the control group to 7.06 (0.04) after 30 min, whereas recovery was delayed in the MHS group and muscle pH attained only 6.64 (0.07) after 30 min. Throughout the recovery period, the muscle pH in the MHS group was significantly less than the control group ($P < 0.01$ from 0 to 10 min recovery and $P < 0.001$ from 10 to 30 min recovery).

Muscle temperature increased similarly in both groups, from 36.1 (0.3) °C to 38.1 (0.1) °C ($P < 0.001$) after exercise in the control group and from 36.2 (0.2) °C to 38.3 (0.2) °C ($P < 0.001$) in the
MH AND RECOVERY OF MUSCLE pH AFTER EXERCISE

FIG. 1. Mean (SEM) muscle temperature and pH changes at rest (Pre) and after exercise. pH changes are shown as a shaded area which represents the range of values measured in the control group, and as lines which represent individual MHS subjects.

MHS group (fig. 1). Recovery of muscle temperature occurred rapidly after completion of exercise and values had decreased to 36.4 (0.1) °C in the control group and 36.6 (0.2) °C in the MHS group after 30 min. There was no significant difference in muscle temperature between the two groups throughout the study.

There was no significant difference in venous lactate concentrations, venous pH, venous $P_{O_2}$ and venous $P_{CO_2}$ between the two groups (table II). Peak heart rate values occurred during the 4th minute of exercise (179 (5) beat min$^{-1}$ in the control group and 186 (4) beat min$^{-1}$ in the MHS group) and were still increased after 30 min recovery (table II). There was no significant difference in the heart rate response to exercise between the two groups.

DISCUSSION

The principal finding of this study is that muscle pH showed both a greater decrease and a delayed recovery after high-intensity, short-duration exercise in MHS subjects. This persistent acidosis of exercised muscle occurred in the presence of similar increases in muscle temperature and comparable changes in venous pH and circulating lactate concentrations.

We have previously used the needle-tipped pH electrode to measure sequential changes after a 30-s sprint in man [11]. The relationship between muscle pH obtained with the pH electrode and with other methods of measurement has not yet been determined. The homogenate technique has been used for nearly 20 years to ascertain the pH of muscle biopsies [13]. Measurement of pH by this technique commonly gives values of about 7.0 [14], which is less than the 7.1-7.2 observed in this study. However, the absolute decrease in pH of 0.5-0.6 in response to maximal exercise in normal subjects is similar with both techniques [11]. The homogenate method of pH determination gives values which represent both intra- and extracellular compartments. We have suggested that the slightly greater resting pH values observed with the pH electrode reflect a greater contribution from the extracellular space.

### TABLE II. Mean (SEM) venous pH, $P_{O_2}$, $P_{CO_2}$, lactate and heart rate before (Pre) and after exercise in control and MHS subjects

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>pH</th>
<th>$P_{O_2}$ (kPa)</th>
<th>$P_{CO_2}$ (kPa)</th>
<th>Blood lactate (mmol litre$^{-1}$)</th>
<th>Heart rate (beat min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>MHS</td>
<td>Control</td>
<td>MHS</td>
<td>Control</td>
</tr>
<tr>
<td>Pre</td>
<td>7.38 (0.01)</td>
<td>7.38 (0.01)</td>
<td>6.0 (0.3)</td>
<td>6.0 (0.4)</td>
<td>6.1 (0.4)</td>
</tr>
<tr>
<td>0</td>
<td>7.01 (0.06)</td>
<td>7.08 (0.02)</td>
<td>5.8 (0.9)</td>
<td>4.9 (0.5)</td>
<td>10.0 (0.9)</td>
</tr>
<tr>
<td>1</td>
<td>7.03 (0.05)</td>
<td>7.12 (0.02)</td>
<td>8.0 (1.1)</td>
<td>6.0 (0.8)</td>
<td>9.6 (1.1)</td>
</tr>
<tr>
<td>2</td>
<td>7.09 (0.03)</td>
<td>7.14 (0.02)</td>
<td>8.9 (0.6)</td>
<td>7.1 (0.8)</td>
<td>6.2 (0.8)</td>
</tr>
<tr>
<td>3</td>
<td>7.10 (0.04)</td>
<td>7.14 (0.02)</td>
<td>9.2 (0.7)</td>
<td>7.8 (0.8)</td>
<td>5.8 (0.5)</td>
</tr>
<tr>
<td>4</td>
<td>7.08 (0.03)</td>
<td>7.13 (0.03)</td>
<td>9.8 (1.0)</td>
<td>8.3 (0.9)</td>
<td>5.3 (0.4)</td>
</tr>
<tr>
<td>5</td>
<td>7.09 (0.03)</td>
<td>7.13 (0.02)</td>
<td>10.1 (1.1)</td>
<td>8.7 (1.1)</td>
<td>5.1 (0.4)</td>
</tr>
<tr>
<td>10</td>
<td>7.11 (0.03)</td>
<td>7.13 (0.02)</td>
<td>9.0 (1.0)</td>
<td>8.7 (0.7)</td>
<td>4.9 (0.2)</td>
</tr>
<tr>
<td>15</td>
<td>7.15 (0.03)</td>
<td>7.16 (0.02)</td>
<td>8.6 (1.1)</td>
<td>8.6 (0.8)</td>
<td>4.7 (0.2)</td>
</tr>
<tr>
<td>20</td>
<td>7.19 (0.03)</td>
<td>7.18 (0.02)</td>
<td>8.4 (0.8)</td>
<td>8.3 (0.7)</td>
<td>4.6 (0.2)</td>
</tr>
<tr>
<td>30</td>
<td>7.28 (0.02)</td>
<td>7.25 (0.02)</td>
<td>7.0 (0.5)</td>
<td>7.5 (0.6)</td>
<td>4.7 (0.2)</td>
</tr>
</tbody>
</table>
with this technique [11]. $^{31}$P-NMR determines the intracellular pH of muscle indirectly and yields resting values for forearm muscle of 7.0–7.1 [15, 16]. The decrease observed with exercise is slightly greater than that found with the biopsy technique with values as small as 6.24 observed [16].

Laschuk and colleagues also reported a delayed recovery in forearm muscle pH after exercise, as measured by $^{31}$P-NMR [7]. Their data showed no difference in resting pH between control and MHS subjects (7.06 and 7.03, respectively) or on mild exercise. It was only in the recovery phase after severe exercise that a difference was observed (6.64 in control subjects and 6.40 in MHS subjects). Our results agree with these initial observations of Laschuk's group [7]. Olgin and colleagues [8] also used $^{31}$P-NMR to study changes in high-energy phosphate compounds during forearm exercise in MHS subjects. They stated that there was no difference in muscle pH between control and MHS subjects at rest or during exercise, but no values were cited for the recovery period. Furthermore, as the total exercise period was 18 min, it is unlikely that the severity of the exercise was sufficient to produce the profound acidosis found in the present study.

The delayed recovery in muscle pH after severe exercise in MHS subjects indicates either continuing production or delayed removal of lactic acid from muscle, or both. Lactic acid production is considered currently to reflect changes in the redox state of the muscle and not simply an oxygen deficient state [17]. In MHS subjects, abnormally increased intracellular [Ca$^{2+}$] during recovery from exercise would result in continuing activation of the myofibrillar ATPase with increased ADP and inorganic phosphate concentrations within muscle. These changes stimulate glycolysis and increase the cytosolic NADH concentrations. This reduction in redox potential shifts the lactate dehydrogenase equilibrium towards increased lactate production. It is interesting that Olgin and colleagues [8] found a slower rate of recovery of the inorganic phosphate:phosphocreatine ratio after forearm exercise in MHS subjects—conditions that would favour increased lactate production.

Lactic acid disposal in muscle occurs by two main pathways. Some lactate is metabolized in situ [18], whilst the remainder is removed by a lactate transporter in the sarcolemma which shows saturation kinetics [19]. The rate-limiting nature of this important mechanism for removal of intracellular lactate may account for the dissociation observed in the present study between muscle pH, and circulating lactate and pH values. Increased intracellular concentrations of lactate after intense exercise cannot be in equilibrium with extracellular concentrations until sufficient lactate has been either metabolized or transported to ensure that the translocation mechanism is not saturated. Subsequent removal of lactate from the extracellular space depends on the local buffering and muscle perfusion. Some of these steps in lactate disposal may be abnormal in MHS subjects and contribute to the persistent acidosis of muscle.

Changes in muscle temperature in response to exercise were similar in both groups, although the mean power output was significantly less in MHS subjects. We cannot exclude the possibility that, at comparable work loads, the MHS group would have shown greater thermogenesis, but our recent work suggests that muscle temperature is not affected greatly by small changes in power output [Hall and Allsop, unpublished data]. The decreased power output in the MHS subjects may reflect the underlying myopathy which is manifest only during high-intensity exercise and is not apparent at normal levels of activity.

In conclusion, we have shown delayed recovery of muscle metabolism after exercise at 120% $V_{O_2 max}$ in MHS subjects. This is in contrast to our previous work in which no metabolic abnormalities were found in MHS subjects after exercise at 40% and 80% $V_{O_2 max}$ [6]. Further studies are required to confirm our results, together with direct measurement of changes in muscle lactate concentrations, by either sequential biopsies or proton NMR.

**ACKNOWLEDGEMENT**

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**REFERENCES**


MH AND RECOVERY OF MUSCLE pH AFTER EXERCISE


