Skeletal muscle metabolism during exercise in patients with chronic heart failure

Maria Schaufelberger, Bengt O Eriksson, Peter Held, Karl Swedberg

Abstract

Objective—To investigate the metabolic response of skeletal muscle to exercise in patients with chronic heart failure and determine its relation to central haemodynamic variables.

Setting—University hospital in Sweden.

Participants—16 patients in New York Heart Association class II–III and 10 healthy controls.

Main outcome measures—Skeletal muscle biopsies were obtained from the quadriceps muscle at rest and at submaximal and maximal exercise. Right sided heart catheterisation was performed in eight patients.

Results—The patients had lower maximal oxygen consumption than the control group (13.2 (2-9) v 26.9 (4-4) ml/kg/min, P < 0.001). They had reduced activities of citrate synthetase (P < 0.05) and 3-hydroxyacyl-CoA dehydrogenase (P < 0.05) compared with the controls. At maximal exercise adenosine triphosphate (P < 0.05), creatine phosphate (P < 0.01), and glycogen (P < 0.01) were higher whereas glucose (P < 0.001) and lactate (P < 0.06) were lower in the patients than in the controls. Citrate synthetase correlated inversely with skeletal muscle lactate at submaximal exercise (r = −0.90, P < 0.003). No correlations between haemodynamic variables and skeletal muscle glycogen, glycolytic intermediates, and adenosine nucleotides during exercise were found.

Conclusion—Neither skeletal muscle energy compounds nor lactate accumulation were limiting factors for exercise capacity in patients with chronic heart failure. The decreased activity of oxidative enzymes may have contributed to the earlier onset of anaerobic metabolism, but haemodynamic variables seemed to be of lesser importance for skeletal muscle metabolism during exercise.

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Keywords: heart failure, exercise, metabolism, skeletal muscle

Patients with chronic heart failure have a limited exercise capacity because of dyspnoea and/or fatigue. The correlation between central haemodynamic variables at rest and exercise performance is poor.1 4 Changed skeletal muscle metabolism may contribute to the limited exercise capacity. Investigations with 31P nuclear magnetic resonance spectroscopy have shown that phosphocreatine is depleted faster and pH falls earlier in skeletal muscles in patients with chronic heart failure than in healthy controls during exercise.1 5 6 In biopsies from the lateral vastus muscle Sullivan and co-workers found less phosphocreatine depletion and lactate accumulation at maximal exercise in patients with chronic heart failure than in controls. This finding was not confirmed by Näveri et al.8

The increase in adrenaline during exercise contributes to the increased glycolysis in healthy people.9 Patients with chronic heart failure have an increased activation of the neurohormonal system,10 which might influence glycolysis during exercise.

Patients operated upon for coarctation of the aorta have an increased gradient between lactate in the quadriceps muscle and blood.11 Sullivan et al did not find such a gradient in patients with chronic heart failure.7

The objective of the present study was to see whether there is any difference in the metabolic response of skeletal muscle to exercise in patients with chronic heart failure and in healthy controls. Another objective was to find out if there is a relation between central haemodynamic variables, neurohormones, oxidative enzymes, and glucose metabolism in skeletal muscle during exercise. We also wanted to examine if there is a blood/muscle lactate gradient in patients with chronic heart failure.

Patients and methods

PATIENTS

Sixteen patients (13 men) with chronic heart failure (New York Heart Association class II–III) were studied (table 1). All had an ejection fraction of ≤ 40% (range 15–40) and had heart failure for at least six months (range 6–134). Patients with diabetes mellitus, intermittent claudication, angina pectoris, pulmonary disease, and other conditions limiting physical performance were excluded. Ten age matched healthy individuals were used as a control group (table 1).

All subjects underwent maximal exercise testing with respiratory gas analysis. A muscle biopsy was taken from the lateral vastus muscle at rest, at anaerobic threshold, and at maximal work. Blood samples from the femoral vein and finger tip were drawn at corresponding times. The protocol was approved by the ethi-
Table 1 Patient characteristics (mean (SD))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 16)</th>
<th>Controls (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>64.6 (10.5)</td>
<td>68.0 (3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>80.0 (15.2)</td>
<td>75.6 (11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of heart failure (mnth)*</td>
<td>51.8 (43.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)*</td>
<td>27.9 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide dose (mg)*</td>
<td>100 (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBlockers</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; ACE, angiotensin converting enzyme.

STUDY PROTOCOL

Three exercise tests were performed with patients and controls in the upright position on a bicycle ergometer. We used a ramp protocol with a 10 W increase every minute until exhaustion. The first exercise test familiarised the subjects with the method and the anaerobic threshold was determined. The Borg scale was used to evaluate fatigue and dyspnoea. The oxygen and carbon dioxide content in expired air was measured on line (Medical Graphics 2001 System minute ventilation, St Paul, Minnesota, USA). VO₂ max was defined as the VO₂ reached when VO₂ increased by < 1 ml/kg/min with an increase in workload. Where no plateau was found VO₂ max was defined as the average VO₂ value during the last 30 seconds. Ventilatory anaerobic threshold was evaluated independently by three observers. Anaerobic threshold was defined according to Wasserman et al and Simonton et al and expressed in ml/kg/min. Before the second exercise test a femoral venous catheter was introduced and placed 10 cm antegrade. Blood samples from the femoral vein and finger tip were taken at the same time as the muscle biopsies. Samples were taken at rest, during a short interruption of exercise at anaerobic threshold, and immediately after peak exercise. In two patients no anaerobic threshold was found. In these subjects the second sample was taken at 65% of maximal exercise time. Lactate content was analysed in blood from the femoral vein and finger capillaries and measured by the method by Lowry and Passonneau. The right heart was catheterised through the internal jugular vein in eight patients within one week of muscle biopsy. Heart rate and rhythm were monitored continuously. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were measured with the Swan-Ganz catheter. Cardiac output (where possible, a mean of three estimates) was measured by the thermodilution technique. The first measurement was made with the subject supine 15 minutes after insertion of the catheter. New measurements were made with the patient sitting on the bicycle, during exercise at anaerobic threshold, and at maximal exercise.

In seven patients venous blood was drawn after 30 minutes rest for analysis of aldosterone, angiotensin II, noradrenaline, and adrenaline. Aldosterone was determined by radioimmunoassay according to the procedure described by Walsh et al using kits from Diagnostic Products (Los Angeles, California). Angiotensin II in EDTA plasma was measured by radioimmunoassay as described by Nussberger et al with kits from Buehlem laboratories (Basel, Switzerland). Noradrenaline and adrenaline were determined in EDTA plasma by a radioenzymatic method using kits from Amersham (UK).

SKELETAL MUSCLE BIOPSY

Percutaneous biopsies were taken under local anaesthesia with a concho tele from the middle part of the lateral vastus muscle. The samples were immediately frozen in liquid nitrogen and stored at −70°C. The biopsy samples were weighed and fluorometrically analysed for adenine triphosphate, creatine phosphate, glycogen, glucose, glucose-6-phosphate, and lactate according to the modified Lowry et al methods as described by Karlsson. All values are expressed in

Table 2 Exercise variables and blood lactate concentrations in patients and controls at rest, anaerobic threshold, and maximal exercise (mean (SD))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest Patients</th>
<th>Controls</th>
<th>Anaerobic threshold Patients</th>
<th>Controls</th>
<th>Maximal exercise Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 (18)</td>
<td>69 (17)</td>
<td>109 (17)</td>
<td>108 (16)</td>
<td>127 (18)</td>
<td>162 (14)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>124 (15)†</td>
<td>148 (14)</td>
<td>140 (18)*</td>
<td>170 (55)</td>
<td>153 (19)†</td>
<td>207 (15)</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>0</td>
<td>0</td>
<td>49.2 (18.5)†</td>
<td>95.3 (25.8)</td>
<td>93.2 (21.9)†</td>
<td>190 (40.7)</td>
</tr>
<tr>
<td>VO₂ (ml/kg/min)</td>
<td>4.6 (1.2)*</td>
<td>6.0 (1.1)</td>
<td>10.1 (2.3)*</td>
<td>16.5 (2.4)</td>
<td>13.2 (2.9)†</td>
<td>25.6 (4.3)</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.76 (0.08)</td>
<td>0.73 (0.07)</td>
<td>0.96 (0.09)</td>
<td>0.95 (0.04)</td>
<td>1.17 (0.10)</td>
<td>1.21 (0.08)</td>
</tr>
<tr>
<td>Capillary lactate (mmol/l)</td>
<td>2.2 (0.9)</td>
<td>3.1 (1.4)</td>
<td>3.6 (1.4)</td>
<td>3.6 (1.1)</td>
<td>7.9 (3.3)</td>
<td>8.4 (2.4)</td>
</tr>
<tr>
<td>Femoral vein lactate (mmol/l)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>3.6 (1.4)</td>
<td>3.6 (1.1)</td>
<td>7.9 (3.3)</td>
<td>8.4 (2.4)</td>
</tr>
</tbody>
</table>

*P < 0.05, †P < 0.01, ‡P < 0.001 patients vs controls.
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Table 4  Skeletal muscle glucose metabolism in patients and controls at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Anaerobic threshold</th>
<th>Maximal exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Adenosine triphosphate</td>
<td>3.6 (0.9)</td>
<td>3.3 (1.0)</td>
<td>3.9 (0.8)†</td>
</tr>
<tr>
<td>Creatine phosphate</td>
<td>12.8 (5.2)</td>
<td>13.3 (4.6)</td>
<td>13.8 (3.7)‡</td>
</tr>
<tr>
<td>Lactate</td>
<td>2.9 (1.7)*</td>
<td>1.7 (0.8)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>Glucose-6-phosphate</td>
<td>0.5 (0.3)</td>
<td>0.4 (0.2)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.7 (0.7)*</td>
<td>2.4 (1.2)</td>
<td>1.8 (0.6)†</td>
</tr>
<tr>
<td>Glycogen</td>
<td>77 (18)</td>
<td>88 (26)</td>
<td>75 (19)</td>
</tr>
</tbody>
</table>

All data are mean (SD) expressed in mmol/kg ww. *P < 0.06, †P < 0.02, ‡P < 0.01, §P < 0.05, ||P < 0.001 patients v controls.

mmol/kg ww. A second biopsy sample was weighed and the glycolytic enzymes, phosphorylase and lactate dehydrogenase, and the oxidative enzymes, citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase, were analysed fluorometrically.20-23 The enzyme activities are expressed in μmol/g ww/min.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). An unpaired, two tailed Student’s t test was used for between group comparisons. For intragroup comparisons a paired, two tailed Student’s t test was used. The relations between variables were examined by simple and multiple regression by using the Statview II statistical program, MacIntosh (version S1-7.1). P < 0.05 was regarded as significant.

Results

All patients and controls stopped exercise...
because of dyspnoea or fatigue, reaching level 17–19 on the Borg scale where 20 is maximum. Workload and VO₂ at anaerobic threshold and maximal exercise were significantly lower in the patient group than in the control group (table 2). Maximal heart rate was also lower in the patients than in the controls but the respiratory quotient at peak exercise did not differ between the groups (table 2).

In eight patients and three controls biopsies could not be obtained at submaximal work. No representative biopsies were obtained in three patients at maximal work.

The activity of the oxidative enzymes citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase was significantly lower in the patients than in the controls (table 3). There was a tendency towards higher activity of lactate dehydrogenase in the patients than in the controls (table 3).

At rest patients had higher lactate concentrations in skeletal muscle than the controls. At submaximal and maximal exercise adenosine triphosphate and creatine phosphate were significantly higher in the patients than in the controls (table 4). Glucose was significantly higher in the controls than in the patients at all points measured. Glycogen were higher in the patients than in the controls whereas the lactate concentrations in skeletal muscle were higher in the controls than in the patients at maximal exercise (table 4). There were no significant differences in the changes in adenosine triphosphate, glucose-6-phosphate, and glucose (fig 1). The increase in skeletal muscle lactate was significantly smaller in the patients than in the controls (fig 1). Decreases in creatine phosphate and glycogen were smaller in the patients than in the controls (fig 1). At the same workload (patients’ maximal workload v controls’ submaximal workload) there was no significant difference in glycolytic intermediates, glycogen, and adenosine nucleotides between patients and controls.

Capillary blood lactate was lower at peak exercise in the patients than in the controls whereas femoral vein lactate did not differ between the groups (table 2). Capillary blood lactate and femoral vein lactate were higher in the patients than in the controls at the same workload (P < 0·001 and P < 0·01). No differences in the lactate gradient between skeletal muscle, capillary blood, or femoral venous blood was found between the groups.

The citrate synthetase activity in the patients was inversely correlated with skeletal muscle lactate at anaerobic threshold (fig 2). 3-Hydroxyacyl-CoA dehydrogenase showed the same trend but it did not reach statistical significance. No correlation was found between the oxidative enzymes and skeletal muscle lactate at maximal exercise.

Angiotensin II and aldosterone were correlated with skeletal muscle lactate at peak exercise (r = 0·86; P < 0·03, n = 6 and r = 0·89; P < 0·02, n = 6). A correlation was also found between skeletal muscle lactate at maximal exercise and cardiac index at rest (r = 0·96; P < 0·003, n = 6). Multiple regression analysis showed that only cardiac index at rest correlated significantly with skeletal muscle lactate at maximal exercise (P < 0·05). No correlations were found between haemodynamic variables and skeletal muscle glycogen, glycolytic intermediates, and adenosine nucleotides during exercise.

Discussion

Patients with chronic heart failure are limited in their exercise performance by dyspnoea, fatigue, or both. Administration of positive inotropic agents does not always increase exercise performance although cardiac output increases. A change in skeletal muscle metabolism has been seen in patients with chronic heart failure.

We investigated whether the limited exercise performance in patients with chronic heart failure was the result of a change in skeletal muscle metabolism. We found higher concentrations of creatine phosphate, adenosine triphosphate, and glycogen in these patients compared with controls at peak exercise. Skeletal muscle lactate was higher at rest but tended to be lower at peak exercise in the patients than in the controls. The decreases in creatine phosphate and glycogen were significantly less in the patients than in the controls whereas the increase in skeletal muscle lactate was significantly lower in the patients than in the controls. When skeletal muscle metabolism at the same workload (patients’ maximal v controls’ submaximal) was compared there was no difference between the groups. We could not find any blood/muscle lactate gradient in our patients in contrast to the observations reported by Eriksson and Hansson patients operated upon for coarctation of the aorta.

In both groups exercise performance was continued to exhaustion and was evaluated by the Borg scale. The lower skeletal muscle lactate concentrations and reduced depletion of phosphocreatine at maximal exercise in patients with chronic heart failure compared with controls accords with the results of Sullivan et al but not with 31P nuclear magnetic resonance studies. The contrasting results may be due to the different kind of exercise performed in the different investigations. In the 31P nuclear magnetic resonance studies only small muscle groups were tested.
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...at a maximal effort whereas in our study and in the investigation by Sullivan et al symptom limited bicycle exercise tests were performed. Thus different factors might limit exercise performance in the different tests.

During chronic hypobaric hypoxia healthy people had lower maximal exercise performance, despite the same degree of fatigue, less phosphocreatine depletion, and lower lactate concentrations at peak exercise than before exposure to hypoxia. When blood flow to exercising limbs in healthy subjects is reduced by external pressure, the blood lactate concentrations increase faster but reach a lower maximum value; this accords with our results in patients with chronic heart failure. These similarities indicate that hypoxia and diminished blood flow may play a part in the changed skeletal muscle metabolism seen in chronic heart failure. Lactate concentrations may be of less importance for leg fatigue in this condition, as suggested by the observation of Wilson et al that dichloroacetate, which reduces lactate formation, did not influence exercise performance in chronic heart failure. Other factors which might influence fatigue, such as neuromuscular junction transmission and central motor drive, do not seem to be altered in patients with chronic heart failure.

Patients with chronic heart failure have a decreased skeletal muscle mass. If a smaller muscle mass must perform the same work as a large muscle mass, it is possible that the smaller muscle mass is more easily fatigued. An increased percentage of type II B fibres and a decreased percentage of type I fibres have been reported in patients with chronic heart failure. This change in fibre type composition might contribute to the earlier fatigue seen in chronic heart failure. The type II B muscle fibres preferentially release lactate, which is used by the type I fibres, but a simultaneous release and uptake of lactate has also been noticed in the type II B muscle fibres. The increased percentage of type II B fibres and decreased percentage of type I fibres seen in patients with chronic heart failure might influence lactate turnover.

Adenosine triphosphate concentrations were higher in patients than in controls at maximal exercise. Sullivan et al reported a similar trend. In our patients glycogen and phosphocreatine were less depleted than in the controls. This is most probably because the total work performed by the patients was lower than in the controls. Sullivan et al did not find any difference in glycogen concentrations at maximal exercise. The difference between their results and ours might be due to the fact that their patients tended to have lower glycogen concentrations at rest than the control group.

The lack of correlation between central haemodynamic variables at peak exercise and glycogen, glycolytic intermediates, and adenosine nucleotides during exercise suggests that haemodynamic variables during exercise are less important to skeletal muscle metabolism at maximal exercise. However, not many patients were investigated to determine central haemodynamic variables.

Like others we found that patients with chronic heart failure had lower oxidative enzyme activity than controls. This may, in part, be due to deconditioning and is partially reversible after training. The inverse relation between skeletal muscle lactate at anaerobic threshold and the oxidative enzymes suggests that decreased activity of oxidative enzymes could influence the earlier onset of anaerobic metabolism seen in patients with chronic heart failure. These results accord with the findings of Sullivan et al. The lack of correlation between skeletal muscle lactate during maximal exercise and oxidative enzymes suggests that decreased oxidative enzyme activity is not the limiting factor for skeletal muscle metabolism at peak exercise in patients with chronic heart failure.

The reason for the limited exercise capacity in patients with chronic heart failure is not yet fully understood, but neither lack of substrate in skeletal muscle nor oxidative enzyme capacity seem to be the limiting factor. Diminished blood flow and decreased skeletal muscle mass are most probably important as is cardiac functional reserve.

LIMITATIONS OF THE STUDY
Experimental studies have shown diverging effects of the influence of β blockers on skeletal muscle metabolism, and one objection to this study may be that six of our patients were taking β blockers. Maximal heart rate was significantly lower in the β blocker treated group (113 with and 135 without β blockers, P < 0.03), but no significant differences between the patients treated with and without β blockers were seen in skeletal muscle metabolism, VO₂ max, and peak workload. Another limitation of the study is that a biopsy at submaximal exercise was not obtained in all subjects. Another objection may be that the metabolic results are expressed in mmol/kg ww. Broqvist et al found increased water content in skeletal muscle in 22 patients with oedema. On the other hand Dyckner and Wester did not see any significant change of skeletal muscle water content in 297 patients with heart failure. None of our patients had oedema, which makes it reasonable to believe that the metabolic results where not influenced by increased skeletal muscle water content.

CONCLUSION
Patients with chronic heart failure have less depletion of glycogen and phosphocreatine and a lower increase of lactate in skeletal muscle during exercise than controls. Neither substrate content nor skeletal muscle lactate concentrations are limiting factors for exercise performance in patients with chronic heart failure.

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