Skeletal muscle lactate accumulation and creatine phosphate depletion during heavy exercise in congestive heart failure

Cause of limited exercise capacity?

H. K. Näveri, H. Leinonen, K. Kiilavuori and M. Härkönen*

Department of Medicine, Division of Cardiology, Helsinki University Central Hospital and
*Department of Clinical Chemistry, University of Helsinki, Helsinki, Finland

Objective To study the mechanisms of limited exercise capacity and skeletal muscle energy production in male patients with congestive heart failure.

Design Muscle biopsy study.

Patients Skeletal muscle metabolic response to maximal bicycle exercise was studied in 10 patients with chronic congestive heart failure (ejection fraction 0.22 ± 0.05; peak oxygen consumption, \( V_\text{O}_2 \) 15.1 ± 4.9 ml. min\(^{-1}\). kg\(^{-1}\)) and in nine healthy subjects (peak \( V_\text{O}_2 \) 33.5 ± 6.7 ml. min\(^{-1}\). kg\(^{-1}\)). Activities of skeletal muscle enzymes were measured from the vastus lateralis muscle of 48 patients (ejection fraction 0.24 ± 0.06, peak \( V_\text{O}_2 \) 17.4 ± 5.4 ml. min\(^{-1}\). kg\(^{-1}\)) and 36 healthy subjects (peak \( V_\text{O}_2 \) 38.3 ± 8.4 ml. min\(^{-1}\). kg\(^{-1}\)).

Results Although blood lactate levels were lower in patients than in healthy subjects (2.2 ± 0.3 vs 5.2 ± 0.6 mmol. L\(^{-1}\); \( P<0.001 \)) at peak exercise (96 ± 11 W for patients and 273 ± 14 W for controls), skeletal muscle lactate was similarly elevated (25.6 ± 3.2 vs 22.7 ± 2.7 mmol. kg\(^{-1}\)) and creatine phosphate was equally depressed (\( P<0.02 \)) to low levels (7.0 ± 1.9 vs 6.7 ± 0.9 mmol. kg\(^{-1}\)). The muscle ATP decreased by 21% (\( P<0.05 \)) and 8% (\( P<0.01 \)) in the patients and controls, respectively. Activities of rate limiting enzymes of the citric acid cycle (alpha-ketoglutarate dehydrogenase) and oxidation of free fatty acids (carnitine palmitoyltransferase II) were 48% and 21% lower than in controls, but the mean phosphofructokinase activity was unchanged in congestive heart failure.

Conclusions It seems that the main limiting factor of exercise performance during heavy exercise is the same in congestive heart failure and healthy subjects, a high rate of skeletal muscle lactate accumulation and high-energy phosphate depletion. In congestive heart failure, the low activity of aerobic enzymes is likely to impair energy production and lead to lactate acidosis at low workloads.

(Eur Heart J 1997; 18: 1937-1945)

Key Words: Heart failure, skeletal muscle, exercise, energy metabolism.

Introduction

Exercise capacity in patients with chronic congestive heart failure is limited by dyspnoea or muscle fatigue. Exercise performance depends on a continuous delivery of energy in the form of ATP in skeletal muscle. If the rate of utilization of ATP exceeds its rate of production, muscle creatine phosphate (PCr) concentration begins to fall. In healthy subjects, the decrease in muscle PCr is related to the intensity of exercise, and low levels of PCr are found at the time of exhaustion\(^{[1,2]}\). The continuous production of ATP is dependent on intact skeletal muscle blood flow, enzyme machinery and the availability of substrates, such as muscle glycogen. All these factors may be affected in congestive heart failure, resulting in a decreased rate of ATP production and an exaggerated fall in muscle PCr during exercise.

Results of non-invasive studies using \(^{31}\)P-nuclear magnetic resonance spectroscopy (NMR) have shown that skeletal muscle energy production may be defective in congestive heart failure patients because of intrinsic abnormalities in their skeletal muscle\(^{[3-7]}\). The NMR method, however, has the disadvantage that only small muscle groups can be studied; the haemodynamic and metabolic responses may be remarkably different in...
Table 1 Clinical characteristics of the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Acute exercise</th>
<th>Enzyme studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n=10)</td>
<td>Controls (n=9)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43 ± 10</td>
<td>43 ± 8</td>
</tr>
<tr>
<td>Peak Vo2 (ml · min^-1 · kg^-1)</td>
<td>151 ± 4-9</td>
<td>33 ± 5 ± 6-7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>22 ± 5</td>
<td>—</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0/2/6/2</td>
<td>—</td>
</tr>
<tr>
<td>Aetiology of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number of patients. LVEF=left ventricular ejection fraction; NYHA=New York Heart Association, Vo2=oxygen consumption.

larger muscles during exercise, such as bicycling or walking, that is, normal daily activity.

The intrinsic abnormalities in skeletal muscle of patients with congestive heart failure may be due to changes in activities of enzymes regulating aerobic or anaerobic energy production. Earlier studies have given conflicting results concerning the activities of enzymes of aerobic energy production in skeletal muscle. No changes have been found in citrate synthetase, cytochrome oxidase or succinate-cytochrome-c-reductase activities^[8,9]. In contrast, decreased activity of hexokinase, citrate synthetase and succinate dehydrogenase have been reported^[10,11]. Furthermore, the results of Drexler et al^[12] suggested that the amount of skeletal muscle mitochondria is reduced in congestive heart failure. Most of the studies dealing with skeletal muscle enzyme activities had small patient groups and important regulatory enzymes were not measured.

The purpose of this study was two-fold; first, to find out whether the depletion of the high-energy phosphate pool and accumulation of lactate in the vastus lateralis muscle during maximal bicycling occurs similarly in male patients with congestive heart failure as in healthy men. In addition are the patients able to exercise intensely, causing biochemical changes of a magnitude similar to those in normal subjects, in spite of dyspnoea and respiratory muscle failure^[13-15]? Second, in order to find intrinsic abnormalities in skeletal muscle energy production, the activities of important rate limiting enzymes^[16] of aerobic and anaerobic energy production were measured in patients with heart failure as well as in healthy subjects.

Methods

Patients

This study consists of two parts, a bicycle exercise study and a muscle biopsy study at rest. A total of 54 male patients with chronic congestive heart failure of at least 6 months duration were studied (Table 1). The cause of congestive heart failure was established at the routine cardiac examination (clinical examination, electrocardiogram, chest X-ray), by two-dimensional echocardiography and heart catheterization. All patients were on digoxin, diuretics and angiotensin converting-enzyme inhibitors. None of the patients were on a beta-adrenoceptor blocking agent. The clinical condition of the patients and the dosage of their medication had been stable for at least 2 weeks prior to the investigation. None had a history of pulmonary disease and the flow-volume spirometry showed no obstruction of the airways; slight lung restriction found in some patients was attributed to chronic congestive heart failure.

Ten patients with moderate to severe congestive heart failure, aged 21–53 years, participated in the bicycle exercise study. Nine of them had dilated cardiomyopathy and one had ischaemic cardiomyopathy. In addition, a muscle biopsy for enzyme activity measurements was taken at rest from 48 patients, aged 25–68 years. Thirty seven of them had dilated cardiomyopathy and 11 had ischaemic cardiomyopathy.

Control subjects

In the bicycle exercise study, the control group comprised nine healthy men, aged 27–52 years. In addition, 27 healthy male subjects, aged 28–49 years, were biopsied at rest. Informed consent was given by all subjects. This study was approved by the ethics committee of the First Department of Medicine, Helsinki University Central Hospital.

Muscle samples

Biopsies were taken from the lateral portion of the quadriceps femoris muscle with a small biopsy needle (Tru-Cut, Travenol Laboratories Inc., IL, U.S.A.). After local anaesthesia of the skin, a small incision (2–3 mm) was made with a scalpel and biopsy needle was advanced 3–4 cm into the muscle at the mid-point between the...
greater trochanter and the articular cavity of the knee. Muscle biopsies before and immediately after bicycle exercise (with the subject still sitting on the bicycle) were taken from the same incision: the first sample was taken by advancing the needle toward the more distal and the second, by advancing the needle toward the more proximal part of the muscle, to avoid the possibility of taking the second sample from the previously sampled muscle area. The muscle samples (5–10 mg) were immediately frozen in liquid nitrogen (within 1–2 s of the cutting movement by the biopsy needle). All muscle samples were stored at −70 °C until analysed.

Exercise protocol

Two days before the study, the patients underwent maximal bicycle ergometry to familiarize themselves with the procedure. The exercise tests were always carried out between 0800 and 1100h, 2 h after a light breakfast. A catheter for blood sampling was inserted in a forearm vein. After a 30-min rest in the supine position, blood samples and muscle biopsies were obtained. An upright bicycle ergometer test with continuous expiratory gas analysis was then started (Ergo-OxyScreen, Jaeger, Germany). The initial workload of 10 W was increased stepwise by 20 W every 2 min until exhaustion (Borg Scale 19–20). Venous blood samples for lactate analysis were taken at each workload. Blood samples at peak exercise were taken during cycling just before exhaustion, and the muscle biopsy was taken (in 2–3 s) immediately after cycling while the subject was still sitting on the bicycle. An additional muscle sample was also taken from the healthy subjects after 2 min of cycling at 90 W.

Analytical methods

Muscle and blood metabolites

Perchloric acid extracts were made for the measurement of muscle and blood lactate and for the determination of muscle ATP and PCr. After alkaline digestion and ethanol precipitation, muscle glycogen was hydrolysed in 1 mmol·L⁻¹ HCl and then analysed for glucose. These parameters were determined using fluorometry with a Transcon 102 FN fluoro-nephelometer (Elomit, Ltd, Helsinki, Finland) by diethylamide adenine dinucleotide-linked enzymatic methods.

Muscle enzyme activities

For the determination of enzyme activities, the muscle samples were homogenized in 10 volumes of 50 mmol·L⁻¹ Tris-HCl buffer, pH 7.4, containing 0.5 mmol·L⁻¹ dithiothreitol (DTT), 2 mmol·L⁻¹ MgCl₂ and 1 mmol·L⁻¹ EDTA. The protein content of the water-diluted homogenates was measured according to Lowry et al.¹⁹.

Phosphofructokinase (PFK)

Assay medium was principally the same as that described by Lowry et al.¹⁹ and contained 50 mmol·L⁻¹ Tris-HCl, pH 7.4, 1 mmol·L⁻¹ ATP, 2 mmol·L⁻¹ MgCl₂, 1 mmol·L⁻¹ AMP, 10 mmol·L⁻¹ K₂HPO₄, 1 mmol·L⁻¹ DTT, 10 μmol·L⁻¹ NADH, 50 μmol·L⁻¹ triosephosphate isomerase, 90 μmol·L⁻¹ aldolase and 1.7 μmol·L⁻¹ glycerin-3-phosphate dehydrogenase. The reaction was initiated by adding 2 mmol·L⁻¹ fructose-6-phosphate, and the disappearance of NADH was followed kinetically at +25 °C for 1–2 min. For the calculations, 5 μmol·L⁻¹ of NADH in assay medium was used as a calibrator.

Alpha-ketoglutarate dehydrogenase (KGDH)

Assay medium was principally as described by Cooney et al.¹⁹ with modifications for fluorometric determination. Assay medium contained 100 mmol·L⁻¹ Tris-HCl, pH 7.4, 250 mmol·L⁻¹ mannitol, 10 mmol·L⁻¹ KH₂PO₄, 10 mmol·L⁻¹ KCl, 5 mmol·L⁻¹ MgCl₂, 1 mmol·L⁻¹ DTT, 0.05% Triton X-100, 1 mmol·L⁻¹ NAD⁺ and 0.5 mmol·L⁻¹ CoA. The reaction was started by adding 1 mmol·L⁻¹ alpha-ketoglutarate. Formation of NADH was followed kinetically at +25 °C for 2–3 min. For the calculations, 5 μmol·L⁻¹ of NADH in assay medium was used as a calibrator.

Carnitine palmitoyltransferase II (CPT II)

Formation of carnitine in the reaction between palmitoyl-carnitine and CoA was used as an index of enzyme activity. The method of Deufel and Wieland was used with the following modifications: carnitine formed in the reaction was measured using carnitine acetyltransferase. CoA formed in the reaction form acetyl-CoA was measured in medium containing 50 mmol·L⁻¹ Imidazole–HCl buffer (low fluorescence blank), pH 6.7, 1 mmol·L⁻¹ MgCl₂, 0.5 mmol·L⁻¹ EDTA, 0.5 mmol·L⁻¹ NAD⁺, 0.5 mmol·L⁻¹ alpha-ketoglutarate, 1 mmol·L⁻¹ DTT, 0.02% BSA, 0.1 mmol·L⁻¹ acetyl-CoA and 250 μmol·L⁻¹ of KGDH. Four hundred μl of this solution and 20 μl of CoA-containing medium were pipetted into Transcon microcuvettes, initial fluorescence was read and the reaction initiated by adding 300 μmol·L⁻¹ of carnitine acetyltransferase. Reaction was completed in 5 min at +25 °C and formation of carnitine was calculated. Carnitine at a concentration of 5 μmol·L⁻¹ in assay medium was used as a calibrator.
Table 2 Exercise parameters (mean ± SEM) in patients with congestive heart failure (n=10) and in healthy subjects (n=9)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submaximal</td>
<td>Peak</td>
</tr>
<tr>
<td></td>
<td>exercise</td>
<td>exercise</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>90 ± 0</td>
<td>273 ± 14</td>
</tr>
<tr>
<td>Heart rate (l. min⁻¹)</td>
<td>120 ± 3</td>
<td>178 ± 3</td>
</tr>
<tr>
<td>Oxygen consumption (ml. min⁻¹.kg⁻¹)</td>
<td>14-9 ± 0-7</td>
<td>33-5 ± 2-2</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>0-84 ± 0-02</td>
<td>1-03 ± 0-02</td>
</tr>
<tr>
<td>B-lactate (mmol. l⁻¹)</td>
<td>1-5 ± 0-3</td>
<td>5-2 ± 0-6</td>
</tr>
<tr>
<td>P-adrenaline (nmol. l⁻¹)</td>
<td>0-83 ± 0-14</td>
<td>5-44 ± 1-11</td>
</tr>
<tr>
<td>P-noradrenaline (nmol. l⁻¹)</td>
<td>4-32 ± 0-65</td>
<td>22-6 ± 4-57</td>
</tr>
</tbody>
</table>

*P<0-005 and **P<0-01 for significance of difference between patients and normal subjects at peak exercise and †P<0-02 for significance of difference between patients at peak exercise and normal subjects at submaximal exercise.

Plasma adrenaline and noradrenaline were measured by a radioenzymatic method.[121]

Statistical analysis

Two-tailed non-parametric tests were used to analyse differences between the group (Mann-Whitney U test) and the changes within the groups (Wilcoxon matched-pairs signed-ranks test).[222] The correlations were studied by linear regression analysis. The results are given as means ± SEM.

Results

Acute exercise

Exercise parameters (Table 2)

The mean workload at peak exercise was nearly three times higher in the control subjects than in the patients, and the submaximal workload of the controls (90 W) corresponded to the highest workload of the patients (mean 96 W); at this workload, the rate of oxygen consumption was similar in both groups. The heart rate and respiratory exchange ratio of the patients did not differ significantly from the values of the healthy subjects during peak exercise.

Plasma adrenaline and noradrenaline

At rest, the mean plasma adrenaline concentration was in the same range both in the patients (0-62 ± 0-10 nmol. l⁻¹) and the controls (0-51 ± 0-10 nmol. l⁻¹), but the mean noradrenaline level was significantly (P<0-05) higher in the patients (3-04 ± 0-46 nmol. l⁻¹) than in the healthy subjects (1-72 ± 0-22 nmol. l⁻¹). After maximal exercise, plasma adrenaline and noradrenaline levels were similarly elevated in both groups (Table 2).

Blood and muscle lactate (Table 2 and Fig. 1)

Blood lactate concentration at the end of exercise was lower (P<0-001) in the patients than in the controls; the same difference was seen 10 min after exercise (2-5 ± 0-3 and 6-1 ± 1-2 mmol. l⁻¹, respectively, P<0-05). Skeletal muscle lactate concentration at rest tended to be higher in patients than in healthy subjects (2-6 ± 0-5 vs 1-8 ± 0-3 mmol. kg⁻¹ wet weight). Furthermore, there was a significant correlation (r=0-84, P<0-005) between muscle lactate concentration and plasma adrenaline level in the patient group. At the end of exercise, muscle lactate concentration was equally elevated in the patients and normal subjects. In the healthy subjects, muscle lactate concentration was only moderately elevated at the submaximal work load of 90 W, corresponding to the mean maximal workload of the patients.

Muscle ATP and phosphocreatine (Figs. 2 and 3)

At rest, the muscle ATP and PCr levels in the congestive heart failure patients were normal (5-2 ± 0-4 and
Limited exercise in congestive heart failure

Figure 2 Skeletal muscle ATP concentration in patients with congestive heart failure (CHF) (n=10) and healthy control subjects (n=9) during graded bicycle exercise. Values are means ± SEM. *P<0.05 for significance of difference from the preceding value. P<0.01 is the significance of difference in the changes from baseline between the patients at peak exercise and controls at submaximal exercise.

Figure 3 Skeletal muscle phosphocreatine (PCr) concentration in patients with congestive heart failure (CHF) (n=10) and healthy control subjects (n=9) during graded bicycle exercise. Values are means ± SEM. **P<0.02 for significance of difference from the preceding values. P<0.005 is the significance of difference in the changes from baseline between the patients at peak exercise and controls at submaximal exercise.

Figure 4 Skeletal muscle glycogen concentration in patients with congestive heart failure (CHF) (n=6) and healthy control subjects (n=7) during graded bicycle exercise. Values are means ± SEM. *P<0.05 and **P<0.02 for significant of difference from the preceding values.

19.5 ± 1.4 mmol kg⁻¹ (wet weight, respectively) when compared with the healthy subjects (5.1 ± 0.3 and 22.9 ± 1.9 mmol kg⁻¹). After maximal exercise, the PCr concentration in the vastus lateralis muscle had markedly decreased to 7.0 ± 1.9 mmol kg⁻¹ (P<0.02) in the patients. This decrease in muscle PCr concentration was similar to that of the normal subjects at peak exercise, 6.7 ± 0.9 mmol kg⁻¹ (P<0.02). However, at the work load of 90 W the muscle PCr of the healthy subjects was only moderately decreased (P<0.02), the mean concentration being 16.3 ± 0.8 mmol kg⁻¹, which was significantly higher (P<0.05) than that of the patients at the mean maximum workload of 96 W (7.0 ± 1.9 mmol kg⁻¹).

There was a slight decrease in muscle ATP concentration at peak exercise in patients (-21%, P<0.05) and in healthy subjects (-8%, P<0.01 for the significance of difference from the value at submaximal exercise level). However, the difference between patients and controls was not significant.

Muscle glycogen (Fig. 4)
At rest, muscle glycogen concentration was (61.2 ± 11.0 mmol kg⁻¹) in the patients and (67.5 ± 14.3 mmol kg⁻¹) in the healthy controls. At the end of exercise, muscle glycogen had decreased to low levels both in patients (26.4 ± 3.0 mmol kg⁻¹) and controls (30.1 ± 4.3 mmol kg⁻¹).

Enzyme activities in skeletal muscle (Table 3)
Skeletal muscle KGDH activity (Fig. 5) was significantly lower (48%) in the patients than in the controls. None of the patients had higher KGDH activity than the mean activity of the healthy controls, and only 33% of the

Table 3 Skeletal muscle enzyme activities (nmol min⁻¹ mg protein⁻¹) in patients with congestive heart failure and in healthy controls

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>CHF (n=32)</th>
<th>Controls (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KGDH</td>
<td>23.5 ± 1.2</td>
<td>42.4 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPT I</td>
<td>45.2 ± 1.5</td>
<td>56.4 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFK</td>
<td>56.8 ± 3.5</td>
<td>78.4 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KGDH</td>
<td>48.2 ± 1.5</td>
<td>60.4 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPT I</td>
<td>49.3 ± 1.5</td>
<td>59.5 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFK</td>
<td>54.4 ± 2.4</td>
<td>78.4 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPT=carnitine palmitoyltransferase; KGDH=alpha-ketoglutarate dehydrogenase; PFK=phosphofructokinase. The P-value indicates the significance of difference between patients and healthy controls.
patients had higher KGDH activity than the lowest activity of the healthy subjects. On the other hand, the KGDH activity in the vastus lateralis muscle of the healthy controls, in every case, was higher than the mean activity of the congestive heart failure patients. Skeletal muscle KGDH activity was directly related to the peak \( \text{VO}_2 \) in the whole study population (\( R = 0.77, P < 0.0001 \)) and in the control population (\( R = 0.49, P < 0.01 \)). There was no relationship between left ventricular ejection fraction and KGDH activity in the congestive heart failure patients.

The mean CPT II activity (Fig. 6) was 21% lower in the patients than in the controls. Most of the patients had low CPT II activity, and in only 26% of them was it higher than the mean activity of the healthy controls. Skeletal muscle CPT II activity tended to be related to the peak \( \text{VO}_2 \) (\( R = 0.32, P < 0.005 \)) in the whole study population. In the control subjects, the relation between CPT II activity and peak \( \text{VO}_2 \) was positive (\( R = 0.35, P < 0.05 \)). No relationship between left ventricular ejection fraction and CPT II activity was found.

In contrast to the activity of the enzymes regulating aerobic energy metabolism, the patients' PFK activity did not differ from that of the healthy controls (Fig. 7). There was no relationship between PFK activity and peak \( \text{VO}_2 \) in the whole population or left ventricular ejection fraction in the patients. No significant differences could be found in skeletal muscle KGDH, CPT II or PFK activity between the patients with ischaemic or dilated cardiomyopathy.

**Discussion**

**Acute exercise**

This muscle biopsy study shows that in chronic congestive heart failure muscle fatigue during strenuous bicycle exercise is associated with depletion of the skeletal muscle high-energy phosphate pool and accumulation of lactate in the vastus lateralis muscle, which is most heavily involved muscle in this type of exercise\[^3\]. Quantitatively, skeletal muscle PCR depletion and the
amount of lactate accumulated at the time of exhaustion in the muscle of patients with congestive heart failure were similar to those seen in healthy subjects. This indicates that the main factor limiting exercise performance in patients with congestive heart failure during vigorous exercise is likely to be skeletal muscle fatigue, as in healthy subjects. However, the changes are seen at a much lower exercise level in patients.

This finding, of the high rate of skeletal muscle lactate accumulation and high-energy phosphate depletion, is in accordance with the results of earlier non-invasive studies using \(^{31}\)P-NMR spectroscopy, showing exaggerated skeletal muscle PCR depletion and high intracellular acidosis in small muscle groups during wrist and plantar flexion in patients with congestive heart failure\(^{[24-26]}\). The main difference between these and the present studies lies in the mass of skeletal muscle involved in exercise; a progressively increasing load during cycling requires maximal circulatory and ventilatory capacity, compared, for example, with plantar flexion which causes a low level of central circulatory strain. In spite of this, exercise could be continued to the point where it seemed to be limited by local muscular factors.

The results of our muscle biopsy study and NMR-studies are contradictory to those of Sullivan \textit{et al.}\(^{[11]}\) and Schaufelberger \textit{et al.}\(^{[27]}\) who found less lactate accumulation and PCR depletion in skeletal muscle at peak exercise in patients with congestive heart failure compared with controls. The level of maximal exercise is not easy to achieve in all patients with severe disease and the different results may simply reflect different exercise end points; in the present study the patients were completely exhausted and the heart rate at peak exercise was markedly higher than in the studies above (162 ± 5 vs 121 ± 25 and 127 ± 18 beats min\(^{-1}\), respectively). Although an attenuated heart rate response to exercise has been found in congestive heart failure, the maximal heart rates in their studies seem to be low. In the study of Roul \textit{et al.}\(^{[28]}\) the maximal heart rate (mean 161 min\(^{-1}\), range 143–179 min\(^{-1}\)) was comparable to that of ours. This suggests that the exercise strain has been lower and may be due to different exercise procedures or patient populations. In the study of Schaufelberger \textit{et al.}\(^{[27]}\), six of 10 patients were on beta-blockers. In the study of Sullivan \textit{et al.}\(^{[11]}\), the duration of exercise stages was 3 min compared to 1 min in the other two studies. The age of the patients may be an important determinant of exercise response. Our patients were considerably younger than those of Sullivan\(^{[11]}\) and Schaufelberger\(^{[27]}\). Our results indicate that in patients with congestive heart failure the main factor limiting exercise performance during strenuous short-term exercise is related to the depletion of the muscle PCR pool and the intracellular accumulation of lactate, not to respiratory failure due to ventilation perfusion abnormalities\(^{[29,30]}\) or speculated central fatigue mechanisms\(^{[11]}\), which may be the case if the duration of exercise is longer.

The high rate of lactate accumulation and PCR depletion in patients with congestive heart failure at low workloads is likely to be due to impaired aerobic energy production. In addition, the rate of ATP utilization may be increased in working skeletal muscles in congestive heart failure. This can result from intrinsic abnormalities in the muscle or lower muscle mass involved in the work. The rate of utilization of ATP in congestive heart failure has not been measured directly. Using NMR-spectroscopy, Massie \textit{et al.}\(^{[4]}\) and Marie \textit{et al.}\(^{[5]}\) found increased ATP turnover in ischaemic conditions during wrist or plantar flexion. However, the amount of work done could not be related to the working muscle mass, which is reduced in patients with congestive heart failure because of muscle atrophy\(^{[6]}\). Therefore, at present, no hard data are available to support the view that skeletal muscle high-energy phosphate utilization is increased due to intrinsic skeletal muscle abnormalities in congestive heart failure. Muscle atrophy results in a higher workload per unit of contracting muscle; thus, a smaller high energy phosphate pool is involved and a smaller total amount of energy can be produced in the working skeletal muscle during exercise in congestive heart failure compared with normal subjects. Skeletal muscle atrophy is likely to enhance, but cannot completely explain the high rate of anaerobic energy production during exercise.

Blood lactate level at peak exercise was lower in patients than in controls. However, the skeletal muscle lactate levels were comparable to those of the normal subjects. The lower blood lactate levels in patients are conceivably due to the smaller absolute amount of muscular work done, which results in a smaller total amount of lactate. Reduced skeletal muscle perfusion in congestive heart failure may also impair the rate of diffusion of lactate from the muscle to the blood stream, and at least partly explain the high muscle–blood lactate difference in severely ill patients. Intramuscular lactate accumulation, with a nearly 60% decrease in muscle glycogen content at the end of maximal exercise, indicates a high rate of anaerobic glycolytic flux in congestive heart failure.

Our result show that during exercise the rate of skeletal muscle energy production could not keep pace with the rate of utilization in patients with congestive heart failure at relatively low work load. Impaired skeletal muscle blood flow, probably due to inadequate muscular vasodilatory capacity\(^{[10]}\) and failure to increase cardiac output in relation to the requirements of exercising muscles, may possibly explain the foregoing. Decreased availability of oxygen as well as blood borne substrates, free fatty acids and glucose, leading to anaerobic metabolism causing muscle glycogen depletion and a high rate of lactate production at low workloads then results.

**Enzyme studies**

In addition to the decreased skeletal muscle blood flow, there is evidence that intrinsic abnormalities might exist in skeletal muscle in congestive heart failure. In...
NMR-studies involving small muscle groups, the muscle PCR level and intramuscular pH seemed to decrease in patients with congestive heart failure but not in controls, despite similar relative workloads and similar skeletal muscle blood flow rates[7]. The intrinsic abnormalities of skeletal muscle affecting aerobic energy production in chronic congestive heart failure could be due to changes in the muscle microcirculation, atrophy of type I muscle fibres, abnormalities in mitochondria, changes in mitochondrial and extramitochondrial enzymes and depletion of muscle energy stores. In addition, humoral changes, such as activation of the sympatho-adrenal system[32,33], may affect the substrate availability of working muscles by facilitating intramuscular glycogenolysis and increasing the rate of lipolysis in the adipose tissue. In this study we found a relationship between skeletal muscle lactate concentration and the plasma adrenaline level at rest in patients with congestive heart failure, which may be due to the sympatho-adrenal stimulation of muscle glycogenolysis. This may result in the reduced muscle glycogen levels in congestive heart failure found in earlier studies[1].

The in vitro measurement of some skeletal muscle enzyme activities can be used to predict the highest capacity of metabolic pathways. The enzymes measured in this study catalyse nonequilibrium reactions and reflect the maximum flux through metabolic pathways[10]. PFK indicates the flux through anaerobic glycolysis and CPT reflects the rate of fatty acid oxidation. KGDH is probably the only enzyme that can provide quantitative information about the aerobic capacity of the muscle[16].

Our finding of low KGDH activity in skeletal muscle indicates a decreased capacity to produce energy aerobically. It is in harmony with the results of earlier studies showing atrophy of type I muscle fibres[10], a decreased amount of mitochondria[12] and decreased activity of hexokinase, citrate synthetase and succinate dehydrogenase[10,11] in skeletal muscle in congestive heart failure. The difference in KGDH activity between patients with congestive heart failure and healthy subjects is greater than earlier reported for the measured enzymes of aerobic energy production. The positive association between peak oxygen consumption and KGDH activity in the control group as well as in the whole study population indicates an important role for KGDH in aerobic energy production.

Also, the activity of CPT was reduced in our patients with congestive heart failure. This is in accordance with earlier studies[8,10,11,23] showing a decrease in beta-hydroxyacyl CoA dehydrogenase activity, an intramitochondrial enzyme participating in the oxidation of free fatty acids. The decreased CPT activity may be due to the atrophy of type I muscle fibres[10], whereas the KGDH activity of patients with congestive heart failure is far too low to be explained solely by the decreased number of type I fibres. Inactivity and deconditioning are associated with impaired skeletal muscle aerobic capacity[34], and this is certainly true in patients with congestive heart failure, and is supported by finding elevated enzyme activity in aerobic metabolism in skeletal muscle in congestive heart failure after physical training[35]. Whether other mechanisms are involved in impaired skeletal muscle aerobic energy production in congestive heart failure remains to be shown. In contrast to the decreased activity of aerobic energy metabolism enzymes, the activity of PFK was unchanged, or tended to be increased, in severe congestive heart failure. This is in accordance with the increased proportion of Hb muscle fibres[8,10] and the high rate of accumulation of lactate at low workloads.

Conclusions

Patients with congestive heart failure seem to have a decreased capacity to produce energy in aerobic processes in skeletal muscle. Despite the high rate of anaerobic energy production, this, together with skeletal muscle underperfusion, results in a markedly decreased capacity to produce energy in the exercising leg muscles in congestive heart failure.

We conclude that during short-term heavy exercise, depletion of the skeletal muscle high-energy phosphate pool and the high rate of lactate accumulation impair performance capacity in chronic congestive heart failure. This is likely to be a secondary phenomenon due to reduced skeletal muscle aerobic capacity and underperfusion.

This study was supported by grants from the Medical Research Council of the Academy of Finland, the Paavo Nurmi Foundation, the Yrjö Jahnsson Foundation and the Aarne Koskelo Foundation

References


Eur Heart J, Vol. 18, December 1997
Limited exercise in congestive heart failure


Eur Heart J, Vol. 18, December 1997