Abnormalities of skeletal muscle metabolism in patients with chronic heart failure: evidence that they are present at rest

R Andrews, J T Walsh, Alison Evans, Sarah Curtis, A J Cowley

Abstract

Objective—To investigate abnormalities of skeletal muscle metabolism in patients with congestive heart failure.

Setting—A university teaching hospital.

Methods—43 patients (22 New York Heart Association (NYHA) grade II, 21 grade III) and 10 controls were studied. A forearm model of muscle metabolism was used, with a cannula inserted retrogradely into an antecubital vein of the dominant forearm. Maximum voluntary contraction (MVC) was measured using handgrip dynamometry. Subjects performed handgrip exercise, 5 s contraction followed by 5 s rest for 5 min at 25%, 50%, and 75% of MVC or until exhaustion. Blood was taken at rest and 0 and 2 min after exercise for measurement of lactate and ammonia. After 30 min the procedure was repeated with fixed workloads of 7 kg, 14 kg, and 21 kg.

Results—MVC (kg, mean (SEM)) was lower in patients than in controls (control 42-45 (2-3); NYHA II 34-13 (1-3), P = 0-003; NYHA III 33-13 (1-94), P = 0-008). Resting lactate (mmol/l) was higher in patients than controls (control 0-65 (0-06); NYHA II 0-84 (0-08), P = 0-13; NYHA III 1-18 (0-1), P = 0-002). Resting ammonia (μmol/l) was higher in NYHA III (65-7 (6-0)) than in NYHA II (48-0 (3-7), P = 0-016); no difference was found between controls (48-0 (7-1)) and patients. The overall lactate and ammonia response to exercise was greater in NYHA III than in NYHA II and controls (P < 0-05). At volitional exhaustion, peak lactate (mmol/l): NYHA III 3-31 (0-26); NYHA II 2-56 (0-16); controls 2-71 (0-22); P = 0-022 NYHA III v NYHA II) and ammonia (μmol/l): NYHA III 126-4 (8-97); NYHA II 92-9 (7-23); controls 109 (16-3); P = 0-006 NYHA III v NYHA II) were higher in severe congestive heart failure.

Conclusions—Skeletal muscle metabolism is abnormal at rest in congestive heart failure. During exercise, the degree of metabolic abnormality is related to the symptomatic status of the patient.

Keywords: skeletal muscle metabolism; congestive heart failure

It has been repeatedly shown that the extent of the exercise limitation in patients with chronic heart failure is unrelated to the degree of the central haemodynamic disturbance.1 It seems much more likely that the pathophysiological changes that limit exercise capability occur in the periphery.2 Abnormalities of skeletal muscle have been extensively described in patients with heart failure.3-5 Blood flow to skeletal muscle is reduced at rest and during exercise and this is thought by some investigators to be the primary abnormality.6 Others, however, have shown intrinsic, usually histological, abnormalities which are said to occur independently of reduced blood flow.7 8 Whatever the real cause of the changes in skeletal muscle they undoubtedly lead to the early onset of fatigue—probably as a result of anaerobic metabolism during exercise—and thereby limit exercise capability.9 10

The usual method for determining the onset of anaerobic metabolism in skeletal muscle is by monitoring lactate production. Other important products of metabolism may also appear in the blood during exercise. Ammonia is produced from the deamination of adenosine monophosphate which is metabolised from adenosine diphosphate. Adenosine diphosphate accumulates when there is failure to synthesise adenosine triphosphate and so ammonia production is a marker for adenosine triphosphate and therefore high energy phosphate bond loss.

Studies with nuclear magnetic resonance (NMR) scanning have shown a rapid reduction in intracellular pH in skeletal muscle during exercise which is presumably also due to the early onset of anaerobic metabolism.9 10 Associated with this is a rapid depletion of high energy phosphate bonds. However, because of the technical limitations of NMR scanning, these investigations have studied only single or small muscle groups which may not be representative of the cumulative changes that occur in all the skeletal muscle bulk of a limb. Support for this is provided by the fact that it has been difficult to relate the changes seen with NMR scanning to the degree of symptomatic impairment of the patients.5

The purpose of this study was to examine the metabolic changes of the skeletal muscle of the forearm during exercise by sampling blood which directly drains the muscle and compare these with the functional status of the patients.
Methods

PATIENTS
Forty three patients (41 male, two female) with chronic stable heart failure of at least three months’ duration took part in the study. All were being treated with a loop diuretic and angiotensin converting enzyme inhibitor. The mean age of the patients was 62.3 (SEM 1.1, range 44 to 76) years. Heart failure was due to ischaemic heart disease in 38 of the patients and dilated cardiomyopathy in the remaining five. The patients were divided into two groups, New York Heart Association (NYHA) II or III, according to their level of symptomatic impairment. Ten age matched (60-8 (2-2) years), fit healthy volunteers with no evidence of cardiovascular disease acted as control subjects.

All patients and control subjects gave written informed consent and the study was approved by the local ethics committee.

PROCEDURES
All patients were studied in a temperature controlled laboratory (23–24°C) in the morning following an overnight fast. They lay supine on a couch and a 21 gauge endhole cannula was inserted retrogradely into an antecubital vein of the dominant arm. The cannula was advanced distally into the vein in an attempt to sample blood as directly as possible from the muscle bed without contamination from blood draining the skin. Another cannula was inserted again retrogradely into a vein on the dorsum of the non-dominant hand. This hand was then positioned in a heated “box” at 55–60°C to arterialise the blood (oxygen saturation 90–95%). The patients then rested supine for 30 minutes.

Forearm exercise
After the rest period, venous blood was sampled for measurement of lactate and ammonia, and paired samples of venous and arterialised blood were taken for gas analysis (Ciba Corning 238 pH/blood gas analyser).

The patients then exercised the dominant forearm using a hand grip dynamometer. Maximum voluntary contraction (kg) was measured from an average of three attempts. After a further 15 min rest, the patients performed dynamic exercise: 5 s contractions followed by 5 s relaxation for 5 min at 25%, 50%, and 75% of maximum voluntary contraction, and then continued at 75% until exhaustion. Immediately after each period of exercise and for a further 2 min following the end of exercise, blood samples were obtained in an identical way to the resting samples. The patients then rested for a further 30 min and the procedure was repeated but next the patients exercised at fixed workloads of 7, 14, and 21 kg.

Biochemical analyses
Lactate: serum lactate was determined from 1 ml samples of blood which were immediately deproteinised in 3 ml of 10% cold perchloric acid and centrifuged. The supernatant was stored at −20°C until later assay.

Ammonia: 3 ml samples of blood were anticoagulated with lithium heparin and centrifuged, the serum was stored at −80°C until assay within 36 h of the sampling.

Oxygen extraction
Skeletal muscle oxygen extraction was calculated as the ratio of arteriovenous oxygen difference and arterial oxygen content, multiplied by 100%. Arterial oxygen content is calculated as haemoglobin concentration/dl × 1.34 × % arterial oxygen saturation.

STATISTICAL ANALYSES
Differences between the two patient groups and the control subjects at rest and at peak exercise were compared with unpaired t tests with a Bonferroni correction. Differences in the overall response to exercise between groups were compared using the area under the curve method. All results are displayed as mean (SEM).

Results
Twenty two of the patients were in NYHA class II and the remaining 21 in class III.

MUSCLE STRENGTH
Maximum voluntary contraction was reduced in the patients compared with the control subjects: in the controls it was 42.45 (2.30) kg; in the patients in NYHA class II it was 34.13 (1.30) kg (control v NYHA II, P = 0.003) and those in class III, 33.13 (1.94) kg (control v NYHA III, P = 0.008). There was no difference between the patient groups.

INDICES OF SKELETAL MUSCLE METABOLISM AT REST
Resting concentrations of serum lactate were higher in the patients than in the control subjects. The mean value in the control subjects was 0.03 (0.06) mmol/l, which was lower than...
Abnormalities of skeletal muscle metabolism in patients with chronic heart failure: evidence that they are present at rest

in the patients classified as NYHA III (1.18 (0.10) mmol/l (P = 0.002)), though not significantly different from those in NYHA II (0.84 (0.08) mmol/l, P = 0.13). Resting lactate was higher in NYHA III than in NYHA II (P = 0.01). Resting ammonia concentrations were also higher in the patients in NYHA III (65.7 (6.03) mmol/l) compared with those in NYHA II (48.0 (3.71) mmol/l (P = 0.016)), and approached significance when NYHA III was compared with control subjects (48.0 (7.07) mmol/l, P = 0.09).

INDICES OF SKELETAL MUSCLE METABOLISM DURING EXERCISE

Variable workload
Figure 1 shows the changes in lactate concentration in the patients and control subjects in response to exercise expressed as a percentage of maximum voluntary contraction. The overall lactate response to exercise was higher in the patients in NYHA class III compared with those in class II (P = 0.006) and the control subjects (P = 0.029). There was no difference between NYHA II and control subjects. The peak lactate concentration in the class III patients, 3.31 (0.26) mmol/l, was higher than those in class II, 2.56 (0.16) mmol/l (P = 0.022) and the control subjects, 2.71 (0.22) mmol/l.

Figure 2 shows the changes in ammonia concentration. The overall response to exercise was greater in patients with class III heart failure than in those with class II (P = 0.009) and in the control subjects. Peak ammonia concentration was also higher in patients in class III (126.4 (8.97) mmol/l) than in those in class II (92.9 (7.23) mmol/l, P = 0.006) and in the control subjects (109.0 (16.3) mmol/l).

Fixed workload
Figure 3 shows the changes in lactate concentration in response to the fixed workload exercise protocol. The patients in class III had a greater overall increase than the patients in class II (NYHA III v NYHA II, P = 0.08) or the control subjects (control v NYHA III, P = 0.006). There was no difference between the class II patients and the control subjects. Peak lactate was also higher in the class III patients (2.79 (0.27) mmol/l) than in the class II patients (2.03 (0.15) mmol/l, P = 0.017) and in the control subjects (1.58 (0.24) mmol/l, P = 0.007).

Figure 4 shows the changes in ammonia concentration. The overall increase in ammonia concentration was higher in the class III patients than in class II patients (P = 0.018) and in the control subjects (P = 0.017).Peak ammonia concentration was highest in the class III patients: 101.86 (7.49) mmol/l > 79.6 (6.46) mmol/l for class II patients (P = 0.03) and 72.6 (7.82) mmol/l for the control subjects (P = 0.023).

OXYGEN EXTRACTION
No significant differences in oxygen extraction or venous pH between groups were found (table).
Oxygen extraction (%) and venous pH at rest and peak exercise. Values are means (SEM)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak exercise (% MVC workload)</th>
<th>Peak exercise (% MVC workload)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Oxygen extraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25.78 (2.89)</td>
<td>38.56 (3.70)</td>
<td>48.53 (3.98)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>30.49 (2.99)</td>
<td>46.38 (2.99)</td>
<td>48.67 (2.87)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>25.53 (3.43)</td>
<td>42.26 (3.29)</td>
<td>42.02 (3.41)</td>
</tr>
<tr>
<td>(B) Venous pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7.38 (0.01)</td>
<td>7.26 (0.01)</td>
<td>7.31 (0.02)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>7.38 (0.01)</td>
<td>7.28 (0.01)</td>
<td>7.31 (0.01)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>7.40 (0.01)</td>
<td>7.26 (0.01)</td>
<td>7.32 (0.01)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association grade.

Discussion

The results of this study confirm other work which has shown abnormalities of skeletal muscle metabolism during exercise in patients with chronic heart failure. Both lactate and ammonia levels were increased during exercise in the patients with heart failure compared with a group of normal control subjects. The increase in the concentrations of these metabolites was also related to the severity of heart failure, assessed by NYHA class. However, much more surprising is that the abnormalities were also present at rest. This has not previously been described in an ambulant outpatient population of patients.

The contribution of the type of abnormality we have described to symptomatic impairment of patients is not fully known but this one pathophysiological process may contribute to the two dominant symptoms of heart failure: the early onset of anaerobic metabolism will lead to muscular fatigue and so limit exercise capability in this way, but it may also contribute to the breathlessness of heart failure. The presence of hyperventilation at rest and on exercise is well recognised in congestive heart failure and may contribute to the sensation of dyspnoea. The recent description of metabolic receptors within skeletal muscle involved in the control of ventilation would support the relevance of these metabolic abnormalities to the pathogenesis of dyspnoea in heart failure. The fact that some of the measurements we made were different in the two groups of patients with different severity of heart failure would also support the hypothesis that they are important in determining patients' symptomatic status.

We deliberately chose two different types of forearm exercise. One was related to the patients' maximum voluntary contraction and would therefore compensate for factors which may influence maximum strength, such as reduced muscle mass. The other used the same absolute workloads. In both tests the results were similar, with an increased concentration of lactate during exercise indicating the early onset of anaerobic metabolism. The increased concentration of ammonia show that there was an accompanying decrease in adenosine triphosphate resynthesis and a reduction in high energy phosphate bonds.

Previous investigators have described an increase in oxygen extraction at rest and on exercise in patients with congestive heart failure in both forearm and leg models. These studies involved patients in NYHA class III/IV, and the failure of the present study to show between-group differences in oxygen extraction and pH is most likely to reflect the relative insensitivity of these measurements in a less symptomatic population. Inadequate oxygenation of the "arterialised" blood would represent an alternative explanation, although the consistency of the values obtained for "arterial" oxygen saturation would mitigate against this possibility.

The interesting finding that some abnormalities were also present at rest was unexpected. The results suggest that skeletal muscle is already stressed in the non-exercising state. It must be remembered that these patients had stable chronic heart failure and were all outpatients at the time of the study, so could not be thought of as having "cardiogenic shock". The reason the abnormalities have not been shown before probably relates to methods used. In this study the sampling catheter was introduced retrogradely into the antecubital vein and was advanced so that it was directly adjacent to a vein draining the forearm skeletal muscle. In this site there should be minimal dilution of blood samples by blood draining other organs, including the skin, which may not be as metabolically stressed as the skeletal muscle and therefore may not have shown the same abnormalities. Other studies which did not advance the sampling catheter into a vein directly draining skeletal muscle may have collected samples diluted by blood from other tissues.

Our results show that the magnitude of the metabolic abnormality in congestive heart failure is related to symptomatic status, as determined by NYHA class. The finding that the degree of metabolic abnormality in NYHA II patients is similar to that of a normal population is of particular interest. This finding suggests that—at least in terms of skeletal muscle metabolism—NYHA III patients are a significantly different population to NYHA II patients; this would be consistent with an important role for abnormalities of skeletal muscle metabolism in the pathogenesis of the symptoms in congestive heart failure.

We deliberately chose to divide our patients by their self reported symptoms according to the NYHA classification, rather than use a laboratory based measurement of exercise capacity. Our aim was to assess the relation of abnormalities of skeletal muscle metabolism to symptoms in congestive heart failure, rather than their relation to an artificial treadmill test. Maximum treadmill exercise is not a part of customary patient activity, and changes in treadmill exercise duration and oxygen consumption correlate poorly with reported symptom changes and changes in daily activity levels.

The clinical relevance of the resting abnormalities is also not clear. Patients obviously develop symptoms during exercise but, as defined by NYHA class, these patients were thought not to have symptoms at rest. As the presence or absence of symptoms is entirely subjective the patients' perception of a lack of
Abnormalities of skeletal muscle metabolism in patients with chronic heart failure: evidence that they are present at rest

Symptoms at rest may have been inadvertently incorrect. Conversely the abnormalities we have found may not cause symptoms at rest. If there is a skeletal muscle ergoreflex involved in the control of ventilation in congestive heart failure then these resting abnormalities may contribute to the hyperventilation at rest described in congestive heart failure. Quality of life data suggest that patients experience impaired quality of life in other aspects of their lives which are not dependent on physical activity. It is therefore possible that these resting metabolic abnormalities impair quality of life but at a more general, possibly psychological, level rather than only affecting skeletal muscle metabolism and exercise capability.

This study has shown clinically important abnormalities of skeletal muscle metabolism during exercise which are also present at rest. The importance of the resting abnormalities is unknown. Furthermore, it is not clear whether effective treatment will modify them.

22. Francis GS, Rector TS. Maximal exercise tolerance as a therapeutic end point in heart failure—are we relying on the right measure? Am J Cardiol 1994;73:304-6.