

# Skeletal muscle alterations in patients with chronic heart failure

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**Aims** To investigate skeletal muscle in patients with chronic heart failure and controls, and relate skeletal muscle variables to functional class, exercise capacity, central haemodynamics, muscle strength and medical treatment.

**Methods** Biopsy from the lateral vastus muscle was obtained in 43 patients and 20 controls. Right sided heart catheterization was performed in 19 patients and maximal exercise testing in 26 patients. In nine patients muscle strength was measured. Patients had higher lactate levels, higher lactate dehydrogenase activity, and lower oxidative enzymes activity than controls. In patients, the percentage of type I fibres and capillarization were decreased while the percentage of type II B fibres were increased. Lactate

dehydrogenase activity correlated with exercise capacity, muscle strength and right atrial pressure. Digoxin-treated patients had significantly lower oxidative enzyme activity than patients without digoxin treatment.

**Conclusion** Patients with chronic heart failure have several skeletal muscle abnormalities. Central haemodynamics and medical treatment may, in addition to inactivity, be important in skeletal muscle changes.  
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**Key Words:** Heart failure, skeletal muscle, central haemodynamics, exercise capacity.

## Introduction

Cardiac performance as well as extra cardiac factors may contribute to symptomatology in chronic heart failure. Reduced skeletal muscle volume<sup>[1]</sup>, strength and endurance have been reported<sup>[1,2]</sup>, as has skeletal muscle blood flow<sup>[3,4]</sup>. A relationship between skeletal muscle volume, muscle blood flow and peak  $\text{VO}_2$  has been observed<sup>[5,6]</sup>. However, muscle blood flow corrected for muscle volume ceased to be correlated with peak  $\text{VO}_2$ <sup>[5]</sup>, which may indicate that muscle volume is of greater importance than blood flow for peak  $\text{VO}_2$  in heart failure. Intrinsic abnormalities in skeletal muscle might also contribute to symptomatology. Abnormal skeletal muscle metabolism during exercise has been demonstrated with  $^{31}\text{P}$  nuclear magnetic resonance spectroscopy<sup>[7–9]</sup>, unrelated to blood flow<sup>[10,11]</sup>. There is also evidence of a decrease in type I and an increase in type II B muscle fibres<sup>[12–14]</sup>. Capillarization is also altered, but the results are conflicting<sup>[12–14]</sup>. A reduction in oxidative enzyme activity has been reported<sup>[12–15]</sup>, but this has not been confirmed by others<sup>[16,17]</sup>.

Although several investigators have reported skeletal muscle changes, the results are not consistent and factors contributing to the abnormalities have not been fully explored. Inactivity and decreased cardiac performance may contribute. Pharmacological treatment in patients with heart failure may also potentially be of importance. Digoxin is, to a great extent, bound to skeletal muscle<sup>[18]</sup>. Whether this affects skeletal muscle metabolism and enzyme activities or not, is to our knowledge not known. Beta-blocker treatment, which improves symptoms in some patients with heart failure<sup>[19]</sup>, might influence skeletal muscle metabolism during exercise<sup>[20,21]</sup>. Treatment with the angiotensin converting enzyme inhibitor enalapril increases muscle fibre area and lactate dehydrogenase activity in skeletal muscle of patients with chronic heart failure<sup>[22]</sup>.

The objective of this study was to evaluate to what extent skeletal muscle metabolism, enzymatic activities, fibre composition, fibre area and capillarization are altered in patients with chronic heart failure. Another aim was to investigate if duration of heart failure, functional class, central haemodynamic variables at rest, exercise capacity and muscle strength are related to skeletal muscle abnormalities. Further objectives were to study the relationships between skeletal muscle variables and treatment with digoxin and beta-blockers.

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**Table 1** Characteristics of 43 patients with chronic heart failure and 20 control subjects

	Patients	Controls	P
Age (years)*	61.9 ± 11.1	65.8 ± 7.4	ns
Sex (male/female)	32/11	15/5	ns
Weight (kg)*	78.0 ± 15.6	75.4 ± 9.8	ns
Diagnosis:			
Coronary artery disease	28	—	
Dilated cardiomyopathy	12	—	
Hypertension	3	—	
Duration of heart failure (months)*	36 ± 40	—	
NYHA class:			
I	3	—	
II	18	—	
III	18	—	
IV	4	—	
Ejection fraction (%)*	26 ± 8	—	
Beta-blockers	14	—	
Vasodilators	16	—	
ACE inhibitors	36	—	
Digoxin	31	—	
Workload (W)*	86 ± 25 (n=26)	190 ± 41 (n=10)	0.0001

\*Data are mean ± SD; ACE=angiotensin converting enzyme; NYHA=New York Heart Association.

## Methods

### Patient population

Forty-three patients with chronic heart failure, in New York Heart Association class (NYHA) I–IV, and 20 age- and sex-matched healthy individuals, were studied (Table 1). Eleven patients were investigated as part of a clinical evaluation for heart transplantation. All patients had a left ventricular ejection fraction of  $\leq 40\%$  and a duration of heart failure of at least 2 months. Patients were divided into two groups, NYHA I–II and III–IV, for evaluation of the relationship between functional class and skeletal muscle variables. Patients on beta-blocker treatment were compared with patients without such treatment. Similarly, patients treated with digoxin were compared with patients without digoxin treatment. There was no difference between the subgroups except that patients in NYHA I–II were older than patients in

NYHA III–IV, and the digoxin-treated patients had worse symptomatology and higher heart rate at rest than patients without digoxin therapy. Patients with diabetes mellitus, intermittent claudication, significant pulmonary disease, angina pectoris or other disorders limiting physical performance were excluded. The protocol was approved by the ethical committee of Göteborg University, and written informed consent was obtained from each subject.

### Skeletal muscle biopsy

A conchotome was used to obtain percutaneous skeletal muscle biopsies under local anaesthesia from the middle part of the lateral vastus muscle in the right leg. Two samples were immediately frozen in liquid nitrogen, stored at  $-70^{\circ}\text{C}$  and used for analysis of metabolites and enzymes. A third sample was trimmed and mounted

**Table 2** Haemodynamic variables at rest in patients with chronic heart failure and control subjects

	Patients		Controls		P
	n	mean ± SD	n	mean ± SD	
Heart rate (beats · min <sup>-1</sup> )	43	76 ± 15	20	72 ± 14	ns
Systolic arterial pressure (mmHg)	43	122 ± 20	20	148 ± 17	0.0001
Diastolic arterial pressure (mmHg)	43	75 ± 11	20	85 ± 8	0.0004
Right atrial pressure (mmHg)	17	8.0 ± 4.7	—	—	
Systolic pulmonary artery pressure (mmHg)	19	52.5 ± 20.4	—	—	
Diastolic pulmonary artery pressure (mmHg)	19	24.8 ± 11.0	—	—	
Pulmonary capillary wedge pressure (mmHg)	19	23.3 ± 10.5	—	—	
Cardiac index (l · min <sup>-1</sup> · m <sup>-2</sup> )	19	2.3 ± 0.4	—	—	
Systemic vascular resistance (dynes · s <sup>-1</sup> · cm <sup>-5</sup> )	17	17.6 ± 4.6	—	—	

**Table 3** Capillary supply of the lateral vastus muscle in patients with chronic heart failure and normal subjects

	Patients		Controls		P
	n	mean $\pm$ SD	n	mean $\pm$ SD	
Capillary density (cap. mm <sup>-2</sup> )	31	244 $\pm$ 101	8	286 $\pm$ 108	ns
Capillary/fibre	31	1.1 $\pm$ 0.2	8	1.4 $\pm$ 0.3	0.008
Number of capillaries in contact with each fibre					
Type I	31	3.0 $\pm$ 0.6	8	3.6 $\pm$ 0.8	0.04
Type II	31	2.4 $\pm$ 0.4	8	2.7 $\pm$ 0.6	ns
Type IIA	31	2.6 $\pm$ 0.4	8	3.0 $\pm$ 0.6	0.05
Type IIB	31	2.2 $\pm$ 0.4	8	2.5 $\pm$ 0.5	ns
Average	31	2.6 $\pm$ 0.4	8	3.1 $\pm$ 0.7	0.02
Fibre area in relation to capillaries in contact with each fibre ( $\mu\text{m}^2 \times 10^3$ )					
Type I	31	1.9 $\pm$ 0.6	8	1.7 $\pm$ 0.8	ns
Type IIA	31	2.0 $\pm$ 0.9	8	1.9 $\pm$ 0.9	ns
Type IIB	31	2.1 $\pm$ 1.1	8	1.9 $\pm$ 1.0	ns

in embedding media, frozen in cooled isopentane and stored at  $-70^\circ\text{C}$ . This sample was used for histochemical analysis.

One biopsy sample was weighed and fluorometrically analysed for adenosine triphosphate, creatine phosphate, glycogen, glucose, glucose-6-phosphate and lactate according to the modified Lowry and Passoneau methods, as described by Karlsson<sup>[23]</sup>. All values are expressed in mmol  $\cdot$  kg<sup>-1</sup> ww. A second biopsy sample was weighed and the activities of phosphorylase and lactate dehydrogenase, as well as citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase, were analysed using a fluorometric technique<sup>[24-27]</sup>. The enzyme activities are expressed in  $\mu\text{mol} \cdot \text{g}^{-1} \text{ ww} \cdot \text{min}^{-1}$ .

Muscle fibre classification and calculation of capillaries were performed in 35 patients and eight control subjects, in a blinded manner, according to Dubowitz, and Andersen and Henriksson<sup>[28,29]</sup>. Fibre areas were measured with a semi-automated method (Comfas system, Bio-Rad Scan Beam A/S, Hadsund, Denmark).

### Exercise testing and right-sided heart catheterization

Exercise tests were performed in the upright position on a bicycle ergometer in 26 patients and 10 control subjects. In 16 patients and among the control subjects a ramp protocol was utilized where the workload was increased by 10 W every minute until exhaustion. In ten patients evaluated for heart transplantation, the exercise tests started at 30 W. All exercise tests were performed within 12 days of muscle biopsy except in four cases where they were performed up to 2 months before the biopsy. All patients were clinically stable between the performance of the test and that of the biopsy.

Right-sided heart catheterization through the internal jugular vein was performed in the supine position in 19 patients, who all, except one, performed an exercise test within a week of muscle biopsy. Right

atrial, pulmonary artery and pulmonary capillary wedge pressures were determined from a Swan-Ganz catheter. Cardiac output was measured with the thermodilution technique.

### Muscle strength test

Muscle strength in the knee extensors was measured in nine patients, all investigated haemodynamically. The patients were seated with the back supported, a seat-belt around the waist, with both legs hanging freely. The knee angle was  $90^\circ$ . A non-elastic strap was placed around the ankle and attached to a pressure transducer with amplifier (Steve Strong, Stig Starke HB, Göteborg, Sweden). The subjects were instructed to pull the ankle strap maximally for 3 s. The best of three efforts in the right leg was reported as maximal isometric quadriceps force (in Newton, N).

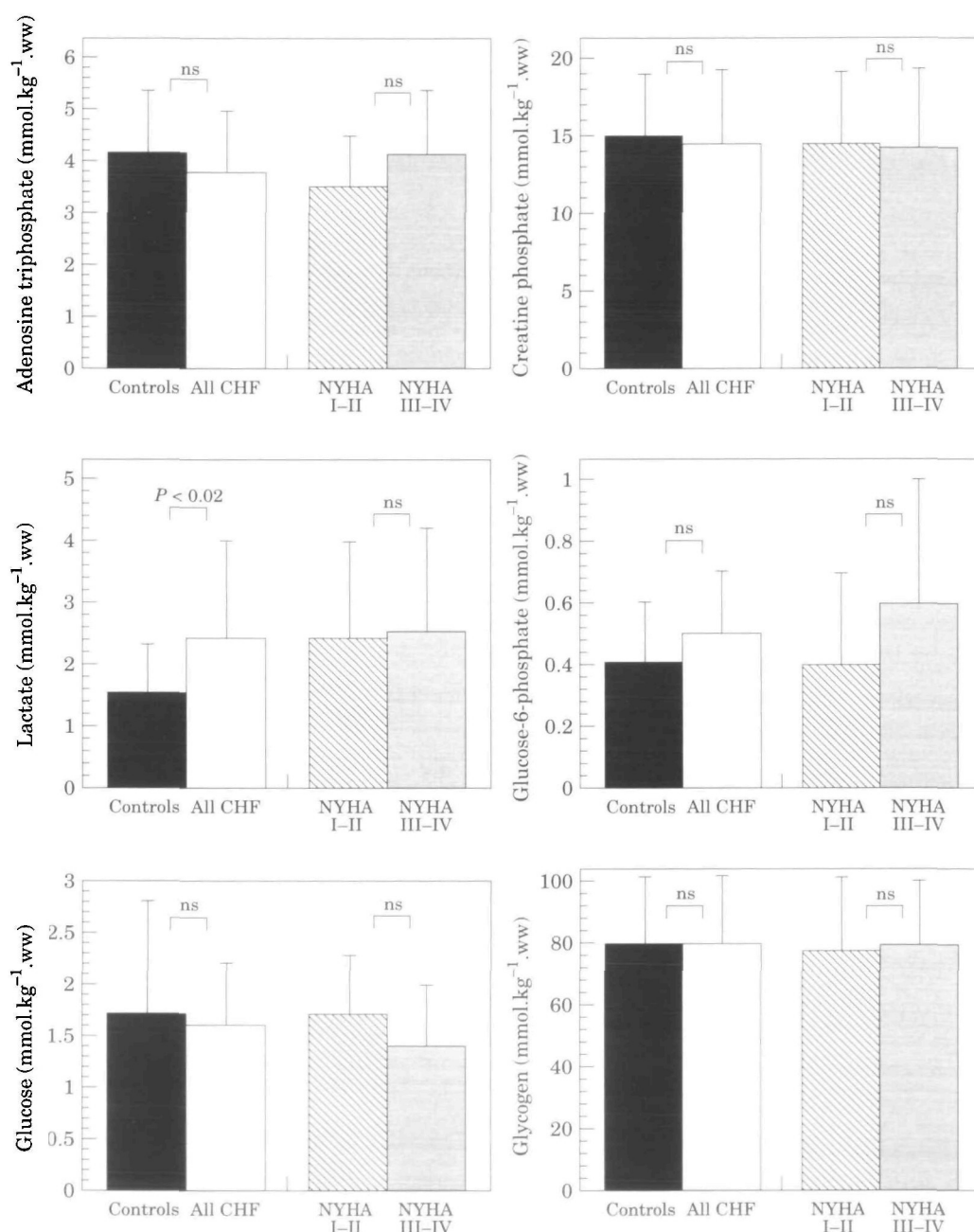
### Statistical analysis

Data are expressed as mean  $\pm$  SD. An unpaired two-sided Student's t-test was used to evaluate possible differences between groups. The relationship between variables was examined by simple regression analysis.  $P < 0.05$  was considered significant.

## Results

Exercise capacity was significantly reduced in patients compared with controls (Table 1). For haemodynamic variables see Table 2. Muscle strength in the right leg was  $491 \pm 190$  N.

Lactate was significantly higher in patients than in controls (Fig. 1), but no difference was noted between patients in NYHA I-II and III-IV. Similarly, lactate dehydrogenase activity was higher in patients than in controls, but with no difference between patients in



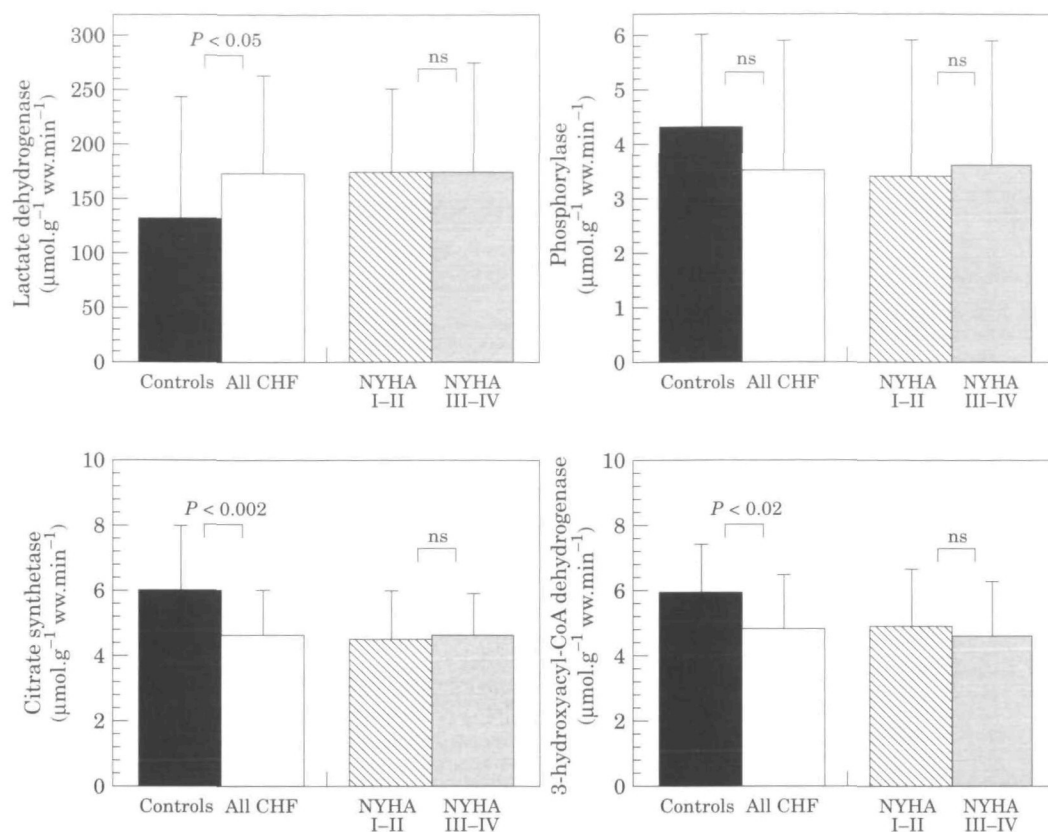
**Figure 1** Skeletal muscle adenosine nucleotides, glycolytic intermediates and glycogen in patients with chronic heart failure (NYHA I-II, NYHA III-IV) and control subjects. CHF=chronic heart failure.

NYHA I-II and III-IV (Fig. 2). Adenosine triphosphate, creatine phosphate, glucose-6-phosphate, glucose and glycogen did not differ between patients and controls (Fig. 1). No significant difference was found in phosphorylase activity between the groups (Fig. 2). Citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase activities were lower among patients than the normal subjects, but again there was no difference between patients in NYHA I-II and III-IV (Fig. 2).

Although there was a decreased percentage of type I fibres and an increase in type II B fibres in patients

compared with controls (Fig. 3), no difference in the percentage of type II A and II C fibres was noted between the groups (Fig. 3), or between the fibre areas (Fig. 4). The patients had fewer capillaries per fibre and fewer capillaries in contact with each fibre than the control subjects (Table 3), but capillary density and fibre area in relation to capillaries in contact with each fibre did not differ between the groups (Table 3).

No relationship between the duration of heart failure and skeletal muscle variables was seen. There was no difference in biochemical and histochemical variables



**Figure 2** Skeletal muscle enzyme activity in patients with chronic heart failure (NYHA I-II, NYHA III-IV) and control subjects.

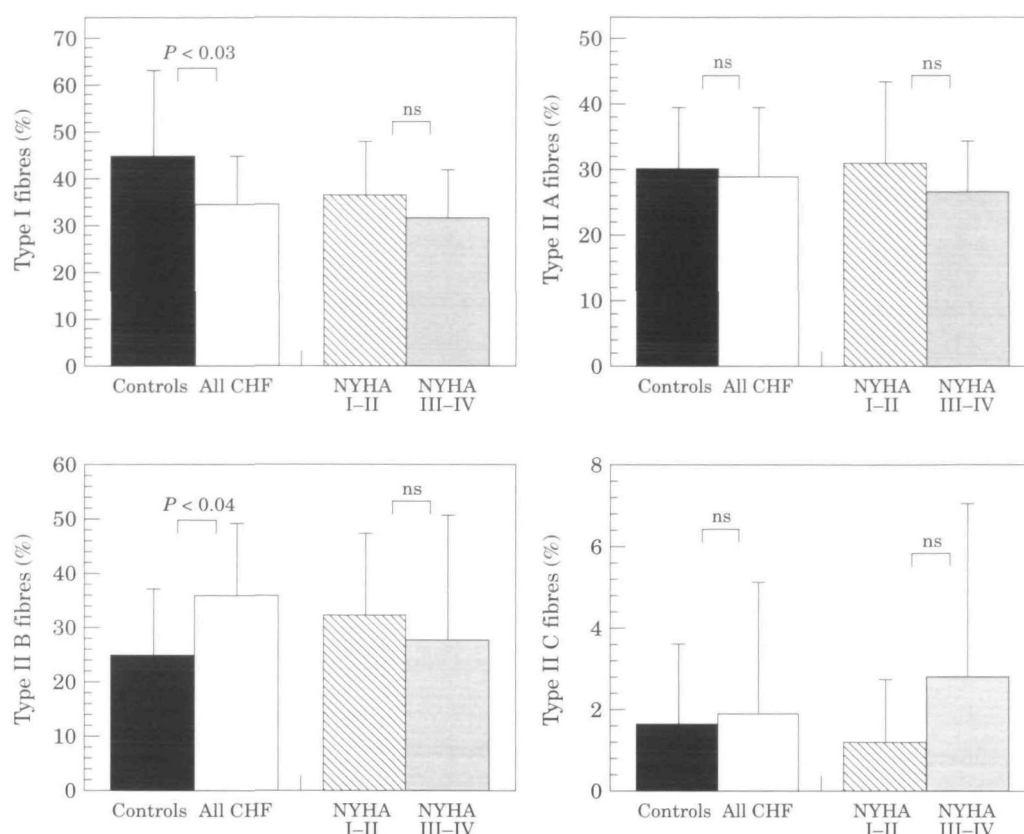
between patients who performed an exercise test and right sided heart catheterization and those who did not. The activities of citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase were not related to central haemodynamic variables. Right atrial pressure correlated with lactate dehydrogenase activity (Fig. 5). There was also a relationship between maximal workload, muscle strength in the knee extensors and lactate dehydrogenase activity (Fig. 5), but none between histochemical variables and central haemodynamic measurements; exercise capacity was positively correlated to the percentage of type I fibres (Fig. 5).

Skeletal muscle variables did not differ between patients treated with beta-blockers vs without beta-blockers. Patients treated with digoxin had lower citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase activity than patients without digoxin treatment ( $3.8 \pm 1.0$  vs  $5.6 \pm 1.8$ ;  $P < 0.005$  and  $4.1 \pm 0.9$  vs  $6.2 \pm 2.4$ ;  $P < 0.002$ ). The patients treated with digoxin had worse symptomatology. If patients in NYHA I-III A were evaluated there was no difference in NYHA class between patients treated with digoxin and those not, but citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase activities were still lower in patients with digoxin than without digoxin treatment ( $P = 0.0004$  and  $P < 0.002$ ).

## Discussion

This study indicates that patients with chronic heart failure have increased levels of skeletal muscle lactate at rest and lactate dehydrogenase activity, while citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase activity is decreased. There was a decreased percentage of type I fibres and an increase in type II B fibres. The patients had fewer capillaries per fibre and fewer capillaries surrounding each fibre than the normal subjects. Lactate dehydrogenase activity was related to exercise capacity, muscle strength and right atrial pressure. The digoxin-treated patients had lower oxidative enzyme activity than the patients without digoxin therapy.

The skeletal muscle abnormalities were probably due to multiple factors, but inactivity may be of importance: several changes in patients with chronic heart failure resemble those found after disuse, e.g. decreased oxidative enzyme activity and capillarization<sup>[30-32]</sup>. However, the lack of correlation between NYHA class and duration of heart failure indicate that other factors may also contribute. The fact that patients in NYHA I-II were older than those in NYHA III-IV might influence the results. However, no change in oxidative enzyme activity has been reported with age<sup>[33]</sup>.



**Figure 3** Fibre type distribution in skeletal muscle in patients with chronic heart failure (NYHA I-II, NYHA III-IV) and control subjects.

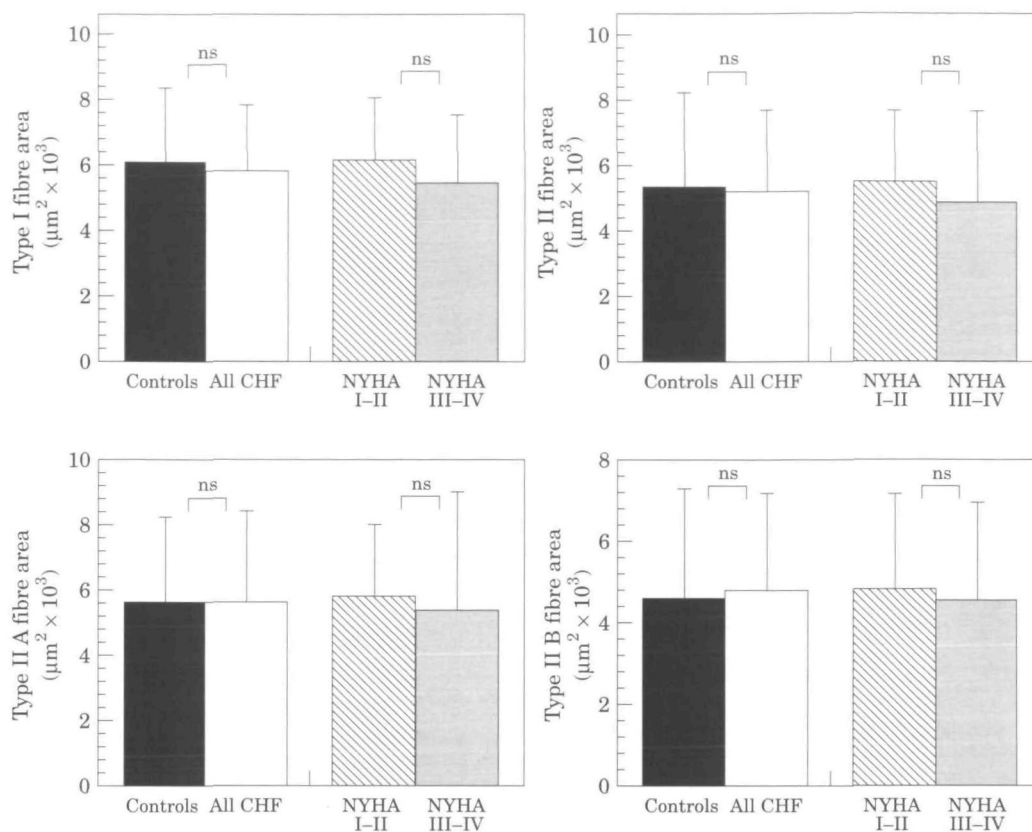
A reduction of glycogen<sup>[13,34]</sup>, as well as of adenosine triphosphate and phosphocreatine in skeletal muscle at rest<sup>[34]</sup>, has been reported in patients with chronic heart failure. These observations must be interpreted cautiously since in another study<sup>[35]</sup> the results could not be replicated and half of the patients investigated by Broqvist and co-workers<sup>[34]</sup> suffered from diabetes mellitus. We found elevated levels of lactate in the skeletal muscle of patients with heart failure. In other studies the same tendencies have been noted but have not reached statistical significance, most probably due to the limited number of patients investigated and the wide distribution of the material<sup>[13,35]</sup>. The increased lactate levels in this investigation may be explained by the increase in glycolytic metabolism which was already present at rest.

The decreased levels of oxidative enzyme activity is in accordance with several other studies<sup>[12-15]</sup>, but the lack of changes noticed by others may be due to the limited number of patients investigated<sup>[16,17]</sup>. Immobilization decreases oxidative enzyme activity<sup>[31,36]</sup>, whereas training has the opposite effect on both healthy individuals<sup>[37]</sup> and patients with heart failure<sup>[38]</sup>. Use of digoxin was related to the decrease in oxidative enzyme activity. About 50% of digitalis is bound to skeletal muscle<sup>[18]</sup> and increases contractility both in cardiac and skeletal muscle<sup>[39]</sup>. In cat and mouse, ouabain is predominantly bound to the type I fibres<sup>[40,41]</sup>, which have high oxidat-

ive capacity. The sodium, potassium-pump is important for excitability and contractility, and is the cellular digitalis glycoside receptor<sup>[42]</sup>. It may be that the digitalis binding to skeletal muscle influences oxidative enzyme activity. Another explanation may be that the stimulation of skeletal muscle by digitalis is so intense that the oxidative enzymes are down-regulated.

In this investigation, lactate dehydrogenase activity was increased among the patients compared to the control group. Others have not reported such an elevation<sup>[12,13]</sup>. We have demonstrated an increase in lactate dehydrogenase activity in skeletal muscle in patients with heart failure after 3 months treatment with the angiotensin converting enzyme inhibitor enalapril<sup>[22]</sup>. This may explain the discrepancy between our results and others, since 84% of the patients in the present investigation were treated with angiotensin converting enzyme inhibitors. The increased lactate dehydrogenase activity may thus be due to angiotensin converting enzyme inhibitor treatment. Another possibility is that the patients had a higher percentage of type II B fibres, which have high glycolytic activity.

Exercise capacity and muscle strength in the right leg were related to lactate dehydrogenase activity. This might be due to a defect in the oxidative pathway and impaired oxygen delivery to working muscles, which may increase the demand on the anaerobic metabolism. Another possibility is that the decreased muscle volume



**Figure 4** Skeletal muscle fibre area in patients with chronic heart failure (NYHA I–II, NYHA III–IV) and control subjects.

found in patients with chronic heart failure<sup>[1]</sup> might increase the demand on each muscle fibre, leading to an increased anaerobic metabolism. There was a weak relationship between lactate dehydrogenase activity and right atrial pressure which is difficult to interpret. It is conceivable that decreased cardiac output, decreased nutritive flow to skeletal muscle and exercise capacity are related to low oxidative enzyme activities, but we could not show such a relationship in patients with heart failure. Magnusson and co-workers saw no relationship between exercise capacity and oxidative enzyme activity in patients with heart failure<sup>[43]</sup>.

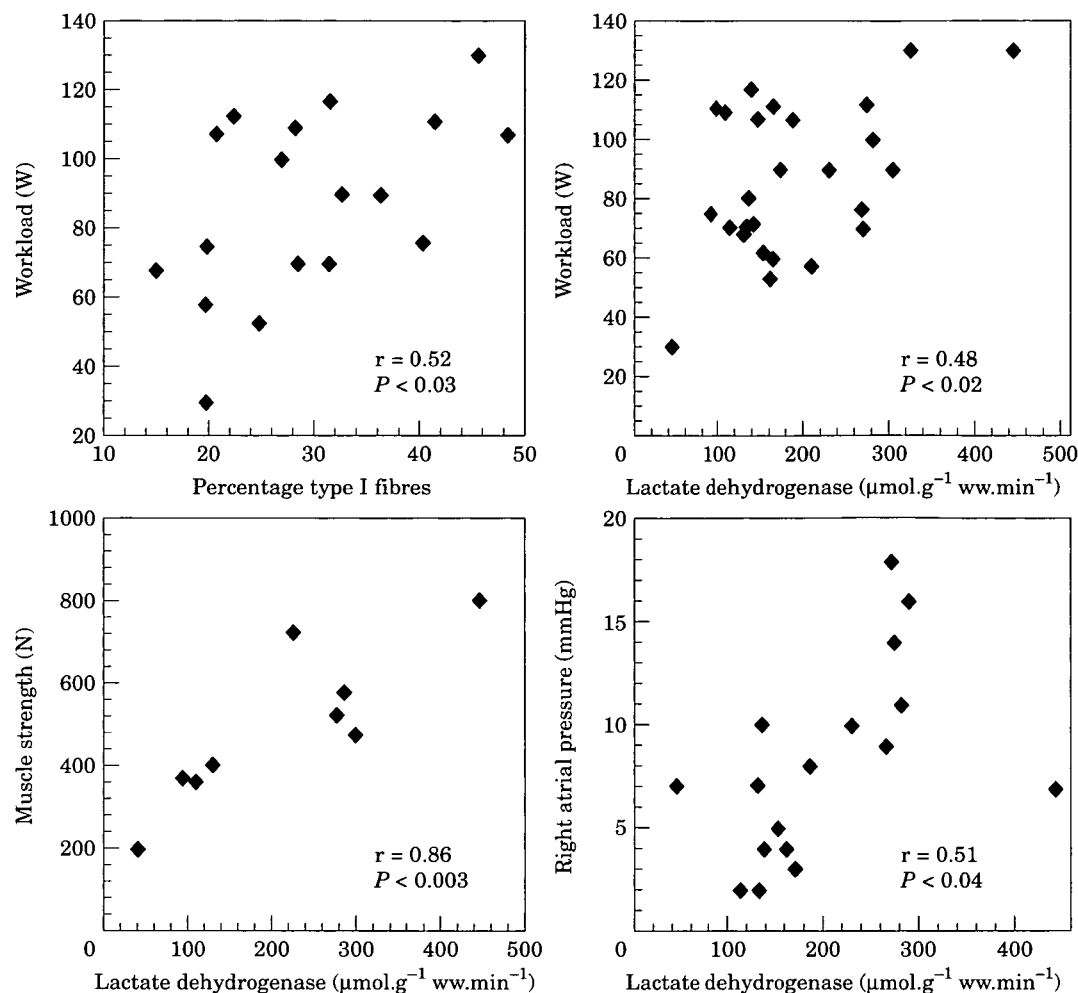
The altered fibre type distribution found in this study is in accordance with other reports<sup>[12–14]</sup>. Muscle fibre area was not altered in the patients with heart failure in comparison with normal subjects. A variety of muscle fibre area abnormalities has been described<sup>[12,13,16,44,45]</sup>, with atrophy of the type II B fibres as the most consistent finding. Disuse leads to muscle fibre atrophy, but change in fibre composition is not a consistent finding in healthy individuals<sup>[30–32]</sup>. The diverging results between the investigations concerning muscle fibre area may be due to the different degree of physical activity in the patients. We noticed decreased capillarization, which is in accordance with results of Sullivan and coworkers<sup>[13]</sup>, but not with others<sup>[12]</sup>, and may have been due to inactivity or decreased blood flow. Capillarization and fibre area increase after training in

patients with chronic heart failure, but the fibre type composition does not change<sup>[46]</sup>. Altered fibre type composition was also reported in respiratory muscles of patients with chronic heart failure<sup>[47]</sup> but after heart transplantation, no change in fibre type composition and capillarization was observed<sup>[48]</sup>. However, treatment with steroids and cyclosporin after heart transplantation may influence skeletal muscle. The fibre type distribution found in our patients with heart failure resembles that in patients with non-insulin dependent diabetes mellitus<sup>[49]</sup>. It is possible that hormonal disturbances might contribute to altered fibre type composition in these disorders. Increased cytokine levels found in advanced heart failure<sup>[50,51]</sup> might also influence the skeletal muscle.

### Limitations of the study

In this study, a set of test methods and possible contributing factors have been applied to elucidate skeletal muscle abnormalities in patients with heart failure. Although this is the largest group of patients with heart failure where muscle biopsies have been investigated biochemically and histochemically, some subjects were not investigated fully. Another objection may be that the metabolic and enzymatic results are expressed in  $\text{mmol} \cdot \text{kg}^{-1} \text{ ww}$  and  $\mu\text{mol} \cdot \text{g}^{-1} \text{ ww} \cdot \text{min}^{-1}$ , respect-





**Figure 5** Relationship between workload, muscle strength, right atrial pressure and lactate dehydrogenase activity, as well as between workload and percentage of type I fibres.

ively. Increased skeletal muscle water content may influence the results. In 22 patients with oedema, increased skeletal muscle water content has been described<sup>[52]</sup>, whereas this has not been confirmed in another investigation of 297 patients with heart failure<sup>[53]</sup>. Our patients were all without obvious oedema and thus it is unlikely that the metabolic results were influenced by increased skeletal muscle water content.

## Conclusion

Patients with chronic heart failure have several skeletal muscle abnormalities which resemble, but are not identical to, alterations seen after disuse. Lactate dehydrogenase, which is related to exercise capacity, muscle strength and right atrial pressure, seems to have a key role in skeletal muscle metabolism in chronic heart failure. Central haemodynamics and medical treatment may, in addition to inactivity, be of importance for skeletal muscle alterations in chronic heart failure.

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