Contribution of Skeletal Muscle Atrophy to Exercise Intolerance and Altered Muscle Metabolism in Heart Failure

Donna M. Mancini, MD; Glenn Walter, BS; Nathaniel Reichek, MD; Robert Lenkinski, PhD;
Kevin K. McCully, PhD; James L. Mullen, MD; and John R. Wilson, MD

Background. The purpose of this study was to investigate the prevalence of skeletal muscle atrophy and its relation to exercise intolerance and abnormal muscle metabolism in patients with heart failure (HF). Methods and Results. Peak VO2, percent ideal body weight (% IBW), 24-hour urine creatinine (Cr), and anthropometrics were measured in 62 ambulatory patients with HF. 31P magnetic resonance spectroscopy (MRS) and imaging (MRI) of the calf were performed in 15 patients with HF and 10 control subjects. Inorganic phosphorus (Pi), phosphocreatine (PCr), and intracellular pH were measured at rest and during exercise. Calf muscle volume was determined from the sum of the integrated area of muscle in 1-cm-thick contiguous axial images from the patella to the calcaneus. A reduced skeletal muscle mass was noted in 68% of patients, as evidenced by a decrease in Cr-to-height ratio of <7.4 mg/cm and/or upper arm circumference of <5% of normal. Calf muscle volume (MRI) was also reduced in the patients with HF (controls, 675±84 cm³/m²; HF, 567±112 cm³/m²; p<0.05). Fat stores were largely preserved with triceps skinfold of <5% of normal and/or IBW of <80% in only 8% of patients. Modest linear correlations were observed between peak VO2 and both calf muscle volume per meter squared (r=0.48) and midarm muscle area (r=0.36) (both p<0.05). 31P metabolic abnormalities during exercise were observed in the patients with HF, which is consistent with intrinsic oxidative abnormalities. The metabolic changes were weakly correlated with muscle volume (r=−0.42, p<0.05).

Conclusions. These findings indicate that patients with chronic HF frequently develop significant skeletal muscle atrophy and metabolic abnormalities. Atrophy contributes modestly to both the reduced exercise capacity and altered muscle metabolism. (Circulation 1992;85:1364–1373)

KEY WORDS • skeletal muscle • exercise testing • heart failure

Exertional fatigue is a major limiting symptom in patients with heart failure. Traditionally, this fatigue has been attributed to skeletal muscle underperfusion. However, recent studies have demonstrated that patients with heart failure also exhibit intrinsic skeletal muscle changes, including fiber atrophy, a reduction in lipolytic and oxidative enzymes, and altered metabolic responses to exercise as assessed with 31P magnetic resonance spectroscopy (MRS).1–5 These skeletal muscle alterations may contribute to exertional fatigue in heart failure. Muscle atrophy may be a particularly important factor as muscle mass is a determinant of exercise capacity in normal subjects.6

The purpose of the present study was to investigate the contribution of skeletal muscle atrophy to exertional fatigue and altered muscle metabolism in heart failure. We examined the prevalence of skeletal muscle atrophy in a large group of ambulatory patients with heart failure by using standard anthropometric measurements and magnetic resonance imaging (MRI) of leg muscles.

Indexes of muscle mass were then correlated with maximal exercise capacity. We also sought to test the hypothesis that muscle atrophy contributes to skeletal muscle metabolic abnormalities in heart failure. Altered forearm and calf metabolic responses to exercise have been demonstrated previously using 31P MRS.7–10 These metabolic abnormalities may result from muscle atrophy. When faced with a given external load, muscle that is atrophied would be subjected to a greater work load per remaining fiber than normal muscle and would therefore develop greater reductions in phosphocreatine (PCr) and intracellular pH.

See p 1621

To investigate this hypothesis, MRI and spectroscopy of the calf were performed in normal subjects and patients with heart failure. The metabolic response to exercise expressed as the work slope was correlated with indexes of muscle mass. Another index of oxidative metabolism, i.e., the time constant of recovery of phosphocreatine after submaximal work, was also measured. The time constant is independent of work intensity and muscle mass.11,12 Therefore, demonstration of comparable time constants in the two groups would further support the hypothesis that the metabolic abnormalities
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Anthropomorphic assessment</th>
<th>Dietary histories</th>
<th>Metabolic measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=62)</td>
<td>(n=32)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59±10</td>
<td>61±9</td>
<td>55±14</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>97</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td>39</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>CAD</td>
<td>39</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>DC</td>
<td>61</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>23±12</td>
<td>23±9</td>
<td>17±6</td>
</tr>
<tr>
<td>VO2 (ml/kg/min)</td>
<td>12.9±3.6</td>
<td>14.1±3.5</td>
<td>15.8±4.6</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; DC, dilated cardiomyopathy; VO2, peak oxygen consumption.

noted in patients with heart failure are primarily due to muscle atrophy. Conversely, demonstration of an abnormal time constant in the patients would indicate that intrinsic muscle changes, such as a reduction in mitochondrial oxidative capacity, contribute to the metabolic abnormalities.

Methods

Subjects

A total of 76 patients were studied. Seventy-one patients were men, and five were women. The average ± SD age was 59±10 years. Six percent of patients had New York Heart Association functional class I, 29% had class II, 59% had class III, and 6% had class IV heart failure symptomatology. Etiology of heart failure was coronary artery disease in 41% of patients, idiopathic dilated cardiomyopathy in 26%, alcoholic cardiomyopathy in 19%, valvular heart disease in 6%, and hypertensive cardiomyopathy in 8%. Ejection fraction averaged 22±11%. Peak exercise oxygen consumption was 13.6±4.0 ml/kg/min (range, 4.0–20.7 ml/kg/min). All patients were receiving therapy with digoxin and diuretics. Patients with alcoholic cardiomyopathy were abstinent from alcohol for at least 6 months. Seven patients were not receiving vasodilators. Forty-one were receiving angiotensin converting enzyme inhibitors, and 14 were receiving hyalurazine and/or nitrates. Eight patients had peripheral edema.

For the MRS studies, 10 normal subjects were recruited; the average ± SD age was 51±9 years. Peak VO2 was 33±9 ml/kg/min.

Sixty-two patients underwent anthropomorphic assessment, 32 patients completed dietary histories, and 15 patients participated in magnetic resonance studies. One patient participated in both anthropomorphic and magnetic resonance protocols. There were no statistical differences between the groups in regard to age, gender, ejection fraction, or exercise capacity (Table 1).

The study was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania, and written informed consent was obtained from all subjects.

All patients underwent maximal treadmill exercise using the modified Naughton protocol with measurement of oxygen consumption (SensorMedics). Normal subjects underwent maximal treadmill exercise using the Bruce protocol with measurement of oxygen consumption. Exercise was limited by dyspnea and/or fatigue in all subjects. Patients limited by chest pain or claudication were excluded.

Anthropometric assessment and dietary history. Sixty-two patients underwent anthropometric evaluation. Height, body weight, and wrist circumference were measured. Percent ideal body weight was derived from actual weight divided by ideal body weight as estimated from standard Metropolitan Life tables adjusted for height and body frame size.13

Triceps skinfold thickness of the nondominant arm was measured using Lange calipers (Cambridge Scientific Instruments, Cambridge, Md.). Each skinfold measurement was estimated to the nearest 1 mm, and the mean was calculated from three readings. Midarm circumference of the nondominant arm was also measured. Midarm muscle circumference was derived from the formula C−πS, and midarm muscle area was derived from (C−πS)2/4π, where S is midarm circumference and is triceps skinfold.13–16

Twenty-four-hour urine collection was performed on an outpatient basis. Specimens were then analyzed for creatinine. Urine collections containing a volume of less than 1,000 ml or less than 1 g creatinine were repeated. Creatinine/height index was calculated from 24-hour urinary measurement of creatinine (mg) divided by height (cm). Lean body mass and skeletal muscle mass were calculated from standard formulas, i.e., lean body mass (kg)=7.138+0.0291 (mg creatinine/24 hr) and skeletal muscle mass = 30% lean muscle mass.13,17

Serum creatinine, transferrin, albumin, and prealbumin were measured from venous blood samples by standard laboratory techniques.

Three-day dietary diaries were issued to all patients. Patients were instructed to record all food consumed as well as the quantity and type of preparation. Thirty-two patients returned completed diaries. Calorie counts were estimated using the USDA handbook.20,21 Nonprotein calories were derived from total calories minus four times protein (g). The Harris-Benedict equation was used to calculate basal energy expenditure (BEE). For males, BEE was 66+13.9 (weight in kg)+5 (height in cm)−6.8 (age in yr), and for females, BEE was 65.5+9.6 (weight in kg)+1.8 (height in cm)−4.6 (age in yr).13,22

A creatinine-to-height ratio of <7.4 mg/cm and/or midarm muscle circumference of <5% of the normal value as obtained from standard tables was considered evidence of reduced skeletal muscle mass. Fat stores were considered reduced if triceps skinfold was <5% of normal and/or ideal body weight was <80% of normal. Visceral protein synthesis was considered abnormal if serum albumin was <3.5 mg/dl, prealbumin was <16.6 mg/dl, and/or transferrin was <180 mg/dl. Caloric intake was considered depressed if daily caloric count was ≤100% of estimated caloric needs adjusted for age, height, and sex.13

31P MRS and MRI protocol. Fifteen patients with heart failure and 10 control subjects underwent 31P metabolic measurements and imaging. None of the patients had a history of intermittent claudication. All subjects had intact distal pulses, or a brachial-to-ankle blood pressure ratio of >1.
MRI

Leg muscle volume was determined by MRI with a 1.5-T imaging system (General Electric). One-centimeter-thick contiguous axial images of the right leg were obtained from the patella to calcaneus. A spin-echo sequence with repetition time of 800 msec, echo time of 20 msec, acquisition matrix of 256×256, and 24-cm field-of-view was used. Images were processed with ANALYZE software (Mayo Foundation, Biodynamics Research Unit, Rochester, Minn.). Bone, subcutaneous fat, vascular, and nerve areas were excluded from area measurements. The volumes of the slices were summed to obtain total muscle volume. It was assumed that muscle volume was proportional to muscle mass.

$^{31}$P MRS Measurements

Two methods were used to assess an individual’s metabolic response to exercise: the inorganic phosphorus ($P_i$)-to-PCr ratio correlated with power output (work slope) and the calculation of the time constant of PCr recovery.

The $P_i$-to-PCr ratio provides an estimate of ADP concentration. ADP level is closely linked to mitochondrial respiration. Thus, the $P_i$-to-PCr ratio provides an index of oxidative metabolism. As described in the transfer function of Chance et al.,$^{23,24}$ the relation during low-level exercise between power output and the $P_i$-to-PCr ratio is linear. Therefore, the calculation of the slope of this relation affords a simple way of comparing oxidative metabolism between subjects.

Another method for comparing oxidative metabolism between subjects is the calculation of the time constant of recovery for phosphocreatine. At the beginning of any work load, ATP use and production are accelerated by the production of ADP. At the cessation of work, ATP use stops, but accelerated production continues. Thus, the rate of oxidative metabolism can be indirectly assessed by monitoring the rate of recovery of PCr, which is proportional to ADP after termination of work. A major advantage of measurement of PCr recovery rate is that it is independent of work level. In human subjects, it is difficult during work to control muscle recruitment and to normalize for muscle mass. The recovery constant provides an index of oxidative metabolism independent of these factors.$^{11,12,25–28}$

To assess calf metabolism, all subjects were placed in a supine position in a 1.8-T, 1-m bore superconducting magnet (Oxford Research Systems, Oxford, England) with the gastrocnemius muscle positioned over an 8-cm surface coil. Data acquisition was accomplished with the application of radiofrequency pulses (pulse width optimized at 25–35 msec) applied every 4 seconds. After optimization of field homogeneity, 1-minute scans were recorded during rest and incremental exercise. During the recovery phase, 8-second spectra were obtained. In some subjects with fast recovery rates, data were collected as 4-second spectra.

The exercise protocol consisted of supine plantarflexion of the foot. The subject’s foot was placed on a pedal (Figure 1) attached via a pulley system to a variable number of elastic bands. A system of Velcro straps was used at the knee, ankle, waist, and shoulders to immobilize the body. Work loads were of 4 minutes’ duration and were continuous. The initial work load was extension of one elastic band via plantar flexion every 8 seconds. This was followed by extension of one elastic
band every 4 seconds. All subsequent work loads were at a frequency of plantar flexion every 4 seconds with increasing numbers of elastic bands. The maximum work load was extension of four elastic bands every 4 seconds.

After completion of the ramp exercise protocol, the subjects rested for 15 minutes. During that interval, the work level that resulted in a PCr-to-PCr ratio of approximately 0.7 was identified by review of the exercise scans. This work level was then selected for the performance of the recovery test. A 2-minute rest scan was obtained to ensure full metabolic recovery. Three minutes of exercise were performed. Seven minutes of recovery scans were then collected.

To quantify work performed, force and distance were measured. The force required to extend the elastic bands was determined by the suspension of known weights from each band. During exercise, the distance and duration the pedal was depressed were monitored using a mercury-in-Silastic strain gauge connected in parallel with the pulley system. Before exercise, the pedal was fully depressed; this corresponded to 6 cm of band extension. Subsequent deflections produced during exercise were compared with the full deflection. Average power was derived from the following equation:

\[
\text{Power (W) =} \frac{(J/\text{band}) \times (\text{deflection/full deflection}) \times (n)}{60 \text{ seconds}}
\]

Full performance of each work load corresponded to a power output of 0.75, 1.5, 3, 4.5, and 6 W, respectively. Duration of contraction was measured at each work load. Analysis of the duration of contraction at a work load of 1.5 W and at peak exercise demonstrated no significant differences between the two groups (1.5 W: controls, 1.2±0.4 seconds; heart failure (HF), 1.5±0.6 seconds; peak exercise: controls, 2.1±1.2 seconds; heart failure, 2.1±0.5 seconds; p=NS for both).

Quantification of PCr-to-PCr ratio and ATP was obtained from the Fourier transformed MRS spectra. An exponential multiplication equal to a line broadening of 15 Hz was used, yielding a width at half height for PCr of less than 1 part per million (ppm). Areas of the P, and PCr signal were measured using computer-generated best-fit analysis developed by Manfred Pframmer, PhD, in the Metabolic Magnetic Resonance Research Center of the University of Pennsylvania. Using best-fit analysis, the data were analyzed by a time domain fitting procedure. The program used the output of a linear prediction–singular value decomposition (LPSVD) algorithm as the input into a nonlinear least squares fit routine based on the Levenberg-Marquardt method. The data window and the prediction filter were fixed to 250 and 125 data points, respectively; no further user input was required. The program generated as output the integral of each peak and its frequency in parts per million. This analysis was 100% automated and without user bias. Intracellular pH was calculated from the chemical shift difference of P, from PCr.

To assess PCr recovery after exercise, the time constant of recovery was calculated by fitting PCr areas to a single exponential curve. This curve can be described by the equation \(\text{PCr} = C_1 + C_2(1 - e^{-kt})\), where PCr is the concentration of PCr, C1 is the initial concentration of PCr, C2 is the difference between the final and initial

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>73±14</td>
</tr>
<tr>
<td>Ideal body weight (%)</td>
<td>104±16</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>18.7±15</td>
</tr>
<tr>
<td>Midarm circumference (cm)</td>
<td>29.6±4.1</td>
</tr>
<tr>
<td>Midarm muscle circumference (cm)</td>
<td>24.1±3.6</td>
</tr>
<tr>
<td>Midarm muscle area (cm²)</td>
<td>46.5±13.3</td>
</tr>
<tr>
<td>Creatinine (mg/dl) (g)</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td>Creatinine (24-hour)</td>
<td>1.23±0.44</td>
</tr>
<tr>
<td>Creatinine/height index (mg/cm)</td>
<td>7.1±2.4</td>
</tr>
<tr>
<td>Lean body weight (kg)</td>
<td>43±13</td>
</tr>
<tr>
<td>Skeletal muscle mass (kg)</td>
<td>13±4</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>4.1±0.6</td>
</tr>
<tr>
<td>Prealbumin (mg/dl)</td>
<td>25±8</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>308±72</td>
</tr>
</tbody>
</table>

PCr, t is time, and k is the rate constant. The time constant of recovery was derived from the reciprocal of k and was expressed in seconds. Resting PCr levels were calculated based on the ratio of PCr area to β-ATP peak area, assuming an ATP value of 5.5 mmol/kg wet wt and correcting for differences in saturation between PCr and ATP with a pulse repetition time of 4 seconds. \(V_{\text{max}}\), the maximal rate of PCr resynthesis, was calculated from the reciprocal of the time constant multiplied by the resting PCr concentration and expressed as millimoles per kilogram per minute.11,12,29

Statistics

Data were compared using unpaired or paired Student’s t tests as appropriate. Nonparametric variables were compared using the Mann-Whitney test. Comparison among more than two groups was performed with analysis of variance. Nonnumeric variables were compared with \(\chi^2\) tests. The relation between variables was examined by linear regression analysis. A value of \(p<0.05\) was considered statistically significant. All data are expressed as mean±SD.

Results

Anthropomorphic Measurements

The data for anthropomorphic measurements and serum chemistries are summarized in Table 2. The distribution curves for triceps skinfold, creatinine/height index, and arm muscle circumference are depicted in Figure 2. To determine the incidence of muscle atrophy in the patients, we divided the patients according to arm muscle circumference and creatinine height index. An arm muscle circumference of >50% is considered normal, whereas <5% is consistent considerable muscle atrophy. Similarly, a creatinine height index of <7.4 mg/cm is consistent with severe protein energy starvation. With this approach, 68% of our patients exhibited evidence of severe muscle atrophy. When patients were stratified by exercise capacity using the classification of Weber,33 similar frequencies of atrophy were observed in patients with mild, moderate, or severe exertional intolerance (Figure 2).
This atrophy was not usually associated with inadequate protein synthetic function or loss of fat stores. Only 24% of patients exhibited serum albumin of <3.5 mg/dl, prealbumin <20 mg/dl, and/or transferrin <180 mg/dl. Similarly, fat stores assessed using triceps skinfold measurements that were <5% standard and/or using percent ideal body weights that were <80% were reduced in only 8% of patients.

To investigate the relation between muscle mass and maximal exercise performance, peak exercise VO₂ was correlated with all parameters of muscle mass. Modest linear correlations were observed between peak VO₂ and calf muscle volume normalized for body surface area, midarm circumference, muscle circumference, muscle area, creatinine height index, and skeletal muscle mass derived from the 24-hour urinary creatinine (Table 3). No significant linear correlations were observed between peak VO₂ and lean body mass, weight, or triceps skinfold (r<0.25, p=NS for all).

The impact of varying medical regimens on anthropomorphic measurements was also assessed. No differences in percent ideal body weight, creatine/height index, or muscle circumference were noted between patients receiving angiotensinogen converting enzyme inhibitors (n=41), hydralazine and/or nitrates (n=14), and no vasodilators (n=7). Similarly, subgroup analysis was performed in patients with and without alcoholic cardiomyopathy. Muscle atrophy was present in 64% of patients without and 67% of patients with alcoholic cardiomyopathy (p=NS).

The contribution of inadequate nutritional intake to muscle wasting was examined using dietary histories. Caloric intake was depressed. The distribution of protein and nonprotein calories was normal (Table 4). Daily caloric intake was only 73% of that needed to maintain present body weight.

### Table 4. Dietary Histories for 32 Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calories (kcal)</th>
<th>% of &lt;20</th>
<th>Protein (g)</th>
<th>% of &lt;20</th>
<th>Fat (g)</th>
<th>% of &lt;20</th>
<th>Carbohydrate (g)</th>
<th>% of &lt;20</th>
<th>Basal energy expenditure (kcal)</th>
<th>% of &lt;20</th>
<th>Maintenance requirements (kcal)</th>
<th>% of &lt;20</th>
<th>Caloric intake/maintenance (%)</th>
<th>% of &lt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,391±336</td>
<td></td>
<td>64±21</td>
<td></td>
<td>50±18</td>
<td></td>
<td>174±64</td>
<td></td>
<td>1,500±204</td>
<td></td>
<td>1,950±264</td>
<td></td>
<td>73±22</td>
<td></td>
</tr>
<tr>
<td>Nonprotein</td>
<td>1,139±280</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 2

**The distribution curves of arm muscle circumference of <5% normal and creatinine height index of <7.4 mg/cm in patients stratified by peak exercise VO₂ (ml/kg/min).**

### Table 3. Correlation of Parameters of Skeletal Muscle Mass With Peak VO₂

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf muscle volume/BSA</td>
<td>0.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Midarm circumference</td>
<td>0.39</td>
<td>0.004</td>
</tr>
<tr>
<td>Midarm muscle circumference</td>
<td>0.31</td>
<td>0.03</td>
</tr>
<tr>
<td>Skeletal muscle mass</td>
<td>0.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Midarm muscle area</td>
<td>0.36</td>
<td>0.006</td>
</tr>
<tr>
<td>Creatinine/height index</td>
<td>0.29</td>
<td>0.05</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>0.25</td>
<td>0.09</td>
</tr>
<tr>
<td>Triceps skinfold</td>
<td>0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Weight</td>
<td>0.24</td>
<td>0.08</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.87</td>
</tr>
</tbody>
</table>

BSA, body surface area.

### 31P MRS Measurements

**Work slope.** Supine plantar flexion against an increasing force resulted in a progressive increase in the P₃-to-PCr ratio in both normal subjects and patients with heart failure. Representative 31P MRS spectra at rest and during exercise in a normal and a heart failure subject are depicted in Figure 3. A rapid depletion of PCr and reduction in intracellular pH are illustrated in the spectra from the patient with heart failure.

The work slope was significantly greater in patients with heart failure than in control subjects (controls, 0.25±0.19 W⁻¹; HF, 0.85±0.70 W⁻¹; p<0.05), indicating abnormal metabolism in our patients. Intracellular pH at peak exercise was significantly reduced in patients with heart failure (HF: rest, 7.0±0.06; exercise, 6.76±0.28; p<0.05) but not in normal subjects (controls: rest, 7.02±0.03; exercise, 6.93±0.17; p=NS).

Because the resolution of the images was insufficient to provide determination of isolated gastrocnemius muscle volume, total calf muscle volume was measured. Analysis was also performed using the largest muscle cross-sectional area that corresponded to the approximate site where scanning was performed; this provided another index of muscle mass.

Calf muscle volume was significantly reduced in patients with heart failure compared with normal subjects (controls, 1,299±286 cm³; HF, 1,051±295 cm³; p<0.05). When muscle volume was normalized for body surface area, this difference remained significant (controls, 675±84 cm³/m²; HF, 567±112 cm³/m²; p<0.01). Representative images of a heart failure and a normal subject are depicted in Figure 4. Fatty infiltration was noted in many of the heart failure subjects.

Linear regression analysis was performed using the work slope relation and muscle volume (Figure 5). A significant negative correlation was observed between the work slope relation and calf muscle volume.
A positive linear correlation was observed between the work slope and the time constant of recovery for all subjects \((r=-0.42, p<0.05)\). However, no significant correlation was observed between the work slope and largest calf muscle cross-sectional area \((r<-0.3, p=NS)\).

The work slope was also normalized for muscle area. In each subject, work loads were divided by the largest muscle cross-sectional area. Work loads expressed as watts per centimeter squared were then correlated with power output. If muscle mass were the predominant variable responsible for the statistically different work slopes between normal and heart failure subjects, then the normalized work slopes should be comparable in the two groups. In fact, the normalized work slopes remained statistically different \((0.11\pm0.09 \text{ cm}^2/\text{W}; \text{HF}, 0.05\pm0.04 \text{ cm}^2/\text{W}; p<0.05)\).

**Recovery data.** Recovery data were inadequate in two normal subjects and one patient with heart failure due to insufficient PCR depletion. For heart failure and normal subjects at the end of exercise, P-to-PCR ratio \((0.69\pm0.22; \text{HF}, 0.73\pm0.35; p=NS)\) and intracellular pH \((6.97\pm0.07; \text{HF}, 6.96\pm0.07; p=NS)\) were similar. PCR recovery curves were well fitted by a single exponential and are illustrated in Figure 6. The PCR time constants were significantly increased in patients with heart failure; they ranged from 38.8 to 259 seconds with a mean of 82.0±60.5 seconds versus from 14.8 to 51.1 seconds with a mean of 40.4±11.3 seconds in the normal subjects \((p<0.05)\).

**Discussion**

The development of skeletal muscle atrophy in patients with severe heart failure is well documented. Hippocrates initially described this condition: “The flesh is consumed and becomes water . . . the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thighs melt away.” More recently, several investigators described severe muscle atrophy and malnutrition in patients with heart failure and related this abnormality to poor outcomes during cardiac surgery. Carr et al. examined the incidence of malnutrition in 48 patients with severe heart failure undergoing intensive medical therapy and/or cardiac transplant evaluation. These investigators noted malnutrition in 50% of the patients, as defined by a decrease in percent body fat determined from skinfold thickness, a decreased weight-to-height index, or reduced serum albumin; muscle volume was not reported but was probably reduced.

The present study confirms that atrophy occurs in patients with severe heart failure and further demon-
FIGURE 4. Representative cross-sectional magnetic resonance images in a normal subject and a heart failure (CHF) subject from the level of the patella (panel A), midcalf (panels B and C), and above the ankle (panel D). Radiolucent areas represent vascular structures or bone marrow. Radiopaque regions are consistent with fat and bone. Gray scale regions represent muscle.
strates that atrophy also occurs frequently in patients with mild-to-moderate heart failure. Substantial muscle atrophy was detected in almost 70% of our patients, based on reductions in the creatinine/height index and/or arm muscle circumference. Fifty percent of patients with VO2 of 10 to 16 and of >16 ml/kg/min, patients typically classified as mild-to-moderate heart failure, had evidence of muscle atrophy. Measurement of calf muscle volume with MRI further documented the presence of atrophy in such patients and demonstrated substantial fatty infiltration of skeletal muscle, suggesting that arm anthropomorphic measurements may underestimate the degree of muscle atrophy.

In our patient population, the muscle atrophy was not usually associated with signs of severe malnutrition. Protein synthetic function was usually maintained. Body weight was also in the normal range due to preservation of fat stores. In fact, preservation of fat stores and body weight produced the false impression of unaltered body composition in the majority of patients with muscle atrophy.

Results of dietary histories suggested that major contributors to the muscle atrophy were decreased caloric and protein intake. It should be emphasized that the dietary history is a crude technique that may have substantially underestimated caloric intake. However, as early as 1932, investigators concluded that anorexia is a major cause of malnutrition in chronic heart failure. The negative nitrogen balance observed in a group of anorexic patients with heart failure became positive with voluntary improvement in food intake.40–42 Anorexia probably is not the sole etiologic factor for the muscle atrophy; other potentially significant factors include inactivity, an increased catabolic state due to heightened sympathetically stimulation, and increases in serum cortisol, ACTH, and tumor necrosis factor.43–45

In normal subjects, the amount of muscle is an important determinant of exercise capacity.6 In younger populations, muscle mass correlates with maximal exercise capacity.6 In women, the reduced peak aerobic capacity compared with that in men is in part due to smaller muscle mass.46 In aged and/or deconditioned populations, loss of muscle mass appears to limit exercise capacity.47,48 Accordingly, muscle atrophy could be an important and potentially reversible contributor to exercise intolerance in patients with heart failure.

To investigate whether the skeletal muscle atrophy observed in our patients contributed to their exercise intolerance, we examined the relation between muscle mass and both peak exercise VO2 and muscle metabolic behavior, as assessed by 31P MRS. Peak VO2 provides an index of a patient’s overall functional capacity.33 Muscle metabolic behavior provides insight into the metabolic changes that ultimately produce muscle fatigue.

Modest but significant correlations were noted between peak exercise VO2 and a variety of parameters of muscle mass derived from anthropomorphic measurements, urinary creatinine, and MRI data. These correlations (r) ranged from 0.29 to 0.48, which is consistent with a modest contribution of muscle atrophy to exercise intolerance in patients.

In previous 31P MRS studies in patients with heart failure, premature muscle fatigue was noted during isolated forearm and calf exercise. This fatigue was associated with increased PCr depletion and lower intracellular pH levels than in normal subjects.7–10 We hypothesized that these metabolic changes may be due at least in part to muscle atrophy. When subjected to the same external work load, muscle fibers in atrophied muscle would experience greater work loads and, consequently, greater metabolic changes. To test this hypothesis, we correlated the calf work slope, a measure of oxidative capacity, with calf muscle volume, as assessed with MRI. We postulated that these variables should be related if atrophy contributed to the altered work slope.
Calf muscle metabolic responses to exercise as assessed with the work slope correlated significantly with total calf muscle volume, suggesting that muscle atrophy contributes to the abnormal work slopes and exercise intolerance experienced by patients with heart failure. However, the correlation between muscle volume and the work slope was relatively weak. This modest correlation suggests that the altered work slopes are primarily caused by factors other than muscle atrophy.

Analysis of calf PCr recovery after exercise further supports this conclusion. Recovery characteristics were abnormal in the patients with heart failure and correlated well with the work slope. Because PCr recovery should be independent of muscle mass, correlations between this index and the work slope implies that abnormalities of the work slope are primarily due to factors other than muscle atrophy. The nature of these factors remains to be determined. One obvious potential contributor is a reduction in the levels of oxidative enzymes. However, in a previous study, we observed no relation between the work slope and muscle citrate synthase activity, suggesting that changes in the level of oxidative enzymes may not be a significant contributor.

Analysis of PCr recovery may be of particular value in describing muscle metabolism in patients with heart failure. In previous reports, we and others have focused on metabolic responses to exercise rather than on recovery characteristics. This approach assumes that patients are exercising at a particular work load. In reality, it is difficult to define precise work load due to differences in duration of contraction, muscle relaxation, muscle mass, and muscle recruitment. The recovery analysis is independent of work and mass and therefore is simpler to perform and probably more reproducible. Time constant of recovery can be used as a parameter of skeletal muscle metabolic function, which can be compared among different laboratories independent of exercise equipment and/or protocols.

Our finding that muscle atrophy is only a modest contributor to exercise intolerance is somewhat limited by the techniques used to assess muscle mass, exercise capacity, and metabolism, all of which are relatively inexact. Arm anthropomorphic measurements may not reflect leg muscle area. The 24-hour urine creatinine may have been reduced for a variety of reasons. Diet, age, and underlying renal function all affect creatinine excretion. The urine collections were not supervised and may have been incomplete. Similarly, the degree of muscle atrophy determined by MRI may have been underestimated in some patients due to marked fatty infiltration. A large percentage of our patients had a prior history of significant alcohol use. In these patients, the prior toxic effect of alcohol on muscle may have contributed to the observed muscle atrophy. However, analysis of the data without this subgroup indicates a high prevalence of atrophy in all patients with heart failure.

In conclusion, our findings demonstrate significant skeletal muscle atrophy in patients with heart failure and suggest that this atrophy contributes modestly to the exercise intolerance and muscle metabolic abnormalities observed in such patients. It is likely that treating this muscle atrophy would improve to some extent the exercise capacity of patients with heart failure. Further efforts to identify the mechanism responsible for the muscle atrophy and to define methods of treating the atrophy are therefore warranted. However, the degree to which atrophy contributes to exercise intolerance in heart failure appears to be small, suggesting that increases in muscle mass will produce only modest improvements in exercise capacity.

Acknowledgments
We thank Andrea Rein, RN, and Nancy Wagner for their technical assistance.

References


35. Ansari A: Syndromes of cardiac cachexia and the cachetic heart: Current perspective. Prog Cardiovasc Dis 1987;30:45–60


Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure.
D M Mancini, G Walter, N Reichek, R Lenkinski, K K McCully, J L Mullen and J R Wilson

Circulation. 1992;85:1364-1373
doi: 10.1161/01.CIR.85.4.1364

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/85/4/1364