

## Skeletal Muscle Function and Its Relation to Exercise Tolerance in Chronic Heart Failure

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**Objectives.** This study sought to define the relation between muscle function and bulk in chronic heart failure (HF) and to explore the association between muscle function and bulk and exercise capacity.

**Background.** Skeletal muscle abnormalities have been postulated as determinants of exercise capacity in chronic HF. Previously, muscle function in chronic HF has been evaluated in relatively small numbers of patients and with variable results, with little account being taken of the effects of muscle wasting.

**Methods.** One hundred male patients with chronic HF and 31 healthy male control subjects were studied. They were matched for age ( $59.0 \pm 1.0$  vs.  $58.7 \pm 1.7$  years [mean  $\pm$  SEM]) and body mass index ( $26.6 \pm 0.4$  vs.  $26.3 \pm 0.7$  kg/m<sup>2</sup>). We assessed maximal treadmill oxygen consumption ( $\dot{V}O_2$ ), quadriceps maximal isometric strength, fatigue (20-min protocol, expressed in baseline maximal strength) and computed tomographic cross-sectional area (CSA) at midthigh.

**Results.** Peak  $\dot{V}O_2$  was lower in patients ( $18.0 \pm 0.6$  vs.  $33.3 \pm 1.4$  ml/min per kg,  $p < 0.0001$ ), although both groups achieved a similar respiratory exchange ratio at peak exercise ( $1.15 \pm 0.01$

vs.  $1.19 \pm 0.03$ ,  $p = 0.13$ ). Quadriceps ( $582$  vs.  $652$  cm<sup>2</sup>,  $p < 0.05$ ) and total leg muscle CSA ( $1,153$  vs.  $1,304$  cm<sup>2</sup>,  $p < 0.005$ ) were lower in patients with chronic HF. Patients were weaker than control subjects ( $357 \pm 12$  vs.  $434 \pm 18$  N,  $p < 0.005$ ) and also exhibited greater fatigue at 20 min ( $79.1\%$  vs.  $92.1\%$  of baseline value,  $p < 0.0001$ ). After correcting strength for quadriceps CSA, significant differences persisted ( $5.9 \pm 0.2$  vs.  $7.0 \pm 0.3$  N/cm<sup>2</sup>,  $p < 0.005$ ), indicating reduced strength per unit muscle. In patients, but not control subjects, muscle CSA significantly correlated with peak absolute  $\dot{V}O_2$  ( $R = 0.66$ ,  $p < 0.0001$ ) and is an independent predictor of peak absolute  $\dot{V}O_2$ .

**Conclusions.** Patients with chronic HF have reduced quadriceps maximal isometric strength. This weakness occurs as a result of both quantitative and qualitative abnormalities of the muscle. With increasing exercise limitation there is increasing muscle weakness. This progressive weakness occurs predominantly as a result of loss of quadriceps bulk. In patients, this muscular atrophy becomes a major determinant of exercise capacity.

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The processes by which exercise is limited in chronic heart failure (HF) remain unclear. There is poor correlation between exercise capacity and central hemodynamic measurements (1-3). Acute improvements in cardiac function do not result in an immediate improvement in exercise capacity (4-7). Exercise tolerance is not determined directly by the extent of the central hemodynamic disturbance (8). As a consequence of

these observations, potential peripheral determinants of exercise capacity have been sought.

The skeletal musculature has been extensively investigated. Muscle bulk is known to be reduced in chronic HF (9), and general muscle and fat tissue wasting (i.e., cachexia) has recently been shown (10) to predict impaired survival in chronic HF. Abnormalities of muscle function (11-14), histologic features (15,16) and metabolism (17,18) have all been described. We and others have postulated that these muscle changes are part of the syndrome of chronic HF and contribute to the symptoms of these patients (19-21). If muscle changes are central to the exercise limitation seen in CHF, then there would be important clinical implications. The poor link between symptoms and hemodynamic disturbance would be explained, and a novel area for therapeutic intervention would arise.

Abnormal muscle function can lead to exercise intolerance. If this were true in chronic HF, a reasonable correlation between exercise capacity and indexes of muscle function would be expected. Although a reduction in muscle bulk has been described (9), most groups have found preservation of

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**Abbreviations and Acronyms**

ACE	=	angiotensin-converting enzyme
ANOVA	=	analysis of variance
BMI	=	body mass index
CSA	=	cross-sectional area
CT	=	computed tomography (tomographic)
HF	=	heart failure
LVEF	=	left ventricular ejection fraction
SC	=	standardized coefficient
$\dot{V}O_2$	=	oxygen consumption

maximal strength (14,22). Two groups have found normal strength per unit area in the quadriceps (i.e., that strength is reduced in proportion to the wasting of this muscle) (12,14). Nevertheless, Buller et al. (12) described reduced, while Minotti et al. (14) reported preserved maximal isokinetic strength. Thus, the existence and extent of weakness and the mechanism by which it may develop are unclear. Because all studies to date have been of limited size (maximum of 21 patients studied), the purpose of the present study was to investigate the relation between muscle strength, muscle bulk, muscle fatigue and maximal oxygen consumption in a large group of patients with chronic HF.

**Methods**

**Patients.** We studied 100 male patients with chronic HF matched for age and body mass index (BMI) with 31 healthy male control subjects (Table 1). The diagnosis of chronic HF was based on the combination of symptomatic exercise intolerance and objective evidence of impairment of left ventricular systolic function on echocardiography or radionuclide ventriculography (mean left ventricular ejection fraction [LVEF]  $26 \pm 2\%$ ). Only patients with chronic HF of at least 6 months in duration due to ischemic heart disease (n = 62) or idiopathic dilated cardiomyopathy (n = 38) were studied. Twelve patients were in New York Heart Association functional class

I; 39 were in class II; 39 were in class III; and 10 were in class IV. Patients were treated with combinations of diuretic drugs (97%, furosemide equivalent dose  $100 \pm 9$  mg/day), angiotensin-converting enzyme (ACE) inhibitors (87%), aspirin (37%), warfarin (29%), digoxin (28%), oral nitrates (26%) or calcium antagonists (2%). Because several drugs have a significant impact on exercise performance, patients that were treated with ACE inhibitors or digoxin had to be taking these drugs for at least 3 months before investigation. All patients had been clinically stable and taking unchanged medication for at least 1 month before study and on the day of investigation had no evidence of fluid retention (peripheral or pulmonary edema or ascites). Patients with chronic lung disease, neuromuscular disease or exercise-limiting angina were excluded from the study. Healthy control subjects were recruited from hospital staff and their friends. All subjects gave written informed consent, and the study was approved by the local ethics committee.

**Study design.** All subjects performed a maximal cardiopulmonary exercise test and an assessment of maximal isometric quadriceps strength. In 93 of 100 patients, LVEF was determined using radionuclide ventriculography. Computed tomographic (CT) scans were acquired to enable an estimate of muscle bulk in all but 17 patients and 6 control subjects. Quadriceps fatigue could not be determined in 18 patients and 2 control subjects for technical reasons.

**Cardiopulmonary exercise testing.** Subjects performed a symptom-limited treadmill exercise test to assess peak oxygen consumption ( $\dot{V}O_2$ ). A standard Bruce protocol with the addition of a "stage 0" (3 min, 1 mph, 5% gradient) was used. During exercise, subjects breathed through a mouthpiece and a one-way valve attached to a mass spectrometer (Amis 2000 system, Innovision, Odense, Denmark). Using a standard inert gas dilution technique, this allowed on-line measurement of metabolic gas exchange and minute ventilation every 10 s (23). Subjects were instructed and encouraged to exercise to their maximal capacity.

**Muscle function.** Muscle function was assessed using a previously described protocol (12). Subjects were positioned in a rigid frame. For each leg the best of three voluntary isometric contractions was taken as the maximal contraction. Subjects were encouraged to achieve a plateau in force generated, and maximal effort was confirmed by the absence of a superimposed muscular twitch induced by a 1-ms, 1-Hz electrical stimulus delivered to the quadriceps. If not indicated otherwise we report the results of strength and muscle mass of the weaker leg. After establishing the strongest leg, patients were asked to complete a fatiguing protocol with that leg. Forty seconds of repeated contractions at 30% to 40% of the previous maximum (every 2 s according to a acoustic signal given by a timer) followed by 20 s of rest was repeated in 1-min cycles for 20 min with reevaluation of maximal strength after each 5 min. Fatigue was then expressed in percent strength of baseline maximal strength for each time point.

**Muscle bulk.** Using ultrafast CT (Imatron), a single slice was obtained at the midfemur level (taken as one-eighth of the

**Table 1.** Clinical Characteristics and Exercise Performance Data

	Patients With Chronic HF (n = 100)	Control Subjects (n = 31)	p Value
Age (yr)	59.0 ± 1.0	58.7 ± 1.7	0.91
BMI (kg/m <sup>2</sup> )	26.6 ± 0.4	26.3 ± 0.7	0.80
Peak $\dot{V}O_2$ (ml/min per kg)	18.0 ± 0.6	33.3 ± 1.4	< 0.0001
Absolute $\dot{V}O_2$ (ml/min)	1,445 ± 56	2,668 ± 118	< 0.0001
Rest pulse (beats/min)	82 ± 2	70 ± 3	0.004
Peak pulse (beats/min)	140 ± 3	162 ± 4	0.003
Rest SBP (mm Hg)	117 ± 2	133 ± 4	0.004
Rest DBP (mm Hg)	74 ± 1	82 ± 2	0.02
Peak SBP (mm Hg)	145 ± 3	190 ± 5	< 0.0001
Peak DBP (mm Hg)	78 ± 3	82 ± 2	0.33

Data presented are mean value ± SEM. BMI = body mass index; DBP = diastolic blood pressure; HF = heart failure; SBP = systolic blood pressure;  $\dot{V}O_2$  = oxygen consumption.

patient's height measured from the most distal part of the femur). The cross-sectional area (CSA) of the total thigh, quadriceps muscle and three other major thigh muscles (hamstrings, sartorius, gracilis) was measured. This area was assessed by semiautomatic generation of an outline of the area of interest using the console software in the CT scanner.

**Statistical methods.** Results are presented as mean value  $\pm$  SEM. Comparison between patients and control subjects was made using unpaired Student *t* tests. Subgroup comparisons were made using analysis of variance (ANOVA); when ANOVA showed significant differences, the Fisher post hoc test was applied. To analyze relations between variables, simple linear regression (least square method) was performed. To analyze the predictors of quadriceps muscle strength and exercise capacity, we analyzed these variables in multivariate analysis as dependent variables in relation to important clinical and pathophysiologic measures that were entered as independent variables (standard coefficients and the adjusted joint  $R^2$  values are also reported). A commercially available statistical software package was used (Statview 4.5). A value  $<0.05$  was considered statistically significant.

## Results

**Exercise data.** Exercise performance data are summarized in Table 1. Exercise time was significantly shorter ( $p < 0.0001$ ) and peak  $\dot{V}O_2$  significantly lower in patients, whether corrected for body weight or expressed as absolute  $\dot{V}O_2$  (both  $p < 0.0001$ ). However, both patients and control subjects achieved similar respiratory exchange ratios at peak exercise ( $1.15 \pm 0.01$  vs.  $1.19 \pm 0.03$ ,  $p = 0.13$ ).

**Muscle function and bulk.** Data for muscle function and muscle bulk for the weaker leg are presented in Table 2, although in all cases similar differences were found when data

**Table 2.** Muscle Bulk and Function in Patients With Chronic Heart Failure and in Healthy Control Subjects

	Patients With Chronic HF	Control Subjects	p Value
CSA (cm <sup>2</sup> )			
Thigh	179 $\pm$ 6	188 $\pm$ 5	0.43
Weaker leg			
Quadriceps	58 $\pm$ 2	65 $\pm$ 2	0.02
Total muscle	115 $\pm$ 3	131 $\pm$ 4	0.0090
Stronger leg, total muscle	118 $\pm$ 3	134 $\pm$ 4	0.0092
Quadriceps strength (N)			
Weaker leg	357 $\pm$ 11	434 $\pm$ 18	0.0009
Stronger leg	409 $\pm$ 12	483 $\pm$ 18	0.0023
Fatigue (% of baseline)			
5 min	85 $\pm$ 1	90 $\pm$ 1	0.012
20 min	79 $\pm$ 1	92 $\pm$ 2	$<0.0001$
Strength/unit muscle (N/cm <sup>2</sup> )			
Weaker leg	5.91 $\pm$ 0.15	7.02 $\pm$ 0.29	0.0008
Stronger leg	6.67 $\pm$ 0.14	7.45 $\pm$ 0.29	0.012

See Methods for details of assessment. Data presented are mean value  $\pm$  SEM. CSA = cross-sectional area.

**Table 3.** Classification According to Heart Failure Severity

	Severe (n = 33)	Moderate (n = 35)	Mild (n = 32)	p Value (ANOVA)
Age (yr)	64 $\pm$ 2*†	59 $\pm$ 1‡	53 $\pm$ 2	$<0.0001$
BMI (kg/m <sup>2</sup> )	25.8 $\pm$ 0.7	27.5 $\pm$ 0.8	26.4 $\pm$ 0.7	0.27
Peak $\dot{V}O_2$ (ml/min per kg)	12.2 $\pm$ 0.5	17.4 $\pm$ 0.3	24.7 $\pm$ 0.8	$<0.0001$
RER at peak exercise	1.15 $\pm$ 0.03	1.13 $\pm$ 0.02	1.16 $\pm$ 0.02	0.80
LVEF (%)	30 $\pm$ 3	23 $\pm$ 3	26 $\pm$ 2	0.16
Strength (N)				
Weaker leg	317 $\pm$ 20†	350 $\pm$ 17‡	407 $\pm$ 19	0.004
Stronger leg	364 $\pm$ 20†	402 $\pm$ 19‡	461 $\pm$ 21	0.004
Fatigue (% of baseline strength)				
5 min	82 $\pm$ 2	86 $\pm$ 2	86 $\pm$ 2	0.16
20 min	73 $\pm$ 2*§	82 $\pm$ 2	81 $\pm$ 2	0.02
Quadriceps CSA, weaker leg (cm <sup>2</sup> )	53 $\pm$ 3§	59 $\pm$ 3	63 $\pm$ 3	0.04
Total muscle CSA, weaker leg (cm <sup>2</sup> )	103 $\pm$ 5*†	119 $\pm$ 5	124 $\pm$ 5	0.02
Strength/quadriceps unit area, weaker leg (N/cm <sup>2</sup> )	5.9 $\pm$ 0.2	5.9 $\pm$ 0.3	5.9 $\pm$ 0.4	0.96

\* $p < 0.05$ , severe versus moderate. † $p < 0.01$ , § $p < 0.05$ , severe versus mild. ‡ $p < 0.05$ , moderate versus mild. Data presented are mean value  $\pm$  SEM. ANOVA = analysis of variance; LVEF = left ventricular ejection fraction; RER = respiratory exchange ratio; other abbreviations as in Tables 1 and 2.

from the stronger leg were analyzed. There was no difference in thigh CSA when patients and control subjects were compared ( $p = 0.43$ ). Quadriceps CSA was significantly lower in patients (weaker leg:  $-11\%$ ,  $p = 0.021$ ; stronger leg:  $-12\%$ ,  $p = 0.010$ ), as was total muscle CSA (calculated by adding quadriceps + hamstrings + gracilis + sartorius) (weaker leg:  $-12\%$ ; stronger leg:  $-12\%$ , both  $p = 0.009$ ). Patients were significantly weaker (weaker leg:  $-18\%$ ,  $p = 0.0009$ ; stronger leg:  $-15\%$ ,  $p = 0.002$ ) and more fatigued than control subjects; the latter was apparent within 5 min ( $p < 0.05$ ) and reached greatest statistical significance after 20 min of the fatiguing protocol ( $79.1\%$  vs.  $92.2\%$  of baseline,  $p < 0.0001$ ). Maximal strength generated per unit of quadriceps muscle was significantly lower in patients ( $5.9 \pm 0.2$  vs.  $7.0 \pm 0.3$  N/cm<sup>2</sup>,  $p < 0.001$ ).

**Subgroup analyses: heart failure severity by peak  $\dot{V}O_2$ .** Patients were classified into three groups according to the severity of their exercise limitation: 1) *severe* (peak  $\dot{V}O_2 < 15$  ml/min per kg), 2) *moderate* (peak  $\dot{V}O_2$  15 to 20 ml/min per kg), and 3) *mild* (peak  $\dot{V}O_2 > 20$  ml/min per kg). BMI and LVEF were similar in each of the three patient groups (Table 3). With increased severity of exercise limitation there was increased quadriceps muscle weakness. There was no difference in fatigue between groups when assessed after 5 min, although at 20 min the most severely affected group had significantly more fatigue than the other two groups. Quadriceps CSA became smaller with increasing disease severity, as did total leg muscle CSA. However, there was no difference in strength per unit muscle between the groups (Table 3). There

was a significant difference in age between the three groups. If the patients in the three groups are aged matched, these results persist, although the differences in quadriceps and total muscle CSA become trends only.

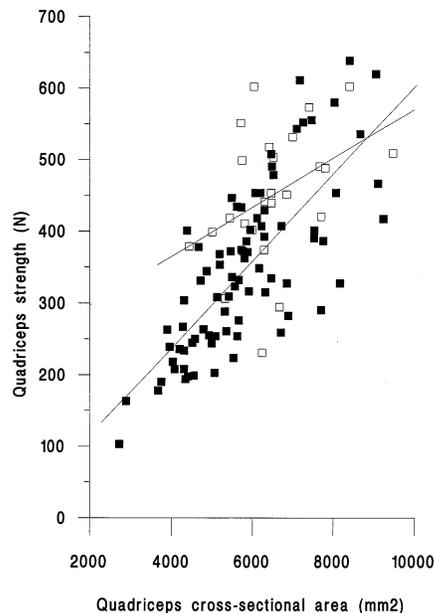
A subgroup of 16 patients with chronic HF and a peak  $\dot{V}O_2 \geq 23.0$  ml/min per kg was compared with 22 healthy control subjects with a peak  $\dot{V}O_2 \leq 36.0$  ml/kg per min and <70 years old. Patients with chronic HF were younger ( $54 \pm 2$  vs.  $61 \pm 1$  year,  $p < 0.005$ ), and they were more fatigued at 20 min ( $84 \pm 3\%$  vs.  $92 \pm 2\%$ ,  $p = 0.02$ ), but all other markers of exercise performance ( $p > 0.17$ ), strength ( $p > 0.87$ ), muscle size ( $p > 0.61$ ) and strength per unit muscle ( $p > 0.11$ ) were not significantly different.

**Subgroup analyses: patients with chronic HF by LVEF or etiology.** When the 93 patients in whom LVEF could be determined were further classified into three groups according to LVEF (LVEF <20% [ $n = 38$ ]; LVEF 20% to 35% [ $n = 35$ ]; LVEF >35% [ $n = 20$ ]), no significant differences for age, BMI, peak  $\dot{V}O_2$ , maximal strength of the weaker ( $p = 0.43$ , ANOVA) or stronger leg ( $p = 0.24$ , ANOVA) or for quadriceps or total muscle CSA of the weaker or stronger leg ( $p > 0.29$ , all by ANOVA) or for fatiguability at 5 or 20 min ( $p > 0.60$ , both by ANOVA) were found. When the patients were stratified according to disease etiology, we found that patients with chronic HF due to ischemic heart disease were somewhat older ( $61 \pm 1$  vs.  $56 \pm 2$  years) and had a lower peak  $\dot{V}O_2$  ( $16.8 \pm 0.6$  vs.  $19.9 \pm 1.2$  ml/min per kg, both  $p < 0.02$ ), but muscle size, strength and fatigue were similar (all  $p > 0.43$ ). When the eight oldest patients with ischemic heart disease and the three youngest patients with dilated cardiomyopathy were excluded from analysis, the mean age was identical (58 years), and again no differences were found for the measures of muscle size or function.

**Predictors of quadriceps strength. Univariate analysis.** Univariate correlation analysis showed that in both patients and control subjects, strength correlated significantly with age (chronic HF:  $R = -0.35$ ,  $p < 0.001$ ; control subjects:  $R = -0.57$ ,  $p < 0.001$ ) and quadriceps CSA (chronic HF:  $R = 0.76$ ,  $p < 0.0001$ ; control subjects:  $R = 0.41$ ,  $p = 0.04$ ) (Fig. 1).

**Multivariate analysis.** In control subjects, multivariate analysis of the predictors of quadriceps strength of the weaker leg (dependent variable) with age and quadriceps CSA as independent variables showed that age (standard coefficient [SC]  $-0.64$ ,  $p = 0.0002$ ) predicted strength independently of quadriceps muscle size (SC  $0.26$ ,  $p = 0.09$ ) (adjusted joint  $R^2 = 0.55$ ,  $p = 0.0001$ ). In patients with chronic HF, multivariate analysis of the predictors of quadriceps strength with age, quadriceps CSA, functional class, LVEF and peak  $\dot{V}O_2$  showed that quadriceps CSA (SC  $0.70$ ,  $p < 0.0001$ ) predicted strength independently of age (SC  $-0.07$ ,  $p = 0.43$ ), functional class (SC  $0.03$ ,  $p = 0.80$ ), LVEF (SC  $-0.01$ ,  $p = 0.88$ ) and peak  $\dot{V}O_2$  (SC  $0.12$ ,  $p = 0.24$ ) (adjusted joint  $R^2 = 0.59$ ,  $p < 0.0001$ ).

**Predictors of exercise capacity.** To investigate the relation between subject characteristics, muscle indexes and exercise capacity, we correlated these variables with weight-adjusted peak  $\dot{V}O_2$  (ml/min per kg) and absolute peak  $\dot{V}O_2$  (ml/min) in



**Figure 1.** Relation between quadriceps strength and quadriceps muscle CSA. **Solid squares** = patients with chronic HF ( $R = 0.76$ ,  $p < 0.0001$ ,  $n = 82$ ); **open squares** = control subjects ( $R = 0.41$ ,  $p < 0.05$ ,  $n = 25$ ).

the patient and control groups (Table 4, Fig. 2). In patients with chronic HF, age, quadriceps strength and quadriceps and thigh muscle CSA correlated with both measurements of peak  $\dot{V}O_2$  (all  $p < 0.01$ ). In the control group, only age and strength correlated significantly with both measures of peak  $\dot{V}O_2$  ( $p < 0.005$ ). Indexes of muscle bulk showed a strong trend toward correlation with absolute peak  $\dot{V}O_2$  in the control group ( $p < 0.09$ ). In patients, multivariate analysis of weight adjusted peak  $\dot{V}O_2$  with age, functional class, LVEF and muscle size showed that age (SC  $-0.32$ ,  $p = 0.0006$ ) and functional class (SC  $-0.62$ ,  $p < 0.0001$ ) were the only independent predictors of weight-adjusted peak  $\dot{V}O_2$ . LVEF (SC  $-0.11$ ) and muscle size (SC  $0.06$ ) did not predict weight-adjusted peak  $\dot{V}O_2$  (both  $p > 0.25$ ). In a separate multivariate analysis with only functional class and age as the independent factors, the joint adjusted  $R^2$  value was  $0.47$  ( $p < 0.0001$ ); that is, these two factors predicted 47% of the variation of the weight-adjusted peak  $\dot{V}O_2$ . In similar multivariate analyses, age (SC  $-0.29$ ), thigh muscle CSA (SC  $0.48$ ) and functional class (SC  $-0.44$ , all  $p < 0.0001$ , joint adjusted  $R^2 = 0.71$ ) were predictors of absolute peak  $\dot{V}O_2$  in patients with chronic HF independently of each other. In the control group, age (independent of muscle size) predicted absolute peak  $\dot{V}O_2$  (age: SC  $-0.57$ ,  $p = 0.0018$ ; muscle size: SC  $0.26$ ,  $p = 0.12$ ) and weight-adjusted peak  $\dot{V}O_2$  (age: SC  $-0.64$ ,  $p = 0.0009$ ; muscle size: SC  $-0.02$ ,  $p = 0.92$ ).

## Discussion

**Changes in muscle bulk and strength.** To our knowledge, the present study is the first to demonstrate a significant reduction in maximal isometric quadriceps strength in a large

**Table 4.** Correlates for Peak Oxygen Uptake in Patients With Chronic Heart Failure and in Healthy Control Subjects

	No. of Control Subjects/Patients	Control Subjects				Patients With Chronic HF			
		Total $\dot{V}O_2$ (ml/min)		Peak $\dot{V}O_2$ /kg (ml/kg per min)		Total $\dot{V}O_2$ (ml/min)		Peak $\dot{V}O_2$ /kg (ml/kg per min)	
		R Coeff	p Value	R Coeff	p Value	R Coeff	p Value	R Coeff	p Value
Age	31/100	-0.55	0.001	-0.56	0.001	-0.47	< 0.0001	-0.37	0.0001
LVEF	0/93	—	—	—	—	0.07	0.5	0.027	0.8
Quadriceps strength	31/100	0.58	0.0006	0.5	0.003	0.53	< 0.0001	0.35	0.0003
Quadriceps CSA*	25/83	0.36	0.08	0.04	0.35	0.6	< 0.0001	0.29	0.007
Total muscle CSA*	25/83	0.38	0.058	0.12	0.55	0.66	< 0.0001	0.32	0.005
20-min fatigue	29/82	0.18	0.35	0.07	0.73	0.08	0.46	0.18	0.12
Furosemide equivalent dose	0/100	—	—	—	—	0.11	0.28	0.12	0.2

\*Correlations with muscle strength and size with data from weaker leg. Coeff = coefficient; — = not applicable; other abbreviations as in Tables 1 to 3.

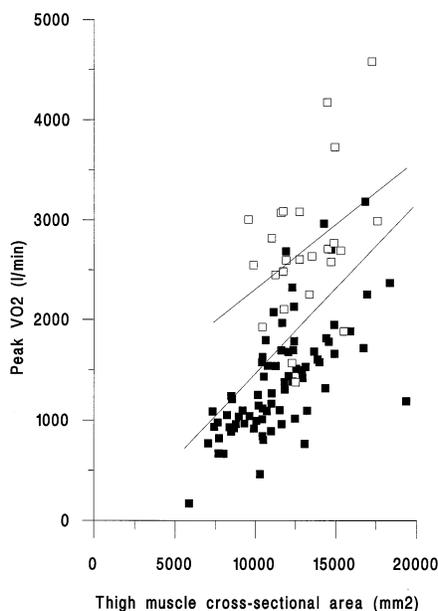
group of patients with chronic HF compared with age-matched healthy control subjects. Our study suggests that this weakness occurs as a result of two separate processes: wasting and reduced muscle efficiency.

A strong correlation between maximal strength and quadriceps bulk was previously reported in chronic HF (14). We confirmed this strong correlation in a larger, more diverse study group. Using single-slice CT scanning, we observed a reduced quadriceps and total thigh muscle CSA in our patients. Magnetic resonance imaging and anthropometric techniques (9) have yielded similar results, with investigators consistently describing wasting and noting its presence even in mild chronic HF. Weakness should be an inevitable consequence of muscle wasting, unless strength per unit muscle is increased. Despite previous investigators (14) not always ob-

serving overall muscle weakness, we believe that our study refutes any possible compensatory increase in strength per unit muscle. We observed a reduced strength per unit muscle CSA in the quadriceps, present in even mildly affected patients with chronic HF. Patients with severe chronic HF have wasting in addition to a reduction in strength per unit muscle and thus have more marked weakness. With increasing exercise limitation, quadriceps weakness becomes more severe. This increasing weakness appears largely to be a result of quadriceps wasting but not to a further reduction in muscle quality. This finding explains the differences between the observations of Buller et al. (12) and Minotti et al. (14). Minotti et al. (14) studied 21 patients with a mean peak  $\dot{V}O_2$  of 18 ml/min per kg (cycle ergometry). Buller et al. (12) studied 10 patients with a mean peak  $\dot{V}O_2$  of 14.8 ml/min per kg (treadmill protocol), which would have been still lower had they used a cycle ergometer (24). The difference between the two studies is thus most likely explained by the marked difference in severity between the two patient groups. Minotti et al. (14) may not have found significant weakness because of the small size of their study group, the lesser severity of chronic HF in their patients or possibly because their control subjects were weaker.

When we compared patients with CHF and control subjects with similar exercise capacity, no significant differences in muscle bulk or function were seen, further suggesting the importance of leg muscle changes to exercise limitations. To our knowledge, our observation that strength per unit muscle is reduced in even mild chronic HF has not been previously reported. Buller et al. (12) compared strength per unit muscle in five patients with chronic HF with the normal range previously reported by Chapman et al. (25). The lack of difference may reflect differences in the techniques used by Chapman et al. (25). Chapman et al. (25) used data from both legs and included some children in the subjects they studied. The small numbers studied by Buller et al. (12) also make the detection of a significant difference less likely. Minotti et al. (14) compared 21 patients with chronic HF with 12 healthy control subjects. They calculated the maximal CSA from nine magnetic resonance imaging slices of the thigh. Their obser-

**Figure 2.** Relation between thigh muscle CSA and maximal treadmill  $\dot{V}O_2$ . **Solid squares** = patients with chronic HF ( $R = 0.66$ ,  $p < 0.0001$ ,  $n = 76$ ); **open squares** = control subjects ( $R = 0.38$ ,  $p = 0.058$ ,  $n = 25$ ).



vation that strength per unit muscle is normal in chronic HF differs from ours; the reason for this discrepancy may be related to a different technique for assessing maximal isometric strength or the smaller patient numbers.

There are several potential reasons for a reduction in muscle bulk in CHF. Patients are less mobile than normal subjects, and disuse atrophy may occur. Patients with chronic HF are often anorectic and may be malnourished (9,26). Additionally, catabolic factors, such as tumor necrosis factor and other cytokines (27,28) and cortisol (29), are elevated in chronic HF, and these factors in association with sympathetic activation and insulin resistance (30) may result in muscle protein loss.

The etiology of the reduced strength per unit muscle is also potentially multifactorial. Some investigators have described an increased fat content of muscle in chronic HF (11,31). Such a fatty infiltration would result in an overestimate of effective muscle CSA and a consequent apparent reduction of strength per unit muscle. Other histologic changes observed in chronic HF may be significant. Patients have an increase in the percentage of type II fibers mainly as a result of increased type IIb fibers. Type I fibers are probably reduced (16,32). In addition, there appears to be a reduction in type II fiber diameter, with some groups also reporting a reduction in type I fiber diameter (11). Larsson et al. (33) in a study of 114 normal subjects found that the only independent histologic variable that correlated with maximal isokinetic strength was type II fiber area. Although the size of type II fibers correlated with strength, it is unclear whether a reduction in type II fiber diameter leads to a reduction in strength generated per unit muscle. Possible changes in anatomic arrangement of muscle fibers could also affect the strength per unit muscle.

**Relation between muscle strength and bulk.** We, like previous investigators (14), observed a highly significant correlation between quadriceps CSA and strength in patients with chronic HF. In normal control subjects, age is the strongest predictor of strength, with quadriceps CSA failing to reach significance as an independent predictor. It is likely that this loss of the effect of age in chronic HF explains the greater closeness of the relation between bulk and strength in chronic HF. Age is no longer a significant predictor of strength in chronic HF because the loss of muscle bulk and type II fiber atrophy, which contributes to strength reduction in the elderly (34), has already occurred in these patients. In our group of normal control subjects, none of the measures of muscle size predicted peak  $\dot{V}O_2$  independently of age, which is consistent with the findings of other investigators (35).

**The significance of changes in muscle function.** Muscle indexes are related to body size. Any association between peak  $\dot{V}O_2$ , which is weight adjusted, and muscle indexes, which are not, will thus be weakened. To correct for this we considered both absolute and weight-corrected peak  $\dot{V}O_2$ . In our patient group, indexes of muscle bulk were significantly associated with peak  $\dot{V}O_2$  and were strongly correlated with absolute peak  $\dot{V}O_2$ , with muscle CSA being an independent predictor of absolute peak  $\dot{V}O_2$ . In chronic HF, therefore, it is muscle bulk

that has a significant effect on aerobic capacity. We, like other investigators (12), found an association between muscle strength and peak  $\dot{V}O_2$ . However, strength in chronic HF is highly dependent on muscle CSA, with the association explained by the variation in muscle bulk.

Muscular fatigue occurred to a much greater extent in patients with chronic HF than in control subjects. This finding is consistent with those of other investigators. However, we found no significant association with severity of chronic HF. Minotti et al. (14) assessed dynamic endurance and noted that it was reduced in chronic HF and correlated with peak  $\dot{V}O_2$  but that isometric (anaerobic) fatigability did not. This second measure of fatigue was probably closer to ours. In normal subjects, resistance to isometric and dynamic endurance is dependent on type I fibers (36). Patients with chronic HF have a reduction in type I fibers, and it is possible that it is this change in fiber type that leads in part to the increased fatigue seen in patients with chronic HF.

**Limitations of the study.** The methods used to study muscle function require maximal patient effort. It is possible that with advancing heart failure, effort is reduced, resulting in an apparent decrease in maximal strength. We attempted to ensure maximal effort by the use of twitch interpolation, by requiring patients to achieve a plateau in force generation and by assessing several maximal contractions. We used CT scanning as an estimate of muscle bulk. Although a relatively crude measure, work from our own institution shows excellent correlation between CT-based estimates of muscle bulk and calculations of leg or total body lean tissue, using dual-energy X-ray absorptiometry scanning (unpublished data). Finally, we studied male subjects only, and our results may not be applicable to female patients.

**Conclusions.** Patients with chronic HF have reduced quadriceps maximal isokinetic strength. This weakness occurs as a result of both quantitative and qualitative abnormalities of the quadriceps. With increasing exercise limitation of patients with chronic HF, there is increased weakness, occurring mainly as a result of loss of quadriceps muscle bulk. Muscular fatigue is common in chronic HF but appears to be a feature of the syndrome itself and does not relate closely to disease severity. In patients with chronic HF, but not healthy control subjects, muscle bulk is a determinant of peak  $\dot{V}O_2$ , which may explain the lack of association between hemodynamic indexes and exercise capacity in chronic HF. Taken together, these findings suggest that in chronic HF peripheral changes rather than a central hemodynamic disturbance limit exercise. Future therapies aimed at increasing muscle bulk may thus be beneficial.

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