Importance of Total Leg Muscle Mass for Exercise Intolerance in Chronic Heart Failure

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SUMMARY

Patients with chronic heart failure symptoms tend to avoid voluntary effort and are thus subject to physical deconditioning. The presence of symptoms in daily life is thought to predispose to physical deconditioning and subsequent skeletal muscle loss. This study was designed to describe the relation among daily physical activities, skeletal muscle loss and exercise capacity in patients with chronic heart failure. We studied 14 patients with severe cardiac dysfunction (left ventricular ejection fraction <40%) and 7 age-matched normal subjects. We measured total leg muscle mass by dual energy X-ray absorptiometry. The patients were divided into 7 asymptomatic and 7 symptomatic individuals using questionnaires for specific physical activities. Peak oxygen uptake and anaerobic threshold were significantly reduced in cardiac patients as compared with normal subjects. The reduction in exercise capacity was greater in the symptomatic patients than in asymptomatic patients. Leg muscle mass was significantly reduced (–17%) in the symptomatic patients, while it remained normal in the asymptomatic patients. Oxygen uptake in unit muscle mass at the level of anaerobic threshold and at peak exercise was decreased in both the asymptomatic (–21% and –21%, respectively) and symptomatic patients (–27% and –30%, respectively) but the difference between these two groups was not significant. In the asymptomatic patients, the reduced exercise capacity was accounted for primarily by muscle mass-independent factors such as an impaired nutritive blood flow to exercising muscles or metabolic abnormalities within the muscle cell. In the symptomatic patients, the marked reduction in exercise tolerance was attributable to a decrease in leg muscle mass and to hemodynamic or metabolic abnormalities. We conclude that the loss of leg muscle mass plays an important role in exercise intolerance in patients who are prone to physical deconditioning as a result of symptomatic heart failure. (*Jpn Heart J* 35: 15–26, 1994)

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PATIENTS with cardiac dysfunction demonstrate a generally reduced, but highly variable, exercise capacity. Despite severe ventricular dysfunction, certain patients may even have normal exercise tolerance. Recent clinical studies have raised the importance of skeletal muscle abnormalities that potentially modify the relation between cardiac dysfunction and disability in these patients. Studies using magnetic resonance spectroscopy have demonstrated intracellular abnormalities of skeletal muscle biochemistry in patients with chronic heart failure.¹⁻³⁾ Minotti et al⁴⁾ measured skeletal muscle function in chronic heart failure using isokinetic dynamometry and found that muscle dysfunction plays a major role in limiting exercise performance, independent of limb blood flow. Recently, Mancini et al⁵⁾ have shown in these patients that skeletal muscle atrophy contributes to the reduced exercise capacity. These abnormalities closely resemble the state of exercise deconditioning in normal subjects. Patients with heart failure symptoms tend to avoid voluntary effort or are advised by the physician to restrict their physical activity, and are thus subject to physical deconditioning. Therefore, the presence of symptoms in daily life induces physical deconditioning and subsequent skeletal muscle loss.

The present study was designed to describe the relation among daily physical activities, skeletal muscle loss and exercise capacity in patients with chronic heart failure. To separate the contribution of the muscle loss to exercise intolerance from other metabolic and hemodynamic abnormalities, we selectively measured total muscle mass of the legs using dual energy X-ray absorptiometry (DEXA) and determined the oxygen utilized by unit muscle mass as an index of aerobic exercise capacity independent of leg muscle mass.

MATERIALS AND METHODS

Study population: We studied 14 male patients with a left ventricular ejection fraction less than 40% assessed by radionuclide ventriculography and 7 age-matched normal subjects (left ventricular ejection fraction: $72 \pm 7\%$). The causes of cardiac dysfunction were dilated cardiomyopathy in 9 patients and old myocardial infarction in 5 patients. Patients with anemia, primary lung disease, angina pectoris or overt peripheral edema were excluded from the study. All patients were in sinus rhythm. Ten patients had been using diuretics and 6 patients had been using isosorbide dinitrate. These medications were withheld for 48 hours while the patients were closely observed. All subjects terminated their progressive exercise because of leg fatigue. We quantified the patients' quality of

Table I. Questionnaires for Specific Activity Scale

1.	Can you sleep comfortably at night? (1 Mets or less)
2.	Do you feel comfortable in the lying position? (1 Mets or less)
3.	Can you eat meals or wash your face by yourself? (1.4 Mets)
4.	Can you go to the bathroom by yourself? (2 Mets)
5.	Can you change your clothes by yourself? (2-2.3 Mets)
6.	Can you do kitchen work or sweep the room with a broom? (2-3 Mets)
7.	Can you make your bed by yourself? (2-3 Mets)
8.	Can you mop the floor? (3-4 Mets)
9.	Can you have a shower without any trouble? (3-4 Mets)
10.	Can you practice radio gymnastic exercises without any trouble? (3-4 Mets)
11.	Can you walk 100 to 200m on level ground at the same speed as healthy persons do (4km/hr) without any trouble? (3-4 Mets)
12.	Can you do light gardening (weeding for a brief time, etc.) without any trouble? (4-5 Mets)
13.	Can you take a bath by yourself? (4-5 Mets)
14.	Can you go upstairs at the same speed as healthy persons do without any trouble? (5-6 Mets)
15.	Can you do heavier gardening (digging the garden, etc.)? (5-7 Mets)
16.	Can you walk 200m on level ground at a quick pace without any trouble? (6-7 Mets)
17.	Can you shovel snow? (6-7 Mets)
18.	Can you play tennis (or ping pong) without any trouble? (6-7 Mets)
19.	Can you jog (at about 8km/hr) over a distance of 300 to 400m without any trouble? (7-8 Mets)
20.	Can you swim without any trouble? (7-8 Mets)
21.	Can you skip rope without any trouble? (≥ 8 Mets)

life using questionnaires for specific physical activities which a patient would perform either customarily or sporadically in daily life (Table I).⁶ We measured the metabolic cost of each physical activity listed on the questionnaire. A patient was asked to specify whether or not he/she could perform each type of activity without symptomatic limitation. Summarizing the questionnaire data, a given metabolic cost (Specific Activity Scale; SAS) was derived for each patient regarding the self-perceived exercise tolerance. Interobserver variation in estimating SAS in 20 patients was very small with a mean difference of 0.4 ± 0.5 Mets.⁶ Subjects were divided into three groups (Table II): normal subjects, consisting of 7 normal men (aged 51 to 66 years; 59 ± 5 years); asymptomatic patients consisting of 7 patients (aged 53 to 66 years; 59 ± 4 years) who had SAS above 7 Mets (New York Heart Association class I); and symptomatic patients consisting of 7 patients (aged 56 to 67 years; 63 ± 4 years) who had SAS of 7 Mets or less (New York Heart Association class II: 3, III: 4). Informed consent was obtained from all subjects as required by our institutional committee on human research.

Leg muscle mass: The skeletal muscle mass of the right thigh and calf was measured in all subjects (Figure 1) using DEXA (Norland Co., XR-26). DEXA is a recently developed method of quantifying the skeletal and soft tissue components of body mass *in vivo*.⁷ Briefly, when low and high levels of X-ray energy are delivered to the body, peaks are attenuated in an exponential fashion by absorption in tissues such as bone, fat and muscle. The following equations represent the relationship between the amount of X-ray attenuation and tissue absorption

Table II. Profiles of Subjects Studied

No.	Age (yr.)	Height (cm)	Weight (kg)	SAS (Mets)	LVEF (%)	Etiology
Normal subjects						
1	57	153	54	>7	63	—
2	53	161	56	>7	65	—
3	66	167	62	>7	71	—
4	51	167	66	>7	72	—
5	62	160	60	>7	73	—
6	63	165	72	>7	75	—
7	59	161	62	>7	87	—
mean	59	162	62		72	
±SD	5	5	6		7	
Asymptomatic patients						
1	61	165	67	>7	25	DCM
2	57	170	68	>7	30	DCM
3	66	170	71	>7	20	OMI
4	60	158	56	>7	39	OMI
5	53	163	52	>7	30	DCM
6	58	159	63	>7	17	OMI
7	58	166	62	>7	32	OMI
mean	59	164	63		28*	
±SD	4	5	6		7	
Symptomatic patients						
1	64	165	54	4-5	17	OMI
2	65	170	62	5-6	21	DCM
3	64	152	50	6-7	29	DCM
4	67	167	50	4-5	28	DCM
5	56	165	62	2-3	9	DCM
6	67	159	48	4-5	21	DCM
7	60	155	55	5-6	23	DCM
mean	63	162	54*+		21*	
±SD	4	6	5		6	

*=p<0.05 vs. Normal subjects, +=p<0.05 vs. Asymptomatic patients. DCM=dilated cardiomyopathy; LVEF=left ventricular ejection fraction; OMI=old myocardial infarction; SAS=specific activity scale.

at each level of X-ray energy:

$$\ln I_l = K_l(\text{BONE}) \cdot M(\text{BONE}) + K_l(\text{SOFT}) \cdot M(\text{SOFT}) \quad (\text{a})$$

$$\ln I_h = K_h(\text{BONE}) \cdot M(\text{BONE}) + K_h(\text{SOFT}) \cdot M(\text{SOFT}) \quad (\text{b})$$

where, I_l and I_h are the amounts of attenuation of low and high energy X-ray, K_l and K_h are the mass attenuations of low and high energy X-ray for bone (BONE) and soft tissue (SOFT) and M is the mass of bone and soft tissue. Accordingly, equations (a) and (b) can be solved for bone and soft tissue mass. The DEXA method can also discriminate between fat mass and muscle mass by the difference in the ratio of low- and high-energy attenuation. If soft tissue consists only of fat, the ratio becomes 0.016; if soft tissue consists only of muscle, the ratio is

Figure 1. Measurements of thigh and calf muscle mass using dual energy X-ray absorptiometry. Muscle mass of the thigh was measured between the tuber ischiadicum and the upper edge of the patella (upper panel). Muscle mass of the calf was measured between the upper edge of the patella and the lower limit of the fibula (lower panel).

0.039.⁷⁾ Using these values, the actual measured ratio gives the proportion of fat and muscle mass. Several studies⁸⁻¹⁰⁾ have documented the accuracy of DEXA-derived estimates of body composition. To validate our DEXA-derived estimate of muscle mass, we compared the actual measured mass of a beef phantom and the mass measured by DEXA. The phantom block was measured under various combinations of muscle and fat layers and bone. The thickness of the phantom ranged from 5 to 20cm. Within the range of 400 to 4000g of muscle mass, the correlation between the DEXA-derived muscle mass and the actual measured muscle weight was highly linear ($r=0.99$) (Figure 2). Accordingly, we corrected the muscle mass measured by DEXA as follows: muscle mass (g) = $0.89 \cdot \text{mass (by DEXA)} - 120$. The mean difference between the corrected muscle mass and the actual muscle weight was within 5%. The total muscle mass of legs was obtained as follows: $2 \cdot (\text{thigh muscle mass} + \text{calf muscle mass})$.

Exercise testing: All subjects were evaluated at least 2 hours after eating. They

Figure 2. Validation of DEXA-derived estimate of muscle mass. Actual weight of beef phantom was compared with the DEXA measurement. The phantom block was measured under various combinations of muscle and fat layers and bone. Within the range of 400 to 4000g of muscle mass, correlation between DEXA-derived estimate and muscle weight actually measured was highly linear ($r=0.99$). DEXA=dual energy X-ray absorptiometry.

performed progressive, maximal, symptom-limited exertion while seated upright on an electronically braked cycle ergometer (Corival-400, Lode, The Netherlands). Initially, subjects performed unloaded cycling for 3 minutes. The work rate was then increased progressively by 3 to 15 watts every minute. The work rate increment was individualized based on the subject's exercise capacity. Heart rate was monitored, together with blood pressure, which was measured by the cuff method at 1-minute intervals throughout testing. Oxygen uptake, carbon dioxide production, ventilatory volume, and end-tidal oxygen (ETO_2) and end-tidal carbon dioxide (ETCO_2) concentrations were continuously measured on a breath-by-breath basis using a metabolic measurement cart (Minato AE-280, Japan) equipped with an oxygen and carbon dioxide analyzer (Minato MG-360). Respiratory flow was measured by the thermal dissipation technique. Exercise capacity was evaluated by peak oxygen uptake (peak $\dot{V}\text{O}_2$) and gas exchange anaerobic threshold (AT). To separate the contribution of the leg muscle mass to exercise tolerance from those of other metabolic and hemodynamic factors, we determined oxygen uptake per unit of leg muscle mass (AT/mass, peak $\dot{V}\text{O}_2$ /mass) by dividing the oxygen uptake at the levels of AT and the peak exercise by total muscle mass of legs. We determined AT by the V-slope method described by Beaver et al⁽¹⁾ and according to the criteria of Davis et al⁽²⁾: 1) a systematic increase in the ventilatory equivalent for oxygen uptake without an increase in the ventilatory equivalent for carbon dioxide production, and 2) a systematic increase in ETO_2 without a concomitant decrease in ETCO_2 .

Statistical analysis: Data are expressed as mean $\pm$ standard deviation. The statistical significance of differences in variables among the three groups was tested by analysis of variance, and multiple comparisons were made by the Bonferroni method. Values of $p < 0.05$ were considered to be statistically significant.

RESULTS

There was no significant difference in height among the three groups (Table II). Left ventricular ejection fraction was comparably reduced in the

Table III. Exercise Capacity and Leg Muscle Mass in Three Groups

No.	AT (ml/min)	Peak $\dot{V}O_2$ (ml/min)	Muscle mass (g)	AT/mass (ml/min/g)	Peak $\dot{V}O_2$ /mass (ml/min/g)
Normal subjects					
1	832	1694	7903	0.105	0.214
2	825	1216	9711	0.085	0.125
3	1179	1641	10087	0.117	0.163
4	783	1608	10467	0.075	0.154
5	742	1304	9013	0.082	0.145
6	635	1284	9965	0.064	0.129
7	860	1743	9157	0.094	0.190
mean	837	1499	9472	0.089	0.160
$\pm$ SD	156	205	796	0.017	0.030
Asymptomatic patients					
1	731	1150	9511	0.077	0.121
2	746	1111	11046	0.068	0.101
3	586	1255	8610	0.068	0.146
4	576	1181	8868	0.065	0.133
5	634	1453	8457	0.075	0.172
6	708	1005	8880	0.080	0.113
7	604	972	9748	0.062	0.100
mean	655*	1161*	9303	0.071*	0.126*
$\pm$ SD	66	150	832	0.006	0.024
Symptomatic patients					
1	367	773	6252	0.059	0.124
2	679	950	8395	0.081	0.113
3	521	889	8247	0.063	0.108
4	468	876	7015	0.067	0.125
5	497	794	9423	0.053	0.084
6	455	884	8298	0.055	0.107
7	572	963	7426	0.077	0.130
mean	508*+	876*+	7865*+	0.065*	0.113*
$\pm$ SD	91	66	968	0.010	0.014

*= $p < 0.05$ vs. Normal subjects; += $p < 0.05$ vs. Asymptomatic patients; AT=gas exchange anaerobic threshold; AT/mass=oxygen uptake in unit muscle mass at the level of AT; Muscle mass=total muscle mass of thighs and calves; Peak $\dot{V}O_2$ /mass=peak oxygen uptake in unit muscle mass.

Figure 3. Relations between exercise tolerance and total leg muscle mass in patients with cardiac dysfunction. In patients with asymptomatic cardiac dysfunction, peak $\dot{V}O_2$ (PEAK) and anaerobic threshold (AT) are decreased independently of leg muscle mass while in patients with heart failure symptoms, a marked decline in the aerobic exercise capacity is accompanied by a reduction in leg muscle mass. $\dot{V}O_2$ =oxygen uptake.

asymptomatic and symptomatic patients. When expressed in absolute terms (ml/min), peak $\dot{V}O_2$ was reduced by $23 \pm 10\%$ in the asymptomatic patients and by $42 \pm 4\%$ in the symptomatic patients, compared with those in normal subjects (Table III). Similarly, AT was decreased by $22 \pm 8\%$ in asymptomatic patients and by $39 \pm 11\%$ in symptomatic patients. The differences in peak $\dot{V}O_2$ and AT between asymptomatic and symptomatic patients were also significant. Total leg muscle mass was $17 \pm 10\%$ lower in symptomatic patients than in normal subjects, while in asymptomatic patients it was within the normal range. Peak $\dot{V}O_2$ /mass fell by $21 \pm 15\%$ in asymptomatic patients and by $30 \pm 9\%$ in symptomatic patients. Similarly, AT/mass was decreased by $21 \pm 7\%$ in asymptomatic patients and by $27 \pm 11\%$ in symptomatic patients, compared with normal subjects. Both peak $\dot{V}O_2$ /mass and AT/mass in symptomatic patients showed a trend to decline compared with those in asymptomatic patients, but did not reach statistical significance.

Figure 3 illustrates the relations between exercise tolerance defined as peak $\dot{V}O_2$ and AT and total leg muscle mass in the three groups. This framework shows that aerobic exercise capacity in cardiac patients initially fell through muscle mass-independent mechanisms such as hemodynamic or metabolic abnormalities (asymptomatic patients). As heart failure symptoms developed, loss of leg muscle mass additionally contributed to a further reduction in exercise capacity (symptomatic patients).

DISCUSSION

Maximal oxygen uptake is closely related to blood flow to the working muscles, the activity of muscular oxidative enzymes, and working muscle mass. A metabolic abnormality within the muscle cell might cause a reduction in oxygen uptake per unit muscle mass, as well as an impaired nutritional blood flow. Our data cannot discriminate between these two influences on the reduction in oxygen uptake per unit muscle mass. In the present study we aimed to describe the importance of leg muscle mass in exercise intolerance in patients with heart failure symptoms. In asymptomatic patients, muscle mass-independent factors such as a hemodynamic or metabolic abnormality appeared to be responsible for the entire reduction in exercise capacity because oxygen uptake per unit muscle mass was significantly decreased while leg muscle mass remained unaltered. In symptomatic patients, however, the marked reduction in exercise capacity was accompanied by decreases in both leg muscle mass and oxygen uptake per unit muscle, compared with those in normal subjects. Thus, a loss of leg muscle mass could occur selectively in patients with heart failure symptoms and play an important additional role in a further reduction in aerobic capacity.

Fleg and Lakkata¹³⁾ recently demonstrated that the age-related decline in maximal oxygen uptake in non-endurance-trained individuals was attributable to the selective loss of muscle mass that accompanies advancing age. Wood et al¹⁴⁾ showed that the preservation of postoperative muscle mass by the administration of intravenous nutritional support could maintain the exercise capacity of patients who were undergoing major surgery. Because nearly all oxygen is consumed in the exercising muscles during aerobic activity, it is highly plausible that a substantial decline in muscle mass, whether mediated by disuse, malnutrition, or even the aging process, leads to a parallel decline in peak $\dot{V}O_2$ and AT.

The exact mechanisms of muscle loss in chronic heart failure are not known, but the most likely cause is chronic physical deconditioning. Recently, Sullivan et al⁹⁾ demonstrated that patients with chronic heart failure show a decrease in slow-twitch type I fibers, which have a high potential for aerobic oxidation, and an increase in fast-twitch type IIb fibers, which was accompanied by a reduction in aerobic oxidative enzyme activity. They also demonstrated in these patients that biochemical alterations of skeletal muscle occurred; i.e., glycolytic enzymes were unchanged, and aerobic oxidative enzymes and glycogen content were reduced. Lipkin et al¹⁵⁾ have documented atrophy of both type I and II fibers in the quadriceps muscles of patients with severe chronic heart failure, and have suggested that muscle fiber atrophy is the cause of the reduced muscle strength in these patients. These alterations in skeletal muscle histology and biochemistry in patients with long-term heart failure are consistent with the effects of

exercise deconditioning. Berg et al¹⁶⁾ showed that 4-week unloading of a unilateral lower limb induced marked decreases in muscle strength and mass similar to those produced by bedrest. Decreased protein synthesis during skeletal muscle unloading has recently been confirmed at levels of specific mRNAs by Howard et al.¹⁷⁾ We observed a loss of leg muscle mass in symptomatic patients, but no appreciable changes in muscle mass in asymptomatic patients. Symptomatic patients restrict their physical activity to avoid the discomfort of dyspnea. The more pronounced the sensation of dyspnea, the greater the voluntary restriction of effort, leading to a more pronounced degree of deconditioning over time. Consequently, deconditioning induces the atrophy of muscle fiber, reinforcing the vicious cycle by preventing the patient from doing more. In addition, deconditioning is accompanied by the reduction of skeletal muscle oxidative enzymes³⁾ and vasodilator capacity mediated by endothelially derived relaxing factors.¹⁸⁾ These factors could also affect exercise tolerance together with the loss of muscle mass in patients with restricted physical activity. Conversely, when the discomfort of dyspnea is relieved by appropriate treatment, the patient's sense of well-being encourages a greater voluntary effort, thus leading to physical conditioning.

We estimated total leg muscle mass with DEXA which permits separate measurements of skeletal muscle mass, fat, and bone mineral density at a specific body site.^{7,9)} In the range of 400 to 4000g of muscle mass, the DEXA-derived muscle mass was highly correlated with actual measured muscle mass. Urinary creatinine excretion is the conventional means of estimating body muscle mass, but it is not suitable for measuring regional muscle mass.¹⁹⁾ In addition, because renal dysfunction is frequently observed in patients with severe heart failure, urinary creatinine excretion may be limited, precluding the estimation of muscle mass by this method. Methods that measure total body water by isotopic techniques or percent body fat by hydrodensity are not specific for muscle mass because they also measure various fat-free tissues, such as bone and viscera.²⁰⁾ Computed tomography or magnetic resonance imaging would be unable to separate fatty infiltration within muscle and underestimate the degree of muscle atrophy.⁵⁾ Thus, DEXA first enables us to estimate total leg muscle mass accurately and to obtain oxygen uptake per unit leg muscle mass.

Certain limitations of the present study should be recognized. First, DEXA may include the bone marrow and skin in the estimate of muscle mass, causing some quantitative error. However, the degree of error is relatively minor because the amount of bone marrow and skin found in healthy men is less than 5% that of skeletal muscle.⁹⁾ Since this technique cannot differentiate water (interstitial or extracellular) from muscle tissue, muscle mass might be overestimated in edematous patients. In the present study, therefore, we excluded heart failure patients with overt peripheral edema and found the muscle mass of nonedematous heart

failure patients to be less than that of normal subjects. Secondly, the cross-sectional design may underestimate the longitudinal decline in anaerobic threshold and muscle mass because of selective survivorship. Duration and intensity of heart failure symptoms would modify the deconditioning process. A longitudinal analysis would reveal the time course and extent of deconditioning-induced decline in muscle mass in patients with long-term heart failure. Thirdly, we normalized oxygen uptake at the AT level and peak $\dot{V}O_2$ by leg muscle mass in this study. At peak exercise, accelerated ventilatory drive results in an additional increase in oxygen uptake which is used by respiratory muscle. Similarly, arm and gluteal muscles are involved in maintaining a constant rate of pedaling during strenuous exercise. However, at the level of AT, ventilatory drive does not show such an increase, and oxygen uptake is considered to represent the oxygen used almost exclusively by exercising leg muscle. Therefore, peak $\dot{V}O_2$ /mass might be somewhat overestimated in this study. Finally, we enrolled patients with left ventricular ejection fractions less than 40% and thus, found no difference in ejection fraction between asymptomatic and symptomatic patients. However, the oxygen uptake is considered to represent the oxygen utilized almost exclusively by exercising leg muscles and correlates well with cardiac output and blood flow to these muscles.²¹⁾ Although we did not examine exercise hemodynamics, the lower peak $\dot{V}O_2$ in symptomatic patients indicates a lower peak blood flow to the exercising legs than that in asymptomatic patients. Thus, cardiac pumping ability in these groups of patients might differ and be partly responsible for the intergroup difference in exercise capacity.

In conclusion, we have found that the loss of leg muscle mass plays an important role in exercise intolerance in patients who are prone to physical deconditioning as a result of the effects of heart failure symptoms on daily life. Further studies are required to gain insight into the mechanisms underlying the loss of skeletal muscle in heart failure and to address the extent to which this diminution of muscle mass can be reversed by the relief of heart failure symptoms.

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