Reduced Peripheral Skeletal Muscle Mass and Abnormal Reflex Physiology in Chronic Heart Failure

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Background—The muscle hypothesis implicates abnormalities in peripheral muscle as a source for the stimulus to the symptoms and reflex abnormalities seen in chronic heart failure (CHF). We investigated the relationship between skeletal muscle mass (with dual-energy x-ray absorptiometry) and activation of the ergoreflex (a peripheral reflex originating in skeletal muscle sensitive to products of muscle work) in CHF patients and whether this rapport is affected by the progression of the syndrome.

Methods and Results—We assessed 107 consecutive CHF patients (mean age, 61.9±10.9 years; 95% male; 25 cachectics) and 24 age-matched normal subjects (mean age, 59.0±11.1 years; 91% male). Compared with normal subjects, patients had a higher ergoreflex (in ventilation, 6.2±6.1 versus 0.6±0.6 L/min; P<0.0001) and a reduction in muscle mass (51.9±10.0 versus 60.3±8.8 kg; P<0.001). The ergoreflex was particularly overactive in cachectics (P<0.05), accompanied by marked muscle mass depletion (P<0.0005). In CHF, ergoreceptor hyperresponsiveness in both the arm and leg correlated with reduced muscle mass, abnormal indexes of exercise tolerance (peak VO₂, V̇E/V̇CO₂ slope), ejection fraction, and NYHA functional class (P<0.0001). In the cachectic population, the ventilatory response from ergoreflex to arm exercise was strongly inversely correlated with arm (r = −0.65), leg (r = −0.64), and total (r = −0.61) lean tissues (P<0.001 for all). Multivariate analysis showed that these relationships were independent of NYHA class, peak VO₂, and V̇E/V̇CO₂ slope.

Conclusions—Depleted peripheral muscle mass is associated with ergoreflex overactivity and exercise limitation in CHF, particularly in cachectic patients. The systemic activation of the muscle reflex system in CHF may reflect progression and deterioration of the clinical syndrome. (Circulation. 2006;114:126-134.)

Key Words: heart failure • reflex • receptors • nervous system • ventilation

Patients with chronic heart failure (CHF) are characteristically limited by symptoms of breathlessness and fatigue, the pathophysiology of which remains unclear. One proposal, the muscle hypothesis, is that peripheral skeletal muscle, which becomes abnormal in heart failure, is the source of the signals, which disrupt normal patterns of cardiorespiratory control.1 We previously demonstrated that neurohormonal activation and an altered balance between catabolism and anabolism (in favor of catabolism) contribute to disease progression and the transition from nonwasted heart failure to cardiac cachexia.2

In addition, we have established that the ergoreflex (a peripheral reflex originating in skeletal muscle sensitive to products of muscle work) is overactive in CHF and contributes significantly to impaired exercise tolerance.3 A clear association exists between symptom severity, NYHA functional class, muscle wasting,2 and ergoreflex overactivity.3

Skeletal musculature becomes abnormal in CHF, which may contribute to exercise intolerance. Interventions specifically targeted at reversing peripheral muscle wasting such as exercise training have been shown to improve muscle function,4 reduce ergoreflex activity,1 and improve prognosis.5 Nevertheless, there has been no direct evidence of a link between abnormal muscle mass and function and the abnormal ergoreflex response seen in CHF.

In the present study, we aimed to investigate specifically whether there is a relationship between the muscle reflex activation and abnormality in the skeletal muscle mass of the limbs of patients with CHF assessed by dual-energy x-ray absorptiometry. This method can provide an accurate, noninvasive evaluation of skeletal muscle mass.6 Furthermore, we investigated whether progression toward cardiac cachexia is associated with overactive muscle reflex.

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Methods

All consecutive CHF patients between January 1999 and September 2002 referred to the outpatient clinics of the Royal Brompton Hospital of London and the Military Hospital of Wroclaw who underwent cardiopulmonary exercise testing, body composition measurement (dual-energy x-ray absorptiometry), and ergoreflex assessments and met the following criteria were considered for the study: >3-month history of CHF, clinically stable with unchanged medication for ≥2 weeks preceding the study, impaired left ventricular ejection fraction (LVEF) (LVEF ≤45% on echocardiography calculated by the Simpson method).

Among the CHF population, cardiac cachectic subjects were prospectively identified in the manner previously defined. Cachexia was deemed to be present if the subject lost >7.5% of his or her body weight unintentionally and not through removal of edema fluid. The previous normal weight of a heart failure patient is considered the average weight before the onset of heart disease (such as before the first myocardial infarction or before the diagnosis of idiopathic dilated cardiomyopathy) and not the onset of CHF. To exclude patients with intentional weight loss, a second criterion of body mass index (weight / height$^2$) of <24 kg · m$^{-2}$ was used. The weight loss amounted to 7 to 20 kg (mean, 11.2±3.4 kg or 14.6±4.3% loss of weight) in the preceding 9 months to 11 years (ie, 4.6±2.8 kg · y$^{-1}$).

Exclusion criteria included significant pulmonary disease and musculoskeletal disorders, an episode of acute coronary syndrome, or coronary revascularization within 3 months preceding the study. A group of age-matched normal control subjects was enrolled from hospital staff and relatives of the patients. All study subjects were white; none was actively exercise training. Subjects and physicians were blinded to the results of the tests.

Patients with pulmonary or peripheral edema (as evaluated during physical examination) were excluded because fluid retention would interfere with measurement of body composition. None of the study subjects was actively exercise trained. The local ethics committees approved the study protocol, and all subjects gave written informed consent. The study was conducted in accordance with the Helsinki Declaration. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Body Composition

Body composition was measured by dual-energy x-ray absorptiometry using a pencil-beam total body scanner (Lunar DPX total body scanner, Lunar Radiation Co, Madison, Wis). A series of transverse scans was made from head to toe at 1-cm intervals. This methodology provides data on fat tissue, bone tissue, and fat-free lean tissue.

Exercise Protocols

Patients underwent treadmill testing (modified Bruce protocol, Amis 2000, Odense, Denmark), encouraged to exercise until exhaustion. Peak oxygen consumption was defined as the highest $V_O_2$ observed during exercise (instantaneous breath-by-breath method) averaged for a 30-second recording during the last minute (mL · min$^{-1}$ · kg$^{-1}$ body weight). Age-, weight-, and sex-adjusted predicted peak $V_O_2$ was determined according to the equation of Wassermann, and percent predicted peak $V_O_2$ was calculated. The slope of the relation between ventilation and carbon dioxide production ($V_e/V_CO_2$ slope) was calculated.

Ergoreflex Test

To evaluate the ergoreflex in either the arm or leg, the postexercise regional circulatory occlusion (PE-RCO) method was used. Details of the methodology are given elsewhere. Briefly, it includes 2 exercise bouts performed in random order: (1) a control handgrip exercise using repetitive finger flexion by pulling a lever of a dynamometer at 50% of the predetermined maximal contraction (by the nondominant arm at the rate of 40 pulls per minute until exhaustion) for arm ergoreflex or a 6-minute session of cycling on a cycle ergometer (ERGY 601, Bosch, Germany) at a load that produced 60% to 70% of the previously determined peak $V_O_2$ for leg ergoreflex for 5 minutes, or (2) the same protocol followed by, from 10 seconds before the end of exercise, 3 minutes of circulatory (venous and arterial) occlusion by inflation of forearm tourniquet (arm reflex) or of bilateral upper thigh tourniquets (leg reflex) to 30 mm Hg above systolic pressure (PE-RCO). Thus, the contribution of the muscle ergoreceptor was evaluated by trapping the metabolites in the exercising muscle after exercise. During assessment of the ergoreceptor activity, subjects breathed air through a mouthpiece with a nose clip in place, and continuous online ventilation and expiratory gas data were collected (mass spectrometer), together with blood pressure results.

The contributions made specifically by the ergoreflex to the ventilatory and blood pressure responses to exercise were derived by calculating the absolute difference between the 3-minute PE-RCO and the 3-minute recovery without PE-RCO and the percentage of the exercise response maintained by PE-RCO.$^{1,3}$

Statistical Analysis

Data are given as mean±SD. Unpaired Student $t$ test and ANOVA were used when appropriate. When ANOVA showed a significant difference, Fisher post-hoc test was applied. Univariate regression analyses was used to assess the impact of muscle ergoreflex on the ventilatory response to exercise (expressed in percentage terms), to assess the impact of clinical and exercise variables on body composition variables in healthy control subjects and CHF patients, and to differentiate cachectic and noncachectic subpopulations. Multivariate analysis was performed to assess factors independently associated with ergoreceptor activity. A value of $P<0.01$ was considered significant.

Results

CHF Populations and Healthy Control Subjects

Within the study period, we identified 107 patients who met the study criteria and were entered into the metabolic study program (58 patients in London, 49 patients in Wroclaw) and 24 healthy control subjects. The 2 populations were matched for age, gender, and body mass index, but the patients had dilated left ventricle, lower LVEF and peak $V_O_2$, and increased $V_e/V_CO_2$ slope compared with the control subjects (Table 1).

Overactive ergoreflex responses were seen in the CHF population in both the arm and leg (Table 2). CHF patients also showed reduced muscle mass, reflected by lower lean tissue and reduced limb lean tissues, and no significant reductions in fat tissues ($P=0.05$) and mineral content ($P>0.05$) (Table 3).

Cachectic and Noncachectic Populations

Among the 107 CHF patients, we identified 25 cachectic and 82 noncachectic patients. The 2 subpopulations were matched for age, gender, and drug therapy, but the cachectic subjects had lower body mass and peak $V_O_2$, and increased $V_e/V_CO_2$ slope (Table 1).

The differences between the CHF patients and control subjects remained significant when the single subpopulations of cachectic and noncachectic patients were considered (Table 1).

Ergoreflex Activity

Overactive ergoreflex responses were seen in both cachectic and noncachectic subpopulations, except for the ergoreflex component of blood pressure response to leg exercise in noncachectic patients. The cachectic patients also showed greater ergoreflex activity compared with noncachectic subjects (Table 2).
Body Composition

Both cachectic and noncachectic patients were different from control subjects, but the cachectic patients also showed reduced total fat tissues and mineral content in the leg. The cachectic and noncachectic subpopulations were different from each other because the former showed lower total lean tissue and reduced upper and lower limb lean tissues, as well as reduced fat tissues and mineral content in the leg (Table 3).

Correlation Between Ergoreflex Sensitivity and Indexes of Body Composition

In the entire CHF population, reduced total body lean tissue was associated with ergoreflex overactivity (arm reflex: \( r = -0.41, P < 0.0005 \); leg reflex: \( r = -0.37, P < 0.0005 \)). Significant correlation was evident when the ergoreflex activity was measured in each limb and the lean tissue in the respective limb (arm: \( r = -0.36, P < 0.0005 \); leg: \( r = -0.45, P < 0.0005 \)) (Figure 1). The reflex assessed in the upper limb correlated with the lean tissue in the lower limb (\( r = -0.30, P < 0.005 \)).

In cachectic patients, the ergoreflex response to arm exercise was strongly inversely correlated with arm lean (\( r = -0.65 \)), leg lean (\( r = -0.64 \)), and total lean (\( r = -0.61 \)) tissues. Similarly, the ergoreflex to leg exercise was strongly inversely correlated with leg lean (\( r = -0.69 \)), arm lean (\( r = -0.66 \)), and total lean (\( r = -0.65 \)) tissues (\( P < 0.001 \) for all). In the noncachectic patients, correlation was evident only between ergoreflex response to arm exercise and total lean (\( r = -0.30 \)) leg lean (\( r = -0.35 \)) tissues (\( P < 0.01 \) for all). There was no significant correlation in the control subjects (\( r = 0.02 \) to 0.15, \( P = NS \)).

Correlations Between Clinical Indexes and Ergoreflex Sensitivity

Ergoreflex contribution to both arm and leg exercises correlated with peak \( V_O_2 \) (arm: \( r = -0.47 \); leg: \( r = -0.40 \); \( P < 0.0005 \)), NYHA
class (arm, $r=0.45$; leg, $r=0.46$; $P<0.0005$), $V_\text{e}/V_{\text{CO}_2}$ slope (arm, $r=0.31$; leg, $r=0.40$; $P>0.0005$), and LVEF (but only for leg exercise, $r=0.33$, $P<0.005$).

In the cachectic subpopulation, the correlations remained significant between ergoreflex activation to both arm and leg exercise and peak $V_{O_2}$ ($r=-0.55$, $P<0.005$ for both comparisons), LVEF (arm: $r=-0.35$, $P<0.01$; leg: $r=-0.37$, $P=0.01$), $V_\text{e}/V_{\text{CO}_2}$ slope (arm: $r=0.55$, $P<0.005$; leg: $r=0.42$, $P<0.005$), and NYHA class ($r=-0.45$, $P<0.005$ for both comparison) (Figure 2). In contrast, in the noncachectic subpopulation, the correlation was significant only between ergoreflex and peak $V_{O_2}$ ($r=-0.35$, $P<0.005$ for both arm and leg exercise comparisons). There was no significant correlation in the control subjects ($r=0.01$ to 0.21, $P=NS$).

**Multivariate Analysis**

In the total CHF population and the cachectic subpopulation, total muscle mass correlated with peak $V_{O_2}$ ($r=0.46$, $P<0.0005$; $r=0.51$, $P<0.0005$), $V_\text{e}/V_{\text{CO}_2}$ slope ($r=-0.27$, $P<0.01$; $r=-0.55$, $P<0.0005$), and NYHA class ($r=-0.37$, $P<0.0005$; $r=-0.55$, $P<0.005$), whereas for the noncachectic subpopulation, total muscle mass also correlated only with peak $V_{O_2}$ ($r=0.30$, $P<0.01$).

Multivariate analyses were performed in the entire CHF population using cachectic versus noncachectic as a covariate to evaluate the relationship between ergoreflex activation and total lean tissue with clinical variables (NYHA class, peak $V_{O_2}$, $V_\text{e}/V_{\text{CO}_2}$ slope). This analysis showed no significance relationship between ergoreflex activity and total lean tissue, having corrected this for cachexia ($P=NS$).

To determine whether the relationships between the ergoreflex contribution to the ventilatory response to leg and arm exercises and total lean muscle mass were a result of a confounding effect of these clinical variables, we performed a series of multiple regression analyses. In the cachectic subpopulation, this relationship was independent of all variables considered (Table 4). In the noncachectic subpopulation, there was no significant relationship between ergoreflex activation and the clinical variables ($P=NS$).

**Discussion**

Three are 3 important and novel findings of this study. First, this study provides for the first time clear evidence of a significant association between peripheral muscle wasting and enhanced muscle reflex.

Second, the strong relationship between more advanced cardiac cachexia and muscle reflex overactivity is consistent with the concept that syndrome progression is related to peripheral maladaptive changes in the muscles. The noncachectic CHF population has intermediate characteristics between cachectic patients and normal control subjects, in keeping with the concept of cachexia being a marker of progression within the heart failure syndrome. Clinical deterioration is accompanied by peripheral muscle abnormalities and altered autonomic reflex control. The loss of peripheral muscle mass is associated with ergoreflex overactivity and exercise limitation in CHF, particularly in more severe status. The multivariate analysis suggested cachectic status as the major driver of the relationship between ergoreflex and body mass.
Third, the ergoreflex assessment in 1 limb (arm) is associated with lean tissue loss measured in a different limb (leg), consistent with a systemic activation of the muscle reflex system in CHF.

Taken together, these findings support the “skeletal muscle hypothesis” of the origin of symptoms in CHF.

**Skeletal Muscle Hypothesis**

Heart failure causes exercise-limiting changes in every step of the oxygen transport system, from the center (the heart, lung, central neural control) to the periphery (circulation, neurohumoral status, reflexes, autonomic nervous systems, and muscle metabolism). A key question among heart failure specialists has been whether these maladaptations were mechanistically important or merely “epiphenomena,” ie, a summation of “bad luck” associated with poor cardiac function and the resultant physical inactivity.12

The past 20 years have witnessed the development of a controversial idea: the muscle hypothesis. Damage to the heart and disturbance of central hemodynamics activate compensatory mechanisms, including neurohumoral and sympathetic activation, with consequent peripheral vasoconstriction and tachycardia.1 On exercise, an inappropriate robust sympathetic activation further limits exercise tolerance by evoking larger- and faster-than-normal increases in peripheral adrenergic responses already increased at baseline. The changes may be beneficial at the beginning to maintain adequate arterial pressure and circulation to the more vital territories, particularly during effort, but in the longer term, they induce modifications in organ systems of the body, including skeletal muscle structure and metabolism. These initially adaptive modifications ultimately contribute to a downward spiral in many elements of the oxygen transport system. One of the negative consequences of this excessive sympathetic response is the further sympathetic restraint of blood flow to the active skeletal muscles and even more skeletal muscle hypoperfusion. Together with the structural and biochemical changes in the muscle noted below, this further restraint of blood flow would limit exercise tolerance more, leading to the cardinal symptoms of CHF such as fatigue and dyspnea.

Objective abnormalities are present in the muscle of CHF, with a predominance of glycolytic over oxidative metabolism and ultrastructural modifications in muscle composition (fiber type, mitochondrial and endothelial function).13 Consequently, early acidosis and depletion of high-energy compounds develop during exercise, which in turn trigger other compensatory mechanisms that would, in normal individuals,
maintain skeletal muscle performance. These mechanisms include stimulation of various afferents, including both central and peripheral chemoreceptors and skeletal muscle ergoreceptors, which communicate to the brain stem information about the level of skeletal muscle work.

Normally, autonomic outflow during exercise is governed by the interplay between so-called central command and afferent information from the exercising muscle. It plays a key role in the blood pressure, ventilation, and perhaps renal sympathetic nerve responses to exercise to be proportional to the muscular effort associated with the exercise. Once activated, they directly stimulate sympathetic drive, ventilation, and vasoconstriction in the nonexercising limbs, the combined effect of which has the beneficial result of diverting more well-oxygenated blood to the working skeletal muscles. However, long-term activation of the ergoreflex system may be harmful because it maintains an abnormal neurohormonal and vasoconstrictor milieu that favors progression of the disease.

Muscle Reflex in Heart Failure

Our group has explored in particular the role of muscle metaboreflex in human heart failure, reporting an overactivation of this reflex in determining exaggerated ventilatory, hemodynamic, and vasoconstrictive drives. A correlation between sympathetic activation and exercise intolerance, which would be consistent with a role for sympathoexcitatory neural reflexes in symptom generation in CHF, also has been demonstrated by others. Comitant overactivation of peripheral and central chemoreflexes has been shown, in keeping with generalized alteration in muscle metabolism. A reversal of hyperactive metaboreflex during exercise obtained by buffering the increased acidotic response in autonomic changes has further supported the contribution of muscle catabolism in symptom generation of fatigue and dyspnea. Others also have provided important support for the hypothesis of a peripheral origin of symptoms in CHF. After myocardial infarction in rats, an overactivity of finely myelinated group III afferents is triggered by mechanical stimuli. The stimulation starts with the beginning of the contraction and contributes to the pressure response. These sensitized muscle mechanoreceptors also may contribute to the augmented renal vasoconstrictions observed during exercise in patients with CHF. Therefore, even mild physical activity would lead a state of almost constant activation of the renin-angiotensin system and the related renal responses. Smith et al have extended this concept by demonstrating that selective abolition of exaggerated mechanoreflex was associated with more physiological hemodynamic and chronotropic responses to exercise.

There is a degree of overlap between the 2 “mechano” and “metabo” receptors in terms of anatomical differentiation and the physiological triggers, and recent observations challenge the classic description of these receptors as distinct entities. Accordingly, we prefer using the term “ergo” receptors, which include both types of afferents.

In CHF, other alterations in the reflex controlling systems, which are not mutually exclusive, contribute to dyspnea. An inappropriately low stimulation of arterial baroreceptors with a consequent lack of inhibition of the discharge of the muscle metaboreflex and carotid chemoreflex and increased renal vasoconstriction and angiotensin II release can also be considered. An increased sympathetic discharge of the carotid

Afferent information is carried by the ergoreceptors, intramuscular fibers sensitive to the muscle work. They are grossly differentiated in metaboreceptors and mechanoreceptors. The mechanoreceptors, finely myelinated group III afferents, respond mainly to mechanical stimuli; the metaboreceptors, unmyelinated group IV afferents, are sensitive to metabolites, especially acidosis, but also prostaglandins and bradykinins. Once activated, they directly stimulate sympathetic drive, ventilation, and vasoconstriction in the nonexercising limbs, the combined effect of which has the beneficial result of diverting more well-oxygenated blood to the working skeletal muscles. However, long-term activation of the ergoreflex system may be harmful because it maintains an abnormal neurohormonal and vasoconstrictor milieu that favors progression of the disease.
chemoreflex also may be secondary to a poor carotid chemoreceptor blood flow from reduced cardiac output. We have documented significant correlations between ergoreflexes, peripheral chemoreflex, and carotid baroreflex, supporting the concomitant alterations in controlling mechanisms in CHF.

β-Blockers, taken by most of our patient population (83%), are a well-recognized, effective therapy on survival in CHF but have controversial effects on exercise tolerance. There is no information on their effect on the muscle reflex. However, β-blockers may well have affected ergoreflex overactivation by reducing sympathetic activation. In our study, the limited size of the subgroup free of β-blocker use did not allow us to derive any conclusions.

A potential weakness of this study is that only a single independent variable of skeletal muscle viability, i.e., muscle mass, was assessed, although it is considered the most meaningful index, being less subject to bias from measure-

Figure 2. Correlations between lean muscle mass and ergoreflex sensitivity to arm (left) and leg (right) exercises in cachectic CHF patients.
considered variables.

state. We adopted a relatively wide definition of cardiac cachexia by documented weight loss measured in a nonedematous state. We considered 21 CHF patients in whom leg muscle strength data were available. A significant inverse correlation between the ergoreflex component and the ventilatory response to leg exercise and muscle strength \( (r=-0.51, P<0.001) \) was found, supporting our findings.

The problems of research into cardiac cachexia start with the definition. The development of a state of cachexia in CHF is a dynamic process that can be diagnosed only a posteriori by documented weight loss measured in a nonedematous state. We adopted a relatively wide definition of cardiac cachexia. Our cachectic CHF patients lost weight in a time span ranging from 9 months to 11 years, with no consideration given to the duration of heart failure, which was shorter. The duration of the syndrome was similar in the cachectic and noncachectic subpopulations \( (4.4 \pm 1.9 \text{ versus } 5.3 \pm 1.6 \text{ years, respectively; } P=\text{NS}) \). The relationship between ergoreflex activation was independent of the syndrome length \( (\text{ventilatory component to arm exercise: } r=0.15, P=\text{NS}; \text{ventilatory component to leg exercise: } r=0.19, P=\text{NS}) \). Consequently, the relationship between ergoreflex and muscle mass also was not a function of the duration of CHF. When the variable CHF duration was considered, the significant relationship between ergoreflex component and exercise was maintained (all CHF patients: standardized coefficient, \(-0.30, P<0.005\); cachectic patients: standardized coefficient, \(-0.61, P<0.005\)).

In conclusion, in some way, the downward spiral of dysregulation in exercising skeletal muscle suggested by the muscle hypothesis is similar to the larger picture of other vicious cycles in heart failure in which the physiological responses initially appear adaptive but turn maladaptive over time.

In an era of aggressive interventions in clinical cardiology and an ongoing focus on the genetic basis of cardiovascular disease, we must keep in mind the importance of the integrated function of the body systems governed by complex regulatory mechanisms and coordinated in turn by the autonomic nervous system. When this coordination is lost, exercise tolerance is perhaps the earliest harbinger of the many problems that are sure to follow. A healthy lifestyle, including regular physical training, may help to break this vicious cycle and promote a successful primary and secondary prevention.

## Disclosures

None.

## References

Clinical Perspective

Patients with chronic heart failure are characteristically limited by symptoms of breathlessness and fatigue, the pathophysiology of which remains unclear. One proposal, the muscle hypothesis, is that peripheral skeletal muscle, which becomes abnormal in heart failure, is the source of a neural signal (ie, the ergoreflex), which disrupts normal patterns of cardiorespiratory control. The neurohormonal activation and an altered balance between catabolism and anabolism (in favor of catabolism) contribute to disease progression and the transition from nonwasted heart failure to cardiac cachexia. The relationship between skeletal muscle mass and the activation of the ergoreflex in heart failure patients is established here in a controlled prospective study. Ergoreflex overactivity to the ventilatory and blood pressure responses to exercise in a patient population is associated with depleted peripheral muscle mass. The ergoreflex was particularly enhanced in the cachectic subjects accompanied by more marked muscle mass depletion, supporting its contribution to the progression of the syndrome of heart failure.
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