Neurophysiological Assessment of Skeletal Muscle Fatigue in Patients With Congestive Heart Failure

John R. Minotti, MD; Prem Pillay, MD; Linda Chang; Lauren Wells, MS; and Barry M. Massie, MD

Background. Recent research has demonstrated that patients with congestive heart failure (CHF) exhibit significant functional impairment of skeletal muscle and that these changes may be important determinants of exercise capacity. Although muscle strength may be mildly reduced, the most significant abnormality is markedly enhanced muscle fatigue. The goal of the present study is to determine whether accelerated fatigue is caused by impaired muscle activation, as a result of inadequate central motor drive or neuromuscular transmission, or by a change in the muscle itself.

Methods and Results. The study population consisted of nine patients with New York Heart Association class I–III CHF and eight sedentary, age- and sex-matched control subjects. Maximal voluntary contraction force of the foot dorsiflexors (primarily the tibialis anterior) was quantified as a measure of muscle strength, isometric endurance was quantified by the time required for force to decline to 60% of maximal during a sustained maximal contraction, and dynamic endurance was defined as the number of maximal contractions required for force to decline to 60% of maximal under a protocol of six repetitions per minute with an incremental duty cycle. The degree of central motor drive failure was quantified by the degree of force augmentation produced by a superimposed tetanic stimulus delivered to the peroneal nerve during the initial maximal voluntary contraction and at the time when force during the sustained isometric contraction declined to 60% of maximal. Neuromuscular junction transmission was examined by quantifying the amplitude of the compound muscle action potential (M wave) in response to a single nerve stimulus during fatiguing exercise. Muscle strength was relatively preserved in the CHF patients versus the control subjects (93±41 versus 105±34 lb; p=NS), but isometric endurance (time to decline to 60%, 34±15 versus 54±19 seconds; p<0.02) and dynamic endurance (number of repetitions before decline to 60%, 30±6 versus 43±7 contractions; p<0.001) were both impaired. Tetanic nerve stimulation increased force by similar degrees in the two groups, and the amplitude of the M wave did not decline in either group during exercise.

Conclusions. These findings indicate that enhanced muscle fatigue in patients with CHF is not caused by impaired central motor drive or an abnormality of neuromuscular junction transmission but rather by an abnormality in the muscle itself. (Circulation 1992;86:903–908)

KEY WORDS • muscle activation • fatigue, central • transmission, neuromuscular • fatigue, muscle

Exercise intolerance and fatigue are the primary symptoms in patients with mild and moderate congestive heart failure (CHF).1 Numerous studies, however, have demonstrated a dissociation between the severity of these symptoms and measurements of cardiac function.2,3 This discordance may be explained by changes in skeletal muscle function, which may play a role in systemic exercise limitation. We4 and others5,6 have reported that the function of the knee extensors is abnormal in patients with CHF. Specifically, we demonstrated that although maximal isometric strength of the knee extensors is relatively preserved, both static and dynamic endurance are markedly impaired. Impaired endurance of both the knee extensors4 and the adductor pollicis6 in CHF patients was also observed during ischemic exercise. A significant correlation between the degree of muscle dysfunction and systemic exercise capacity measured by cycle ergometry was apparent in patients with CHF.4,5,6 These findings suggest that impaired muscle endurance is, in part, independent of limb blood flow and may play a role in determining systemic exercise capacity in these patients.

The force produced by muscle contractions involves a cascade of events, any of which may fail and impair function. The potential sites for failure are within the
central nervous system, in the neuromuscular junction, and in the muscle itself.7 Although abnormalities in metabolism,8,9 biochemistry,5,10 morphology,5,10,11 and blood flow,12-15 have been observed in skeletal muscle of CHF patients, the mechanism of accelerated muscle fatigue has not been systematically examined. Factors operating outside the muscle, such as abnormal muscle activation, have not received consideration as a cause of accelerated fatigue in these patients.

Therefore, the present study was conducted to determine whether muscle activation is abnormal in CHF patients and if so, whether it contributes to accelerated fatigue. Normal muscle activation depends on adequate central motor drive and neuromuscular transmission. We assessed central motor drive by determining the degree of force augmentation elicited by a superimposed tetanic stimulus to the peroneal nerve during maximal voluntary contraction of the foot dorsiflexors7 and neuromuscular junction transmission7,16-19 by quantifying the compound muscle action potential (M wave) that was evoked by single nerve stimuli during fatiguing exercise in CHF patients and in sedentary age-matched control subjects.

**Methods**

**Study Subjects**

Nine men with a history of New York Heart Association (NYHA) class I–III chronic CHF of at least 6 months’ duration were recruited from the Veterans Affairs Medical Center in San Francisco. Clinical information concerning these patients is given in Table 1. The diagnosis of CHF was based on a history of dyspnea on exertion, fatigue, or fluid retention, along with left ventricular dysfunction confirmed by a radionuclide ejection fraction of <40% (range, 8–37%). Five patients had ischemic cardiomyopathy, and four had primary myocardial disease. Patients were excluded if they had had a myocardial infarction within 6 months or if systemic exercise was limited by symptoms other than fatigue or dyspnea. Other exclusion criteria were initiation of therapy with angiotensin converting enzyme inhibitors, long-acting nitrates, diuretics, or digitalis within 3 months; hemodynamically significant valvular disease; chronic obstructive pulmonary disease; neurological disease; arthritis; or other mechanical limitations to exercise. All patients were free of overt peripheral vascular disease as indicated by the presence of normal peripheral pulses and lack of symptoms.

Eight age-matched sedentary male control subjects (mean age of control subjects, 59±9 years versus 61±10 years for the patients with CHF; p=NS) were recruited from patients and employees at the Veterans Affairs Medical Center in San Francisco. These subjects had no history of heart disease and no cardiac, peripheral vascular, or muscular abnormalities on physical examination. The protocol was approved by the Committee on Human Research at the University of California San Francisco, and written informed consent was obtained from all participants.

**Protocol**

Two exercise protocols involving the foot dorsiflexors were performed in an identical sequence in all subjects (as illustrated in Figure 1) to assess muscle strength and endurance, central motor drive, and neuromuscular junction transmission during exercise. These were conducted with the subjects in a sitting position with both legs extended on a table. The dominant leg was secured into a specially constructed device with the foot anchored to a pedal fixed at an angle of 115°. A force transducer was fastened to the foot pedal, and force was recorded and displayed continuously on a Gould physiological recorder. A 2-cm patch electrode was placed over the proximal peroneal nerve for stimulation, and a recording electrode was affixed to the muscle. A grounded electrode was taped to the skin between the recording and stimulating electrodes. The nerve was stimulated with a Mysro stimulator. For single-twitch stimulations, a pulse length of 50 μsec at 200 V was used. For tetanic stimuli, a train of 12 stimuli was delivered at a pulse length of 50 μsec at 200 V in 240 msec.

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**TABLE 1. Clinical Characteristics of CHF Patients**

<table>
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<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Meds</th>
<th>Peak VO₂ (ml·kg⁻¹·min⁻¹)</th>
<th>Ejection fraction%</th>
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CHF, congestive heart failure; D, digoxin; F, furosemide; I, isosorbide dinitrate; H, hydralazine; C, captopril.

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**FIGURE 1. Schematic of exercise protocols used in this study. In the first protocol (panel A), the sustained exercise protocol, three brief (3-second) maximal voluntary contractions (MVC) were performed to determine maximal strength. Tetanic nerve stimulation was performed during the second MVC. After 5 minutes’ rest, the subjects maintained a maximal voluntary contraction until force declined to 60% of maximal, at which point a second tetanic nerve stimulation was delivered to the peroneal nerve. Panel B: Schematic of intermittent protocol that followed the sustained protocol in all subjects. This exercise protocol was performed in 2-minute progressive work loads. Twitch nerve stimulation was performed after the sixth contraction of each work load.**
The first protocol involved sustained isometric exercise. The subjects performed three brief (3-second duration) maximal voluntary contractions (MVCs), each separated by 1 minute of rest. During the second of these three MVCs, a tetanic stimulus was delivered to the peroneal nerve. Five minutes of rest followed the third MVC; then the subjects maintained a maximal voluntary contraction until force declined to 60% of the previously determined MVC, at which time another tetanic stimulus was delivered to the peroneal nerve (Figure 2).

Maximal voluntary strength (the maximal force produced by the MVCs) and isometric endurance (the time that was required for the sustained isometric contraction force to decline to 60% of maximal) were compared in the patients and control subjects. The percentage that maximal voluntary force was augmented by tetanic nerve stimulation either during the brief MVC or at the point of 60% decline in force quantified the degree of central motor drive failure.

Sustained maximal contractions have significant advantages in examining fatigue, because they are accompanied by complete motor unit recruitment. Contractions sustained at the level of force production used in this study severely restrict blood flow, however, and are not representative of usual activity. In addition, sustained contractions may interfere with neuromuscular junction transmission caused by ischemia. To minimize the effect of reduced blood flow on the assessment of neuromuscular junction transmission, another protocol involving intermittent foot dorsiflexion was used. In this second protocol, patients performed intermittent maximal isometric contractions with a 10-second duty cycle. During the first 2 minutes of exercise, contraction was maintained for 2 seconds, followed by 8 seconds of rest. To increase the work load, every 2 minutes the contraction time was extended by 2 seconds while the 10-second duty cycle was maintained. This duty cycle would allow resumption of blood flow during the relaxation period. During each 2-minute workload, after the sixth contraction (at the end of the first minute of exercise), a brief single-twitch stimulus was delivered to the peroneal nerve, and the compound muscle action potential (M wave) was recorded. Fatigue was quantified as the number of contractions required for force to decline to 60% of maximal force.

**Maximal Exercise Testing**

To determine the functional class of the CHF patients and the conditioning status of the control subjects, cycle ergometry with respiratory gas analysis was performed. An electronically braked cycle ergometer (Quinton) that maintained a constant work load at pedal frequencies of 40–110 rpm was used. Testing was performed in an air-conditioned laboratory at an ambient temperature of 22–24°C and a humidity of 30–40%. Before exercise, the subject rested upright on the cycle for 5 minutes. Exercise was initially performed unloaded for 2 minutes. The load was then increased to 200 kg · m/min for 2 minutes and then by 100 kg · m/min every 2 minutes until exhaustion. Exhaustion was defined as the inability to maintain a pedal frequency of greater than 40 rpm. Standard verbal encouragement was used for all subjects.

Peak oxygen consumption was measured as an index of systemic exercise performance in both the CHF patients and control subjects. For these measurements, expired gases were collected into a mixing chamber from a mouthpiece, and VO2 and VCO2 were measured at 15-second intervals throughout exercise with a metabolic cart (Sensormedics). Peak systemic oxygen consumption was defined as the highest oxygen consumption reached during exercise.

**Statistical Methods**

Comparisons between the measurements of muscle function and neurophysiological assessments in the CHF patients and the control subjects were made by Student’s paired and unpaired t tests. A value of *p* < 0.05 was taken as the threshold of statistical significance. All values were expressed as mean ± SD.

**Results**

**Subject Population**

The clinical characteristics of our CHF subjects are shown in Table 1. The severity of heart failure symptoms ranged from NYHA class I to class III. The control subjects were age-matched sedentary males, and none were actively trained or had a peak oxygen consumption greater than normal for their age. Although the control subjects had a somewhat higher peak oxygen consumption than the patients (18 ± 0.7 versus 25 ± 5 ml · kg⁻¹ · min⁻¹; *p* = 0.04), their relatively low oxygen consumption confirms their sedentary status.

**Exercise Protocol**

The exercise protocol was well tolerated by all subjects without complications. Both the patients and control subjects attributed the decline in force during exercise to local muscular fatigue. No subject attributed the decline in force to nonmuscular complaints, such as shortness of breath, chest pain, or joint pain.

Isometric strength was defined as the highest MVC force and was somewhat, but not significantly, lower in the CHF patients than in control subjects (93 ± 41 versus 105 ± 34 lb; *p* = NS). Although the sustained isometric exercise protocols were terminated at the same percentage of maximal force (57 ± 5 versus 54 ± 5%; *p* = NS) in
the CHF patients and control subjects, the CHF patients fatigued more rapidly, as reflected by the shorter static endurance time (34±15 versus 54±19 seconds; p<0.02) (Table 2). In the intermittent exercise protocol, six of the control subjects were able to complete all four work loads of exercise (48 contractions) before force declined below the 60% threshold. However, only two of the CHF patients completed all work loads. In this protocol, the force generated fell faster and the number of contractions required for force to decline to 60% of maximal was less in the CHF patients than in control subjects (30±6 versus 43±7 contractions; p<0.001) (Figure 3 and Table 2).

**Nerve Stimulation**

During the initial MVC, maximal voluntary force was augmented minimally but significantly in both groups by superimposed tetanic stimulation, from 93±41 to 99±39 lb (p<0.02) in the CHF patients and from 105±34 to 110±34 lb (p<0.05) in the control subjects. There was no difference, however, in the degree of force augmentation between the two groups (Table 2). During the sustained contraction, when maximal force declined to 60% of maximal, tetanic peroneal nerve stimulation produced far greater augmentation of force in both the CHF patients (66±29 to 81±19 lb; p<0.01) and control subjects (61±12 to 83±34 lb; p<0.01); however, the degree of force augmentation was similar in both the patients and control subjects.

**Compound Muscle Action Potential**

The amplitude and area of the M wave during fatiguing exercise was not significantly different from the amplitude and area of the M wave at baseline in either the patients or the control subjects (Figure 4).

**Discussion**

The first major finding of this study is that in the tibialis anterior muscle, maximal strength is relatively preserved, although both static and dynamic endurance were markedly reduced in CHF patients. The second major finding is that muscle activation is not abnormal and, thus, is not the cause for accelerated muscle fatigue in CHF patients.

The finding that endurance of the tibialis anterior muscle is impaired is identical with our previous findings in the knee extensors, which also demonstrated that patients with CHF have a modest decrease in strength but a marked decrease in muscle endurance.
These results are particularly interesting because of the important differences between a large weight-bearing muscle group, the knee extensors, and the relatively smaller postural muscle, the tibialis anterior. It is known that non-weight-bearing muscles of the leg are less affected by disuse than the proximal muscles of the thigh.\textsuperscript{20,21} Also, as the tibialis anterior is used for locomotion,\textsuperscript{22} to further minimize differences in activity on muscle function between the CHF patients and control subjects, we specifically chose CHF patients with mild and moderate exercise intolerance and sedentary control subjects who had peak systemic oxygen consumptions only modestly greater than those of the patients. In addition, these muscles differ morphologically. The knee extensors are composed of approximately equal proportions of slow- and fast-twitch fibers\textsuperscript{23}; in contrast, the tibialis anterior is composed predominantly of slow-twitch fibers.\textsuperscript{24} The combination of our abnormal findings in the knee extensors\textsuperscript{4} and the tibialis anterior, together with similar findings reported in the adductor pollicis,\textsuperscript{6} suggests that CHF patients have a generalized abnormality of muscle that may not be solely a result of deconditioning.

As decreased endurance is the primary abnormality of muscle function in CHF patients, it is of considerable importance to determine whether fatigue is caused by abnormal muscle activation or by changes in the muscle itself. Normal muscle activation depends on adequate central motor drive and neuromuscular junction transmission. We used standard neurophysiological approaches to assess the integrity of central motor drive\textsuperscript{7} and neuromuscular transmission\textsuperscript{16,17} by use of tetanic and single-twitch nerve stimulation. Inadequate central motor drive, so-called central fatigue, will cause force to fall if the motor drive from the central nervous system is inadequate for sufficient muscle activation. In fact, researchers in our laboratory have recently demonstrated that failure of central motor drive is a major mechanism of muscle fatigue in the chronic fatigue syndrome.\textsuperscript{25}

In the present study, tetanic nerve stimulation during the initial MVC produced minimal, although significant, force augmentation, but the magnitude of force augmentation was similar in both groups. During the sustained isometric contraction, tetanic nerve stimulation produced a far greater degree of force augmentation, although the magnitude was again similar in both the patients and control subjects. We interpret these findings as showing that a component of central fatigue exists during exercise in the CHF patients and control subjects but does not account for the more rapid decline of force in the patients.

Our results do differ from previous reports\textsuperscript{16,18} in which no augmentation of force was observed by tetanic nerve stimulation during brief (\textgtrless 60 seconds) maximal voluntary contraction. Those studies, however, included younger and more active subjects than the subjects examined in the present study and examined other muscles than the tibialis anterior. Using the same muscle, stimulation protocol, and exercise device, researchers in our laboratory have found no augmentation in force in an MVC during a tetanic nerve stimulation.\textsuperscript{25} Whether older, less trained subjects or different muscle groups are more susceptible to central fatigue\textsuperscript{26} cannot be determined from this study. The comparison between CHF patients and age-matched sedentary individuals, however, indicates that central fatigue is not responsible for the accelerated muscle fatigue under these conditions.

Similarly, our results also do not support an abnormality of neuromuscular junction transmission as the cause for accelerated fatigue in CHF patients. Neither the amplitude nor the area of the M wave declined in either group during progressive, fatiguing exercise. These results are consistent with most\textsuperscript{7,16,17} although not all,\textsuperscript{27} previous studies, which have observed no decline in the M wave during relatively short fatiguing exercise protocols.

Thus, these findings indicate that the accelerated muscle fatiguability in CHF patients reflects either a primary or secondary change in the muscle itself and not reduced muscle activation. It is tempting to ascribe accelerated fatigue to impaired blood flow during exercise, as this would be consistent with the attenuated exercise cardiac output response and reduced peripheral vasodilator capacity that characterize CHF patients.\textsuperscript{3,12–15} The presence of accelerated fatiguability was demonstrated during the sustained isometric exercise, however, which maintained force at >60% of maximal, a level that severely restricts blood flow.\textsuperscript{28} This would suggest that decreased endurance in the CHF patients is in part independent of blood flow and indicates that factors other than reduced blood flow during exercise are responsible for accelerated fatigue. However, the role of chronic muscle underperfusion as a mechanism for intrinsic muscle changes that result in accelerated fatigue was not addressed by this study. The independence of endurance and exercise blood flow is also supported by previous research, which demonstrated that when blood flow was occluded, accelerated fatigue of the knee extensors\textsuperscript{4} and the adductor pollicis\textsuperscript{6} was present in CHF patients.

Muscle atrophy has recently been documented in CHF patients. If similar external work is performed with less muscle, accelerated fatigue would be expected. Since it has been shown that maximal strength is proportional to muscle size in normal subjects and CHF patients,\textsuperscript{29} the exercise protocols in this study used maximal contractions and quantified fatigue as a percentage of each individual’s maximal force to minimize the effect of muscle atrophy in the CHF patients. Also, maximal contractions recruit all muscle fibers, which, therefore, would exclude differences in the pattern of muscle recruitment in the interpretation of fatigue.

In conclusion, this study again demonstrates that CHF patients exhibit abnormalities of muscle function, manifested primarily as increased muscle fatiguability. Our results, for the first time, exclude abnormalities of central motor drive or neuromuscular junction transmission as the cause for accelerated fatigue. Therefore, it appears that accelerated muscle fatigue results from intrinsic changes in the muscle itself. Finally, as these muscle abnormalities were present in a relatively small postural muscle in subjects who remained active compared with the control subjects, and as the same abnormalities were previously observed in the knee extensors\textsuperscript{4–6} and adductor pollicis,\textsuperscript{6} we believe that this combination of findings reflects changes beyond that which can be attributed solely to disuse.
References


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