Skeletal muscle endurance and muscle metabolism in patients with chronic heart failure

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BACKGROUND: Alterations in skeletal muscle function are known to contribute to exercise intolerance in patients with chronic heart failure (CHF).

OBJECTIVES: To evaluate whether muscle isometric endurance can be objectively measured and whether it is related to skeletal muscle metabolism in CHF.

METHODS: Isometric endurance of the vastus lateralis, measured as time to fatigue (T_F), was evaluated in 25 patients with CHF (55 ± 8 years of age [mean $\pm$ SD]) and 18 healthy subjects (HS) (62 ± 6 years of age [mean $\pm$ SD]). Median frequency of surface electromyography was obtained from spectral analysis using a fast Fourier transformation. Citrate synthase (CS), 3-hydroxyacyl-CoA dehydrogenase (HADH), hexokinase (HK) and phosphofructokinase (PFK) activities were determined from the right vastus lateralis muscle.

RESULTS: T_F was lower in CHF patients than in HS (49 ± 4 s and 80 ± 7 s, respectively; $P < 0.01$). Muscle fatigue was present at the end of the endurance test in both groups (median frequency breakpoint at mid-exercise for both groups [$P < 0.05$]). CS ($P < 0.01$) and HK ($P < 0.01$) activities were lower in CHF patients than in HS, but PFK activity was higher ($P < 0.05$). T_F correlated significantly with CS ($r = 0.50$), HADH ($r = 0.42$), PFK ($r = -0.47$) and HK ($r = 0.41$) activities and the PFK/CS ratio ($r = -0.39$) when both groups were considered, and with HADH ($r = 0.47$) and PFK ($r = -0.57$) activities for the CHF group alone (all $P < 0.05$).

CONCLUSIONS: These results suggest that isometric endurance of the vastus lateralis muscle is reduced in patients with CHF and that it is related to a reduced muscle oxidative capacity.

Key Words: Heart failure; Oxidative metabolism; Skeletal muscle

Exercise intolerance is an important consequence of chronic heart failure (CHF). Many studies have demonstrated the existence of a poor relationship between central hemodynamic measurements and exercise capacity (1-4). Indeed, Franciosa et al (1,2) confirmed that left ventricular filling pressure, stroke volume, cardiac output and left ventricular ejection fraction at rest do not correlate with exercise capacity in patients with dysfunction of the left ventricle. The contribution of impaired skeletal muscle function to exercise intolerance in these patients has also been recognized (5-9). Reduced

L'endurance des muscles squelettiques et le métabolisme musculaire chez les patients atteints d'insuffisance cardiaque chronique

HISTORIQUE : On sait que les modifications à la fonction des muscles squelettiques contribuent à l'intolérance à l'exercice chez les patients atteints d'une insuffisance cardiaque chronique (ICC).

OBJECTIFS : Évaluer si l'endurance isométrique musculaire peut être mesurée objectivement et si elle est reliée au métabolisme des muscles squelettiques en présence d'ICC.

MÉTHODOLOGIE : L'endurance isométrique du muscle vaste externe, mesurée selon le temps jusqu'à la fatigue (T_F), a été évaluée chez 25 patients atteints d'ICC (55 ± 8 ans [moyenne $\pm$ ÉT]) et 18 sujets en santé (SS) (62 ± 6 ans [moyenne $\pm$ ÉT]). La fréquence médiane d'électromyographie de surface a été obtenue à l'analyse spectrale au moyen d'une transformation de Fourier rapide. L'activité de la citrate synthase (CS), de la 3-hydroxyacyl-CoA déshydrogénase (HADH), de l'hexokinase (HK) et de la phosphofructokinase (PFK) ont été déterminées à partir du muscle vaste externe droit.

RÉSULTATS : Le T_F était plus court chez les patients atteints d'ICC que chez les SS (49 ± 4 s et 80 ± 7 s, respectivement; $P < 0,01$). La fatigue musculaire est apparue à la fin du test d'effort au sein des deux groupes (point de rupture dans la courbe de fréquence médiane à mi-chemin de l'exercice dans les deux groupes [$P < 0,05$]). L'activité de la CS ($P < 0,01$) et de la HK ($P < 0,01$) était plus basse chez les patients atteints d'ICC que chez les SS, mais l'activité de la PFK était plus élevée ($P < 0,05$). Le T_F était corrélé de manière significative à l'activité de la CS ($r = 0,50$), de l'HADH ($r = 0,42$), de la PFK ($r = -0,47$) et de la HK ($r = 0,41$) ainsi qu'au ratio PFK : CS ($r = -0,39$) lorsque les deux groupes étaient évalués, et à l'activité de l'HADH ($r = 0,47$) et de la PFK ($r = -0,57$) lorsque seul le groupe d'ICC (tous $P < 0,05$) était évalué.

CONCLUSIONS : D'après ces résultats, l'endurance isométrique du muscle vaste externe est réduite chez les patients atteints d'ICC et est reliée à une diminution de la capacité oxydative du muscle.

skeletal muscle oxidative capacity is often quoted as being among the peripheral factors that may be related to the exercise intolerance in CHF. The reduced activity of citrate synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HADH) (10) without alteration in glycolytic enzyme activity (11) suggests an increased use of the glycolytic metabolism leading to intramuscular acidosis and muscle fatigue (8).

Consequently, the need for an objective and noninvasive way to quantify muscle fatigue has emerged. Surface electromyography (sEMG) is useful to identify skeletal muscle

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fatigue and can be used to assess neuromuscular fatigue during dynamic muscle contraction (12,13). The signal acquired during an isometric contraction is modulated by several parameters, such as the firing rate of the recruited motor units and the shape and number of the motor-unit action potentials. Furthermore, several parameters can be derived from sEMG to help identify the presence of muscle fatigue. The root-mean-square and mean integrated rectified values, median frequencies (MDFs), mean frequencies and conduction velocity are the principal measurements derived from a spectral analysis of the sEMG signal (12,14,15). More specifically, the MDF pattern recorded during an isometric constant-force contraction has been recognized as an index of localized muscle fatigue (16). A fall in the frequency elements of the sEMG signal occurring during a fatiguing contraction is seen in conjunction with the development of fatigue (17). The MDF is considered to be the best reflection of this downward shift toward low frequencies (18). As well, Merletti et al (16) reported that MDF of the sEMG signal was influenced by ischemic conditions in the muscle, conditions found in an isometric contraction above 60% of maximal voluntary contraction (MVC) (19).

We thus hypothesized the following: that time to fatigue (T_F) during isometric contraction, if corroborated by the sEMG MDF signal, is an objective and handy tool to measure muscle endurance; that skeletal muscle endurance of the vastus lateralis is reduced in patients with CHF compared with healthy subjects (HS); and that this reduction is related to the muscle oxidative metabolism.

METHODS

Subjects

Twenty-five patients (20 men and five women) with idiopathic or ischemic CHF were recruited to participate in the study. The diagnosis of CHF was based on the combination of exercise intolerance (New York Heart Association functional class II or higher) and objective evidence of impaired left ventricular systolic function on echocardiography or radionuclide ventriculography (left ventricular ejection fraction less than 40%). Patients with viral cardiomyopathy were excluded. The control group included 18 nonsmoking HS (15 men and three women) who were recruited from the staff at the Hôpital Laval (Québec). None of the HS were involved in regular exercise training. Subjects suffering from documented myopathy or diabetes were excluded. All patients had to be clinically stable for eight weeks before testing. In regards to the regulation for experiments involving humans, the procedures followed were in accordance with the Helsinki declaration of 1975 and the ethical standards of the Hôpital Laval.

Evaluations

Exercise testing: All subjects performed a symptom-limited progressive exercise test (Quinton Corival 400, A-H Robins, USA). After 5 min of rest, patients underwent a progressive and symptom-limited stepwise exercise test while breathing room air (Quinton Q-plex, A-H Robins, USA). Each exercise step lasted 1 min, and increments of 10 and 20 watts were used in patients with CHF and HS, respectively. Peak oxygen consumption in relative values (mL/kg/min) was used as the index of peak exercise capacity. **Peripheral muscle function:** Isometric strength (MVC) and endurance of the right quadriceps muscle were first evaluated. Subjects were securely seated on an exercising chair (CHFStar, Henley Healthcare Belton, USA) and were asked to perform a maximal isometric 120° leg extension against a strain gauge with

their right leg. MVC was recorded at the ankle level with a high-precision 3 kN load cell, whose signal was amplified via a high-gain strain gauge amplifier interfaced to a Biopac MP100 board (Biopac Systems, USA). Measurements were continuously displayed and recorded (AcqKnowledge software, Biopac Systems, USA). Following three trials at 5 min intervals, the best MVC was recorded. Subsequently, after a 5 min rest, the subjects had to maintain, to exhaustion, a tension corresponding to 60% of their MVC, as previously described (13). Subjects received verbal encouragements to maintain contraction as long as possible. The output from the strain gauge amplifier was simultaneously displayed on the computer monitor to provide immediate feedback to subjects to maintain a tension corresponding to the selected target of percentage MVC.

sEMG analysis

Skin preparation and electrode placement: The sEMG readings were recorded from the vastus lateralis muscle using preamplified radio-translucent silver/silver chloride surface electrodes (Quinton Quick-prep Dx, AH Robins, USA) that were 15 mm in diameter using a bipolar configuration with an interelectrode distance of 7 cm. The differential electrode was placed on the quadriceps femoris tendon. The electrodes were mounted on the skin longitudinally with respect to the underlying muscle fibre arrangement right over the location of the muscle biopsy. To optimize the signal to noise ratio, the electrode sites were shaved, decornified by abrading the skin using sandpaper and cleaned with alcohol. Thus, the interelectrode impedance was kept to less than 4 k Ω , as determined by the Quinton Quick Prep Gun (Quinton, AH Robins, USA).

Analysis of the sEMG sampling: The sEMG signal was filtered with a band pass (8 Hz to 250 Hz) and samples of 2 s were analyzed afterward at times corresponding to 0%, 25%, 50%, 75% and 100% of T_F . A spectral analysis was performed with a fast Fourier transformation to derive the MDF of the sEMG signal, a procedure that has been previously described (13).

Muscle biopsy

Needle biopsies of the vastus lateralis muscle were performed at rest using a technique described by Bergström (20) and routinely performed in the authors' laboratory (21). Briefly, after local anaesthesia with lidocaine 2%, a 1 cm incision was made and muscle samples were obtained with a biopsy needle. Muscle specimens were prepared and then immediately frozen in liquid nitrogen and stored at -80°C until processing.

Enzymology

Activities of CS (enzyme commission [EC] 4.1.3.7), HADH (EC 1.1.1.35), hexokinase (HK) (EC 2.7.1.1), lactate dehydrogenase (EC 1.1.1.27) and phosphofructokinase (PFK) (EC 2.7.1.11) were measured with a spectrophotometric technique as previously described and performed in the authors' laboratory (21).

Statistical analyses

Student's unpaired *t* test was used to evaluate differences between groups. Differences within groups were evaluated with Student's paired *t* test. The Mann-Whitney U test was used for data not normally distributed. Furthermore, a two-way ANOVA (group and time) was performed to evaluate data of both groups over time. Within-group multiple comparisons were performed to determine the time when the MDF became significantly different from its resting value. Pearson's correlation coefficients were used to evaluate

TABLE 1
Subjects' characteristics and exercise parameters*

	CHF patients	Healthy subjects	P
Characteristics			
n	25	18	—
Age, years	55±8	62±6	0.006
Sex, male/female	20/5	15/3	—
Weight, kg	84±15	75±13	0.04
BMI, kg/m ²	30±4	26±4	0.004
Ejection fraction, %	27±2	—	—
Exercise parameters			
VO ₂ peak, mL/kg/min	18±5	28±8	<0.001
MVC, kg	40±3	45±3	0.24
Time to fatigue, s	49±4	80±7	<0.001

*Data are presented as mean ± SD unless otherwise specified. BMI Body mass index; CHF Chronic heart failure; MVC Maximal voluntary contraction; VO₂ peak Peak oxygen uptake

relationships between T_F and different enzyme activities. All data are presented as mean ± SD unless otherwise specified. A P value <0.05 was considered statistically significant.

RESULTS

Subjects' characteristics are presented in Table 1. When compared with HS, the group of patients with CHF was younger, had a lower peak oxygen uptake, and had a higher body weight and body mass index (all P<0.05) (Table 1). T_F was lower in patients with CHF than in HS (49±4 s versus 80±7 s, respectively; P<0.01) (Table 1). All pairwise multiple comparison procedures over time within CHF patient and HS groups indicated that the fall in MDF was already significant at midexercise, suggesting that muscle fatigue occurred (Figure 1). When comparing CHF patients with HS, lower CS and HK activities (CS: 20.28±7.10 µmol/min/g for CHF patients versus 27.57±3.58 µmol/min/g for HS [P<0.01]; HK: 1.00±0.49 µmol/min/g for CHF patients versus 1.69±0.43 µmol/min/g for HS [P<0.01]) and higher values for PFK activity (52.20±25.24 µmol/min/g for CHF patients versus 38.10±11.89 µmol/min/g for HS [P<0.05]) were observed (Figure 2). However, there was no significant difference in HADH (6.6±2.1 µmol/min/g versus 6.8±1.8 µmol/min/g) or lactate dehydrogenase (187.3±76.4 µmol/min/g versus 146.9±68.0 µmol/min/g) activities in CHF patients and HS, respectively. Furthermore, T_F was significantly associated with CS (r=0.50), HADH (r=0.42), PFK (r=-0.47) and HK (r=0.41) activities and the PFK/CS ratio (a discriminating enzyme ratio representing the potential for aerobic compared with anaerobic energy metabolism) (r=-0.39) for the whole group (CHF patients + HS), and to HADH (r=0.47) and PFK (r=-0.57) for the CHF group alone (all P<0.05) (Figure 3).

DISCUSSION

The results of the present study demonstrate that vastus lateralis muscle endurance is decreased in patients with CHF compared with HS, and that this decrease is correlated with indices of muscle oxidative capacity (CS and HADH activities). The significant fall in the sEMG's MDF during isometric contraction also suggests that this test can be used to assess muscle fatigability in CHF.

Figure 1 Time course of the surface electromyography median frequencies (MDFs) in patients with chronic heart failure (closed circles) and healthy subjects (open circles). *P<0.001 for 0% versus 50%, 0% versus 75% and 0% versus 100% of time to fatigue in patients with chronic heart failure and healthy subjects. All P<0.001 between patients with chronic heart failure and healthy subjects for each percentage of time to fatigue

In the absence of an objective confirmation of muscle fatigue, the validation of any endurance test based on the motivation of the individual to perform the required task or the attitude of the investigator can be questioned (17). To address this limitation, the sEMG was used as a direct marker of fatigue, as previously suggested (12,14,15,17). More precisely, MDF is now recognized as an important parameter reflecting muscle fatigue (15,16). Based on this sEMG parameter, we found that both HS and patients with CHF experienced isometric skeletal muscle fatigue, as characterized by the presence of a breakpoint in the MDF time course (Figure 1).

Interestingly, an elevated MDF was observed throughout the exercise in CHF patients compared with HS. The relatively high proportion of type II fibres in CHF patients may explain these observations (11). Indeed, in vivo studies have demonstrated that fast-twitch fibres have higher depolarization and repolarization frequencies than do slow-twitch fibres. This phenomenon produces action potentials of shorter length (22) and would likely contribute to high frequencies of the sEMG spectral analysis. Moreover, the motor unit size of the fast-twitch fibres is generally bigger than the slow-twitch fibres (23). Thus, their total electrical activity contribution to the sEMG signal is proportionally higher than slow-twitch fibres (24). The MDF values obtained from CHF patients were similar to those previously observed in chronic obstructive pulmonary disease patients, who also show a greater proportion of type II fibres (13). Indeed, these two populations show similar alterations of skeletal muscle function (6), for example, skeletal muscle atrophy and weakness, changes in fibre types, redistribution and muscle capillarization, altered metabolic capacity and, as we observed in our study, a similar pattern of the MDF during isometric muscle contraction. Added to the existing literature, the results of the present study suggest that these two diseases lead to a common problem of peripheral muscle dysfunction.

Specifically, there was a progressive decrease in the MDF values throughout isometric relative constant-force contraction

Figure 2) A Citrate synthase (CS) activity in patients with chronic heart failure (CHF) compared with healthy subjects. **B** Hexokinase (HK) activity in patients with CHF compared with healthy subjects. **C** Phosphofructokinase (PFK) activity in patients with CHF compared with healthy subjects

in both HS and CHF patients. Several studies (12,15-17) have proposed that reduced conduction velocity is an important mechanism explaining this downward frequencies shift, and that MDF provides the most accurate estimate for this sEMG parameter. Decreased conduction velocity depends on factors such as lactic acid accumulation (12) and muscle ischemia (16). However, other factors might be responsible for the decreased conduction velocity, such as the diameter of muscle fibres or an increase of potassium ions in the extracellular fluid during contraction (17).

Figure 3) A Correlation between time to fatigue and citrate synthase (CS) activity in patients with chronic heart failure (closed circles) and healthy subjects (open circles). **B** Correlation between time to fatigue and phosphofructokinase (PFK) activity in patients with chronic heart failure (closed circles) and healthy subjects (open circles). **C** Correlation between the PFK/CS ratio in patients with chronic heart failure (closed circles) and healthy subjects (open circles)

Skeletal muscle dysfunction may reduce exercise tolerance in patients with CHF (5-9). In the present study, skeletal muscle endurance was lower in CHF patients than in HS. Several peripheral muscle abnormalities may explain this altered skeletal muscle function. Indeed, muscle atrophy (25), muscle weakness (8), morphological changes (9,11) and altered metabolic capacity (10,11) have all been described in these patients. Reduced mitochondrial volume and aerobic capacity have been observed in the vastus lateralis muscle in patients with CHF (9). Furthermore, a reduced activity of

mitochondrial and beta-oxidation enzymes and normal glycolytic enzyme activity has also been reported (10,11). Hence, the reduction of CS and HK activities and the higher activity of PFK observed in the present study are in agreement with the existing literature (10,11). An increased PFK activity in patients with CHF is consistent with the greater proportion of type II fibres in these individuals than in controls. With PFK being a key enzyme of the glycolytic energetic pathway, the finding of greater PFK activity in patients with CHF would indicate a higher reliance on glycolytic metabolism. This interpretation is consistent with previous studies reporting impaired oxidative metabolism in CHF (10,26). A similar finding has also been reported in patients with chronic obstructive pulmonary disease who show a muscle disease similar to what is found in CHF (13,27).

The significant relationships observed between isometric skeletal muscle endurance and the activity of key enzymes of the aerobic pathway suggest that poor muscle oxidative capacity could be a possible mechanism for the reduced skeletal muscle endurance observed in CHF (8). As a consequence of this reduced oxidative capacity, an earlier onset of anaerobic glycolysis is thus expected, leading to an accumulation of lactate, premature intramuscular acidosis and fatigue (8). Although we acknowledge that these relationships are not necessarily causal, previous studies (28,29) have demonstrated that exercise training induces a concomitant increase in muscle oxidative capacity and skeletal muscle endurance in patients with CHF, thus supporting the existence of a link between skeletal muscle endurance and oxidative capacity. Of note, we cannot exclude the possibility that the increased susceptibility to fatigue in CHF may, in part, be related to abnormal motor unit recruitment (30). However, the existing relationships between T_F and various muscle enzyme activities also support the contention that the metabolic capacity of the vastus lateralis muscle was equally important in explaining reduced muscle endurance.

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CONCLUSION

Our findings provide a sound physiological rationale for the use of exercise training in patients with CHF, whereby improved muscle oxidative capacity should lead to enhanced skeletal muscle endurance and functional status.

An interesting feature of the isometric contraction test performed at 60% of MVC is that during such a manoeuvre, oxygen transport (respiratory and circulatory components) is not a limiting factor because blood flow to the contracting muscle is very low (19) due to arterial contraction by high intramuscular pressure. Thus, compared with dynamic exercises such as cycling, treadmill walking and simple dynamic contraction of the quadriceps femoris (dynamic knee extension), the isometric contraction is testing the skeletal muscle as an 'isolated' system with no additional requirement for the cardiocirculatory and respiratory systems above resting condition. Furthermore, the use of relative (percentage MVC) isometric contraction takes into account differences in muscle mass because MVC is highly determined by muscle volume (31), which would not be the case if a fixed weight load were used for all subjects.

Our results suggest that isometric endurance of the vastus lateralis muscle is reduced in patients with CHF and that the reduction is related to altered muscle oxidative capacity. The occurrence of a fall in sEMG MDF during the isometric muscle endurance test suggests that it can be used as a handy and objective tool to assess skeletal muscle fatigability and dysfunction in these patients.

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