The Relation between Skeletal Muscle Myopathy and Exercise Capacity in Chronic Heart Failure

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Abstract

Chronic Heart Failure (CHF) is characterised by a leg skeletal muscle disorder with atrophy and shift from the "slow" aerobic fatigue resistant MHC1 to the "fast" more fatigable MHC2a and MHC2b. Atrophy has been shown to be, at least in non-cachectic patients, related more to TNFα-triggered myocyte apoptosis, rather than ubiquitin-dependent muscle waste. The CHF myopathy is specific and not secondary to detraining or atrophy. In fact the shift in MHCs is independent from muscle bulk loss since it appears before myocyte apoptosis and atrophy develop. It is due to adaptation to the relative ischemia of muscle fibres that is secondary to the capillary network damage. Moreover myofibres apoptosis is not selective. The shift in MHCs is, at least in part, responsible for the reduced exercise capacity in CHF patients. In fact there is a strong correlation between indices of severity of CHF, such as NYHA class, diuretic consumption and exercise time, and gastrocnemius MHC composition. The strongest correlation is however with cardiopulmonary exercise testing parameters (peak VO₂, VT and O₂ pulse) that are the most objective measurements of exercise capacity.

Muscle fatigue which limits exercise capacity, appears earlier in patients that have a greater skeletal muscle expression of MHC2a and MHC2b. These isoforms have in fact higher speed of shortening, ATP consumption, and lower threshold for lactate production, so that they reach anaerobic metabolism and symptoms of muscle fatigue much earlier.

Key words: chronic heart failure, skeletal muscle, myosin heavy chains, exercise capacity.

Exercise Tolerance and Origin of Symptoms in CHF

Chronic heart failure (CHF) is characterised as a clinical disorder by exercise intolerance. The symptom causing a subject to stop exercising is usually given by shortness of breath or fatigue. During exercise, there is an early and prolonged release of lactate from exercising muscles in patients with CHF, even during light exercise [26]. Lactate threshold which corresponds to a measurable ventilatory anaerobic threshold has been found to occur at a lower level of exercise in CHF [12, 43]. At first sight, fatigue may be thought simply due to failure of perfusion of the exercising musculature and the consequent early onset of intramuscular acidosis; however, evidence increasingly points to there being intrinsic abnormalities of muscle metabolism and structure in patients with CHF. In fact there is a close correlation between exercise capacity and measurements of metabolic gas exchange, particularly peak VO₂. However peak VO₂ poorly correlates with indices of central haemodynamic function [10, 34] and with measurements of peripheral blood flow as suggested by Wilson et Al. [44]. These latter showed in fact that exertional fatigue is due to skeletal muscle dysfunction rather than to reduced skeletal muscle blood flow. For these reasons investigations have been carried out looking at skeletal muscle abnormalities. Neither pulmonary capillary wedge pressure [34], nor blood lactate [11] correlates well with exertional breathlessness, suggesting a crucial missing link in the mechanisms of exercise limitation in CHF. A neural linkage between ergoreceptors (afferents sensitive to skeletal muscle work) and responses to exercise has been demonstrated in CHF [25], their overactivation determines higher ventilatory, blood pressure response and leg vasoconstriction.
The Muscle Hypothesis

There is strong suggestion that changes in the leg skeletal muscle can limit exercise capacity, and be therefore responsible for symptoms in CHF. In the early eighties Lipkin et al [15] observed in the quadriceps femoris of patients with CHF a greater expression of fast type II fibres. Mancini et al [18] studied biopsies of the gastrocnemius and found a shift from Ia to Ib. These changes were present regardless of aetiology of CHF. The type II fibres appeared to be increased in number, but decreased in size. Sullivan et al [32] in the vastus lateralis found type I to be decreased and type II to be increased. They extended the study to biopsy taken during submaximal and maximal exercise [33] showing lactate accumulation, PCr depletion, acceleration of glycolysis and glycogenolysis at peak exercise. The reason for this, when NMR studies show early acidosis, drop in ATP and lactate generation, is not entirely clear [18, 19, 21]. Drexler [9] examined the contribution of mitochondrial abnormalities to the CHF myopathy and they found a reduction of mitochondria volume and surface density of cristae. Broqvist [4] reported in the quadriceps femoris of patients with CHF a reduction of high energy metabolic substrates (ATP, glycogen and PCr). The net result of the abnormalities of lower limb skeletal muscle and blood flow appears to be the early onset of intramuscular acidosis and excessive lactate production. It has been recently reported that K⁺ may be responsible at the level of the myocyte cell membrane for the sensation of fatigue. Intracellular calcium rises during exercise causing an increase in K⁺ conductance leading to membrane inactivation. This mechanism protects from excessive rise in intracellular Ca²⁺ during excessive work and may equate with fatigue [30]. K⁺ handling is abnormal in CHF being higher at matched workloads [2]. However Clark et al have shown [6] that K⁺ is unlikely to be important as a circulating determinant of the ventilatory response to exercise, nevertheless K⁺ may be important as a local intramuscular mediator.

Skeletal muscle has been advocated as a possible determinants of symptoms in CHF via a neural linkage between peripheral abnormalities and the exaggerated exercise responses, such as the ventilatory one in heart failure [25]. The metabolic state of the skeletal muscle is centrally monitored by the activation of ergoreceptors, whose fibres, travelling in the lateral spino-talamic tract, increase ventilation and sympathetic outflow, producing vasoconstriction in distant non-exercising vascular beds, with consequent effects on BP and possibly a small increase in heart rate. They are sensitive to the metabolic state of the muscle, but their triggers are still unclear. They have the properties necessary to link the skeletal muscle abnormality to the fatigue, dyspnea, hyperpnea and sympathoexitation characteristic of CHF. The muscle hypothesis proposes another cycle of deterioration similar to those of neuroendocrine activation. The reduction in left ventricular function determines a series of metabolic abnormalities in the skeletal muscle that triggers an exaggerated ergoreflex activation that is perceived by the patient as fatigue and dyspnea and leads reflex to vasoconstriction in the non-exercising muscles and excessive ventilatory response.

Muscle Waste and Exercise Capacity

Lipkin et al [15] originally showed that quadriceps femoris muscle strength is reduced and there is indeed a correlation between quadriceps strength and exercise performance as assessed by peak VO₂ [5]. This is due to the fact that muscle mass is reduced in CHF and the more severe the limitation in exercise capacity the greater muscle bulk loss. In fact Minotti et al [24] showed that there is no reduction in mean force per unit area, implying that myofibril force production was normal, but that loss of skeletal muscle mass is an important determinant of muscle strength. Mancini et al [20] showed that muscle wasting occurred in even mild heart failure. Volterrani et al [42] showed that exercise capacity correlates well with both strength and mass and that reduced leg blood flow may be a consequence of muscle wasting. Flow per unit muscle bulk is not a determinant of exercise capacity. Recently it has been shown that in cardiac cachexia, where an extreme degree of muscle waste is present, the relationship between muscle mass, exercise capacity and peak VO₂, is lost [1]. Even the strength per unit area is decreased because of the severe alterations in muscle fibres and their replacement with interstitial tissue.

Myosin Heavy Chain Composition and Fibres Type

Skeletal muscle fibres type is determined by the myosin heavy chain pattern. There are three major Myosin Heavy Chains (MHCs) that can be separated electrophoretically on the basis of their relative mobility (Fig 1). MHC1 is the slow anaerobic isoform and is characterised by low ATP consumption, low speed of shortening and is defined as fatigue resistant. Type I fibres are mainly composed by MHC1. MHC2a is the fast oxidative component and MHC2b the fast glycolitic. They possess higher ATP consumption, higher speed of shortening and they are both more fatigueable since they reach anaerobic threshold earlier. Fibres type Ia and Ib are mainly constituted by MHC2a and MHC2b respectively. We have recently shown that in the gastrocnemius of patients with CHF there is a shift from the slow to the fast isoforms [39]. The magnitude of this shift correlates with indexes of severity of CHF syndrome such as NYHA class, exercise test tolerance measured in minutes, diuretic consumption, and Ejection Fraction, though the relationship with this latter parameter was much weaker. There was however no relationship with
ventricular diameters. A comparison with patients with normal cardiac function and extreme disuse atrophy, in whom the prevalence of MHC1 was found, made us think that the myopathy of CHF patients was specific. Similar observations were made at the same time by Sullivan [31] in the vastus lateralis. This myopathy is generalised and involves diaphragmatic muscle [14, 35]. We have tried to answer the question whether the skeletal muscle composition was in some way responsible for the reduced exercise capacity in patients with CHF. To do so we correlated the gastrocnemius MHCs composition with objective indices of exercise capacity [38] measured with maximal, symptom limited, cardiopulmonary exercise testing, namely peak VO2, VT and O2 pulse. We found a strong positive correlation between MHC1 and peak VO2, VT and O2 pulse (Fig. 2), while there was a negative correlation between MHC2a, MHC2b and the same cardiopulmonary parameters. We therefore raised the possibility that a high percentage of glycolitic fibres reduces exercise capacity because of the early appearance of anaerobic metabolism, which is determined by the prevalence in the muscle of fast fatigueable fibres with low anaerobic threshold and high ATP consumption. That skeletal muscle composition plays an important role in limiting exercise capacity in CHF patients is also demonstrated by the improvement in exercise tolerance obtained after endurance training [3, 17] or pharmacological treatment [27] that is accompanied by favourable histologic, metabolic and functional parameters occurring in the leg skeletal muscle. We have recently demonstrated [37] that 6 months treatment with either Losartan or Enalapril in patients with CHF was able to improve exercise capacity as demonstrated by the significant changes in peak VO2, VT and O2 pulse. At the same time a significant reshift from the fast to the slow MHCs in the gastrocnemius of patients with CHF occurred. When the absolute changes in exercise capacity were compared with the net gain in MHC1 a significant correlation between these two parameters was found. This strengthen the hypothesis that exercise tolerance and skeletal muscle composition are tightly linked. The observed changes were not accompanied by any change in muscle mass as measured by the gastrocnemius CT scan cross sectional area. Since there is no correlation between MHC composition and neither force generation, nor muscle mass [37] we can speculate that the improved exercise capacity in mild to moderate CHF patients is related to “fibres fatigability” rather than to muscle strength or force generated. The observation that muscle strength depends on muscle mass and that there is no correlation between fibres type, and therefore MHC composition, and muscle trophism, confirm the hypothesis that the CHF myopathy is specific and not related to muscle atrophy. This may not be true for patients with severe CHF where muscle endurance, VO2, atrophy and exercise tolerance are in same way related [40].

**Muscle Atrophy and Changes in Fibres Type and MHC Composition**

It has been debated for very long time on the origin of this myopathy. Atrophy due to deconditioning has been thought to play a role in the genesis of this myopathy, but we have recently observed that muscle bulk loss due to extreme inactivity is actually accompanied by an increased expression of MHC1 [39]. However the debate on the possible causes of this myopathy is still open. It has been hypothesised that cytokine activation and loss of anabolic function [23], ergometaboloreceptors dysfunction [7] or changes in blood flow [22, 45] may be of importance.

We have recently demonstrated in a well known model of CHF, the monocrotaline treated rat, [41] that the expected shift toward the fast isomyosins occurred both in the fast and slow muscles, (soleus and EDL) with the appearance of CHF. However this shift correlates neither with the degree of muscle atrophy, nor with the...
skeletal muscle blood flow, suggesting that these two factors do not play a pivotal role in the genesis of the myopathy [36]. This observation is also in agreement with that of Simonini et al [28, 29] who suggested that in rats with CHF the changes in skeletal muscle morphology and gene expression are not explained by the reduced activity. They also showed that myosin redistribution is due to a specific increased activity of mRNA encoding MHC2b rather than specific atrophy of type I fibres. We have recently confirmed this hypothesis showing in the tibialis anterior of the monocrotaline treated animals with CHF [41] an increased number of apoptotic myonuclei both in fibres positive to staining with antibodies against MHC2a and MHC2b+2x. The pro-apoptotic caspase-3 was significantly increased, while Bcl-2, that is protective against apoptosis, dropped significantly [8]. Apoptosis is also responsible for the appearance of muscle atrophy in the fast muscles (as demonstrated by the reduced Muscle Weight/Body Weight and fibres cross sectional area). We also showed [41] that atrophy is preceded by the shift toward the fast isoforms once again confirming that biochemical changes are independent from muscle waste. Apoptosis in the skeletal muscle appear at the same time that CHF worsen and is paralleled by increased levels of circulating TNFα. This cytokine is known to produce muscle waste by increasing apoptosis [13] and by activating ubiquitin, therefore triggering the protein-waste pathway [16]. In our model the ubiquitin pathway seems not to be involved in that tissue levels of this molecule are not increased in CHF [8]. We therefore think that muscle atrophy is apoptosis-dependent. Since endothelial cells show in CHF [41] a very high degree of apoptosis, that is much higher than myocyte apoptosis, we hypothesise that endothelial apoptosis, even in the absence of changes in skeletal muscle blood flow, could alter myofibres nutrition. A decreased oxygen delivery through a damaged or even decreased capillary network, can cause relative ischemia to which muscle could adapt by increasing the synthesis of 2b anaerobic fibres. When ischemia is more pronounced, fibres can be irreversibly damaged and undergo apoptosis, which ultimately leads to muscle loss and atrophy.

We have recently confirmed the observations made in the animal models of CHF in humans [40], showing that there is a close relationship between exercise capacity (as measured by peak VO2), endurance (measured as fatigability), muscle atrophy (measured as fibres cross sectional area) and skeletal myocytes apoptosis, which is in turn the determinant of muscle atrophy.

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References


Myosin heavy chains in CHF


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