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Review Article

Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure

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Introduction

The syndrome of chronic heart failure is characterized by exercise limitation usually associated with breathlessness or fatigue. The mechanism by which this exercise intolerance is generated remains unclear. Although muscular atrophy has been recognised as a part of the chronic heart failure syndrome for many years[1–3] only recently has skeletal muscle been studied in any detail. Widespread abnormalities have been discovered and it has been proposed that these muscle abnormalities may contribute to the symptoms suffered by patients[4–7]. This review will consider what is known of these muscle abnormalities, how they may be generated and the evidence that they may limit exercise capacity in chronic heart failure.

Exercise capacity in chronic heart failure

In evaluating the determinants of functional capacity, an objective assessment of exercise tolerance is required. Exercise testing with concomitant assessment of metabolic gas exchange enables this. The role of exercise testing in the evaluation of chronic heart failure has been extensively studied and reviewed[8–11]. The peak oxygen consumption ($\dot{V}O_2$) achieved during a symptom limited test is reproducible[12,13] and has prognostic significance[14–16]. The ventilatory response to exercise, as reflected in the slope of the near linear relationship[17] between carbon dioxide production ($\dot{V}CO_2$) and ventilation ($\dot{V}E$), can also be assessed. Chronic heart failure patients have a steeper $\dot{V}E/\dot{V}CO_2$ slope, this slope being inversely related to peak $\dot{V}O_2$ and itself a measure of the severity of chronic heart failure[18].

Central haemodynamics as a determinant of exercise capacity

Patients with chronic heart failure have impaired ventricular systolic and/or diastolic function leading to a reduced cardiac output often associated with raised ventricular filling pressures. Since these are the principal abnormalities of the condition, it is a reasonable assumption that the severity of them will determine the extent of exercise intolerance. Studies have, however, failed to demonstrate such a simple relationship. Weber *et al.*[19] demonstrated a lack of correlation between resting values of cardiac index, ejection fraction, pulmonary capillary wedge pressure and peak $\dot{V}O_2$ observations confirmed by several other groups[20–22]. During exercise Metra *et al.*[23] have observed a correlation between peak $\dot{V}O_2$, cardiac index and stroke work. A modest correlation between pulmonary capillary wedge pressure, pulmonary artery pressure and peak $\dot{V}O_2$ has also been reported[22]. An analysis of ambulatory pulmonary artery pressures, however, showed no association between the pressures recorded and exercise capacity[24], and no association between ventilatory response to exercise and the pulmonary capillary wedge pressure has been found[25]. Further evidence failing to support central haemodynamics as the sole determinant of exercise capacity in chronic heart failure comes from various interventional studies. Pharmacological agents which increase cardiac output and/or reduce pulmonary capillary wedge pressure do not result in an immediate increase in exercise tolerance[26–28]. Similarly, percutaneous mitral valvuloplasty for mitral stenosis or cardiac transplantation for chronic heart failure do not result in an immediate but rather a delayed increase in exercise capacity[29–31]. Other potential determinants of exercise capacity have thus been sought.

Key Words: Heart failure, skeletal muscle, exercise.

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Table 1 Skeletal muscle function in chronic heart failure

Authors	Muscle group	Number of patients	Strength	Correlation with peak $\dot{V}O_2$	Strength per unit muscle	Fatigue resistance	Correlation with peak $\dot{V}O_2$
Magnusson *et al.*[35]	Quadriceps	8	↓ (ISK/ISM)		←→	↓	
Minotti *et al.*[34]	Quadriceps	21	←→ (ISK/ISM)	No	←→	↓	
Lipkin *et al.*[36]	Quadriceps	9	↓ (ISM)	Yes			
Buller *et al.*[37]	Quadriceps	15	↓ (ISM)	Yes	←→	↓	Yes
Buller *et al.*[37]	Adductor pollicis	15	←→ (ISM)			←→	
Minotti *et al.*[38]	Quadriceps	16	←→ (ISK/ISM)	No		↓	Yes
Wilson *et al.*[39]	Wrist flexors	9	←→				
Minotti *et al.*[40]	Foot dorsiflexors	9	←→			↓	

ISK = isokinetic, ISM = isometric.

Table 2 Skeletal muscle histology and metabolism in chronic heart failure

Authors	Number of patients	Fibre type				Glycolytic pathways	Krebs cycle	Lipid oxidation	Capillary density	
		I	IIa	IIb	IIc				/fibre	/mm^2
Lipkin *et al.*[36]	9	↓		↑*						←→
Yancy *et al.*[42]	6	↓		↑*		←→	↓		↓	↓
Mancini *et al.*[45]	22	←→	↓	↑	↑	←→	←→	↓	←→	↑
Sullivan *et al.*[43]	11	↓	←→	↑	←→	←→	↓	←→	↓	←→
Drexler *et al.*[44]	57	↓		↑*		←→		↓		↓
Belardinelli *et al.*[46]	27	↓		↑*						

*Studies in which type II fibres were not subtyped, data is given for all type II fibres.

Skeletal muscle

Muscle bulk and function

Muscle atrophy is a recognised feature of chronic heart failure with some patients developing 'cardiac cachexia'. It has been consistently demonstrated, however, that atrophy is also present in many patients without documented weight loss. Using a creatinine/height index and mid arm muscle circumference Mancini *et al.*[32] found severe muscle atrophy in 68% of 76 patients studied. This result has been confirmed by this group and others using computerized tomography, magnetic resonance imaging or dual energy X-ray absorpometry to demonstrate thigh, calf or total muscle atrophy[33–35].

As muscle atrophy appears common in chronic heart failure, abnormalities of muscle function should be expected (Table 1). Initial small studies reported reduced quadriceps strength[35–37], although this was not observed in later larger studies[34,38] or in other muscle groups[36,39,40]. Since quadriceps strength is dependent upon bulk[34], strength per unit of muscle is normal[37,38] and muscular atrophy is common in chronic heart failure, weakness should be a predominant feature. The reason for this discrepancy is unclear, although may in part be due to the small numbers of patients studied.

Whether assessed using a fatiguing protocol, or as isokinetic, or isometric endurance[34,37,40], early onset of fatigue has been consistently reported in chronic heart failure. This early onset of fatigue has been confirmed using electromyograms[41] and does not appear to be a result of failure of neuromuscular transmission[40].

Muscle histology

With the observed abnormalities of skeletal muscle function, various groups have attempted to define a characteristic underlying histological pattern (Table 2). An increase in the percentage of type II[36,42–44] or IIb fibres[43,45] has been observed. Reduction in fibre size accompanies this alteration in fibre distribution. Some groups report that this affects all fibre types[36,46], while others describe a reduction in type II[45] or only type IIb fibre diameter[43]. While fibre distribution and size is abnormal, the percentage area occupied by each fibre type may remain normal[45]. Vascularity, as reflected in capillary density, has been variably reported[36–44]. Despite this variation, taken in concert with the muscle atrophy the net effect of most observations would be a reduction in skeletal muscle vascular conductance. Mitochondrial density and morphology have been

documented, in most detail by Drexler and co-workers[44]. The volume density of mitochondria and the surface density of mitochondrial cristae were both reduced in chronic heart failure patients when compared to normal controls. Abnormalities of lipid and glycogen storage have been observed, although results are inconsistent and arise from small studies only[36,43].

Only one group has reported histology of the diaphragm. No alteration in fibre type distribution was observed, although there was a mild increase in fibre size variability in six patients with ischaemic heart disease. In addition, histological abnormalities have been reported in some patients with pathological cores, tubular aggregates and bizarre myosin type[47].

Skeletal muscle metabolism

Using skeletal muscle biopsies, metabolism has been investigated by measuring enzyme and metabolite levels in muscle homogenates and by staining biopsies for enzymes of the metabolic pathways. Reduced glycogen levels associated with normal levels of glycolytic intermediates and lactate but increased pyruvate levels have been reported, suggesting an increased level of glycolysis[43,45]. This assumption has been supported by the majority of studies reporting decreased activity of the oxidative enzymes of the Krebs cycle[42–44]. Fat metabolism also appears to be impaired since B-hydroxyacyl CoA dehydrogenase levels have been found to be decreased[44,45]. The activity of enzymes of the glycolytic pathway has, however, been consistently reported as normal[42–45].

Impaired muscle oxidative capacity is also suggested by data from 31p magnetic resonance spectroscopy studies. Analysis of the phosphorus spectra allows evaluation of the relative concentrations of inorganic phosphate, phosphocreatine and ATP in intact tissues and an estimation of intracellular pH. During exercise of a particular muscle group, phosphocreatine decreases and inorganic phosphate increases while pH falls more than in healthy controls[39,48,49]. Skeletal muscle thus appears to exhibit increased glycolytic metabolism (resulting in an earlier intramuscular acidosis) and is metabolically less efficient in relation to the external work performed. Reduced blood flow could account for these observations and patients with peripheral vascular disease have abnormalities of phosphocreatine metabolism similar to those seen in chronic heart failure[50]. Studies using plethysmography have, however, shown that blood flow is normal in the presence of spectroscopic abnormalities[51,52] and that differences between patients and controls persist when exercise is performed under ischaemic conditions[53]. Muscular metabolism has also been monitored invasively, with the onset of anaerobic metabolism being assessed by many groups noting changes in femoral venous, mixed venous and arterial lactate concentrations. Lactate release early during exercise has been recognised for many years[54–56] and has been a consistent finding amongst more recent investigators[57–59]. Wilson *et al.*[57] measured leg blood flow using femoral venous catheters and observed that with increasing exercise intolerance there was a progressively earlier increase in femoral venous lactate associated with a lower cardiac output response to exercise, a lower leg blood flow and a higher leg vascular resistance. Their results suggested that the early onset of lactate release could be explained both by pump failure and by impaired vasodilatation in the exercising muscle group. However, further work by this group and others has suggested that the early onset of lactate production is not solely a result of muscle underperfusion. Wilson *et al.*[60] identified a subgroup of previously studied patients who had a normal leg blood flow during exercise. Compared with other chronic heart failure patients, this group had a better cardiac output response to exercise and their leg arteriovenous oxygen differences were normal. Despite this, they still had an abnormal lactate response to exercise, suggesting that in some patients at least the abnormal lactate release is a result of intrinsic muscle abnormalities and not simply a consequence of impaired muscle perfusion. Intrinsic metabolic abnormalities are also suggested by experiments in which leg blood flow has been acutely improved. Hydralazine increases cardiac output and leg blood flow both at rest and during exercise in chronic heart failure when given intravenously[27]. It does not, however, change lactate production and actually decreases leg oxygen extraction, suggesting that the increased oxygen supplied as a consequence of increased flow is not utilised by the ischaemic muscle. Similar results have been observed following infusion of dobutamine[26,28].

Respiratory muscle abnormalities

The skeletal muscles which constitute the respiratory musculature are worth special consideration. Respiratory muscle weakness can result in dyspnoea[61] and abnormalities of the respiratory musculature have been found in chronic heart failure (Table 3). A reduction in maximal inspiratory mouth pressure and maximal expiratory mouth pressure has been noted by most[62–69]. These tests of strength are volitional and Mancini *et al.*[67] thus used a non-volitional technique[70] to measure maximal transdiaphragmatic pressure. They could demonstrate no difference in transdiaphragmatic peak pressure, and/or in maximal rates of contraction or relaxation, although the time–tension index for the diaphragm, an index of diaphragmatic work, was greater in patients at rest and throughout exercise. Fatigue of the diaphragm and respiratory muscles has been considered. Following exercise, Davies *et al.*[71] reported a fall in maximal inspiratory mouth pressure and maximal expiratory mouth pressure seen only in patients, while others describe similar falls in mouth pressures both in patients and controls[67]. Maximal voluntary ventilation and maximal sustainable

Table 3 Respiratory muscle function in chronic heart failure

	Number of patients	MIP	MEP	Correlation with exercise capacity
Hammond *et al.*[62]	16	↓	↓	
McParland *et al.*[63]	9	↓	↓	Yes (MIP and Mahler dyspnoea index)
Evans *et al.*[64]	20	↓	↓	No
Ambrosino *et al.*[65]	45	↓	↓	
Chua *et al.*[66]	20	↓	←→ (Trend to ↓)	Yes (MIP and peak $\dot{V}O_2$)
Mancini *et al.*[67]	10	←→ (Trend to ↓)	←→ (Trend to ↓)	
Mancini *et al.*[68]	15	←→ (Trend to ↓)	←→ (Trend to ↓)	
Nishimura *et al.*[69]	23	↓ (In NYHA III/IV)	←→	Yes (MIP and peak $\dot{V}O_2$)

MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure.

ventilation (ventilation using a three minute incremental work rate programme while maintaining isocapnia) have been documented as indices of diaphragm endurance and are both significantly reduced in chronic heart failure patients[68].

The aetiology of muscle changes in chronic heart failure

There are several potential causes for the changes outlined. Inactivity results in alterations in skeletal muscle superficially similar to those observed in chronic heart failure[72,73]. It is possible to envisage a cycle in which muscle change leads to inactivity, which in turn leads to a greater change in skeletal muscle. Although regular exercise training is at least in part able to reverse the muscle abnormalities in chronic heart failure it is unlikely that the changes are simply a result of disuse. Abnormalities have been documented in the hand flexors, a muscle group in which normal use may be expected[49]. Moreover abnormalities of the respiratory musculature, as described, have been documented while these muscles are more likely to experience increased rather than decreased usage. Further evidence refuting inactivity as the sole cause of muscle changes comes from biopsy studies. Vescovo *et al.*[74] compared muscle biopsies from inactive patients (following a cerebrovascular accident) and chronic heart failure patients. Significant differences existed between the two groups with lower levels of myosin heavy chain 1 and higher levels of myosin heavy chain 2b in the chronic heart failure patients. In a rat model of heart failure, changes in muscle phenotype were unrelated to the degree of locomotor inactivity[75]. Malnutrition may cause muscle changes, and a reduced calorific intake or a negative net energy balance has been documented in some patients. Dietary supplementation has, however, failed to produce any improvement in the muscle abnormalities or exercise capacity[76]. Reduced muscle blood flow may play an important role, although as discussed many of the observed metabolic and functional abnormalities appear to be independent of blood flow. Additionally, exercise training has resulted in improvements in muscle abnormalities with no change in total limb blood flow, although the possibility that shunting of blood within skeletal muscle has been improved has not been excluded.

A further possible explanation is that chronic heart failure constitutes a catabolic state and that the observed muscle changes are a result of this. There is sympathetic activation and in addition to documented insulin resistance[77] catabolic factors, such as tumour necrosis factor are known to be elevated in severe chronic heart failure[78–80].

The role of skeletal muscle abnormalities in symptom generation in chronic heart failure

Although widespread abnormalities of the skeletal musculature have thus been described in chronic heart failure their significance is less clear. They may simply be an inevitable component on the chronic heart failure syndrome. Alternatively they may have greater importance and be responsible in part for exercise interolance. A clue to the existence of such a role comes from Jondeau *et al.*[81]. They assessed peak $\dot{V}O_2$ during cycle ergometry and then repeated this exercise test, but near the point of peak exercise they asked their subjects additionally to perform work with their arms. In control subjects and patients with mild chronic heart failure there was no change in peak $\dot{V}O_2$ between the two tests. However, in the remaining patients the addition of arm exercise resulted in a further increase in the peak $\dot{V}O_2$. They concluded that in severe chronic heart failure muscle bulk could influence peak $\dot{V}O_2$. Further evidence

for such a link between muscle and exercise capacity can be divided into three types. Firstly the various abnormalities of skeletal muscle have been correlated with indices of exercise performance. Secondly the response of patients treated with therapies which correct or circumvent the muscle changes in chronic heart failure have been observed. Finally the exercise characteristics of patients without cardiovascular disease but with muscle abnormalities have been documented.

Correlations between muscle changes and exercise

Volterrani *et al.*[82] considered a number of potential determinants of exercise performance in chronic heart failure. They found muscle bulk characteristics to be the best predictors of exercise capacity, with a strong correlation between quadriceps cross-sectional area and peak $\dot{V}O_2$. Correlations with peripheral and respiratory muscle function have been variable (Tables 1 and 3) while some associations have been observed with the various histological abnormalities. A positive correlation between peak $\dot{V}O_2$ percentage type IIb fibres has been reported[45]. Mitochrondrial indices correlate modestly with peak $\dot{V}O_2$ and an association with oxidative enzyme activity has been noted by some[43]. Despite this, the abnormalities of muscle metabolism implied by spectroscopic studies are not significantly associated with exercise capacity.

Treating the muscle abnormalities in chronic heart failure

As outlined, the changes observed in skeletal muscle in chronic heart failure have some similarities to those observed in individuals who have been immobile and have developed disuse atrophy. Training programmes may be expected to improve such abnormalities. Sullivan *et al.*[83] first demonstrated that following training exercise tolerance improved in patients with severe left ventricular dysfunction. Subsequently, others[46,84–86] have confirmed these findings despite little effort on central haemodynamics. Muscle metabolism improves at submaximal workloads[87] and despite no alteration in cardiac output or leg blood flow there is a reduction in both arterial and venous lactate levels[88]. Magnetic resonance spectroscopy has confirmed the improvements in muscle metabolism following training[87,89], with Minotti *et al.*[89] again demonstrating independence from central haemodynamic changes. The histological changes underlying these metabolic improvements have received limited attention. Hambrecht *et al.*[86] performed quadriceps biopsies in 18 patients, half of whom underwent a training programme. Training resulted in an increase in the total volume density of mitochondria and an increase in the volume density of cytochrome oxidase positive mitochondria (this being an objective measure of cytochrome oxidase activity). Interestingly, there was an excellent correlation between the improvement in peak $\dot{V}O_2$ and anaerobic threshold and the changes in cytochrome oxidase-positive mitochondria. Following a low level exercise programme Belardinelli *et al.*[46] report similar results.

Besides the modest correlations between exercise tolerance and indices of respiratory muscle function, the significance of the abnormalities of the respiratory musculature has been suggested by two further studies. In a novel approach based upon experience in patients with chronic obstructive pulmonary disease, respiratory muscle training has been employed in chronic heart failure[90]. Compared with an untrained group, trained patients had significant increases in maximal inspiratory mouth pressure, maximal expiratory mouth pressure and maximum voluntary and maximum sustainable ventilation. This was associated with an increase in peak $\dot{V}O_2$ and exercise time, and a reduction in the $\dot{V}E/\dot{V}CO_2$ ratio at 1 litre and the sensation of dyspnoea. In a further provisional report this group reduced the work of breathing by exercising patients and controls while breathing room air or a low density mixture of 21% oxygen with the balance being helium. The low density mixture had no effect on normal subjects while exercise duration was significantly prolonged in the patients[91].

Exercise capacity in patients with muscle diseases

Patients who have muscular atrophy as a result of other conditions suffer breathlessness and fatigue similar to chronic heart failure patients[92]. Individuals who suffer from mitochrondrial myopathies have abnormalities of their respiratory chain activity, in some cases similar to those observed in chronic heart failure. Limited studies have suggested that these patients have a hyper-dynamic circulatory response to exercise. Despite this, they have a low peak oxygen consumption and an increased $\dot{V}E/\dot{V}CO_2$ slope similar to that seen in chronic heart failure[93]. Interestingly the ventilatory abnormalities persisted in two patients who had undergone cardiac transplantation for a dilated cardiomyopathy[94].

Possible mechanisms of symptom generation

Chronic heart failure patients are usually limited by either breathlessness or muscular fatigue. These two symptoms have been considered as discrete entities. The mode of exercise (cycle vs treadmill), however, appears to affect the symptoms limiting exercise[95] and a comparison of patients limited by breathlessness or fatigue shows them to have identical clinical characteristics and ventilatory responses to exercise[96]. The same process may thus be generating the two symptoms. Intuitively one would expect the sensation of fatigue to relate to the

metabolic state of the exercising muscle. Lactate does not appear to generate the sensation. A reduction in lactate production in chronic heart failure achieved by infusing dichloroacetatae does not result in an increase in exercise capacity[97]. Local levels of potassium may be important[98] and abnormalities of potassium handling have been observed in chronic heart failure[99]. The method by which such a metabolic disturbance is sensed is uncertain, although small myelinated and unmyelinated nerve fibres originating from skeletal muscle have been identified. It is possible that these fibres receive input from work sensitive or ergo-receptors, and that it is impulses from these fibres that help to generate the sensation of fatigue and perhaps the sensation of dyspnoea. Some evidence for this hypothesis exists. Piepoli *et al.*[100] observed the blood pressure, pulse and ventilatory responses during recovery from a period of hand grip exercise. Their observations were then repeated with the addition of regional circulatory occlusion during the recovery period. (This was achieved by placing a cuff around the upper part of the exercising arm and inflating it to a suprasystolic pressure at the onset of recovery.) Any difference in the measured variables during control and circulatory occlusion recovery must be due to a non-humoral signal, termed the 'ergo-reflex'. This group observed that the ergo-reflex dependent components of recovery ventilation, diastolic blood pressure and non-exercising limb vascular resistance were greater in chronic heart failure patients than controls, implying that this reflex was more active in these patients. It is possible that this heightened ergo-reflex provides a link between the peripheral abnormalities and the abnormal ventilation seen in chronic heart failure. Interestingly a 6-week period of local forearm training was able to reduce the activity of this reflex in chronic heart failure patients[101].

Conclusions

Extensive intrinsic abnormalities of lower limb musculature have been described in chronic heart failure. It is intriguing to hypothesize that the muscle changes are not simply the consequence of disturbed haemodynamics, but that they may contribute to the symptoms suffered by patients. Although no definitive evidence for such a concept exists, the improvements in exercise capacity with training make therapies aimed at the muscle an attractive possibility. The wider application of training regimes, and possible the use of drugs aiming to reverse the muscle changes, may help to reduce the significant morbidity still suffered by chronic heart failure patients.

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