HEART FAILURE

What causes the symptoms of heart failure?

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Chronic heart failure (CHF) is a common condition with a poor prognosis. It is associated with debilitating limiting symptoms, even with optimal modern medical management. Foremost among these symptoms is severe exercise intolerance with pronounced fatigue and dyspnoea at low exercise workloads. The UK National Health Service has highlighted it as a key target for improved treatment with the aim of symptom relief and restoration of optimal functional capacity.[1] The severity of symptomatic exercise limitation varies between patients, and this appears to bear little relation to the extent of the left ventricular systolic dysfunction measured at rest, or to markers of central haemodynamic disturbance (fig 1).[2] There may be several reasons for this. It may be that measurements of ventricular function at rest bear only a poor relation to changes in central haemodynamic function that occur on exercise,[3] and therefore predict only poorly exercise capacity. It may be that on the background of left ventricular impairment, variability in preservation of right ventricular function and the adequacy of the pulmonary vasculature to dilate and accept a blood flow and to match this flow with ventilation is impaired. Thirdly, it may be that changes, which occur in the periphery as a consequence of the systemic effects of heart failure, may have become the factors limiting exercise more than the heart dysfunction that initiated the syndrome.[4] There is evidence in the literature for all three of these hypotheses.

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Exercise capacity in normal subjects

In normal subjects exercise is usually possible until maximal cardiac output is achieved, at which time a further increase in workload will produce extra carbon dioxide (CO_2) but with no commensurate increase in oxygen (O_2) uptake.[5] This is termed maximal oxygen uptake (Vo_2max). At between 85–95% of Vo_2max a point in exercise is reached where there is an excessive release of CO_2 for the rate of O_2 uptake caused by a limitation in the rate of delivery of O_2, leading to the onset of anaerobic muscular metabolism with lactate production. This produces arterial acidosis and directly stimulates the chemoreceptors to produce relative hyperventilation. This point is called the anaerobic threshold. In most normal subjects exercise is limited by cardiac reserve, with lung function rarely being the limiting factor. Training status and genetic factors determine the overall fitness to exercise.

Exercise capacity in CHF

In non-oedematous stable and optimally treated patients with CHF submaximal exercise and the haemodynamic response accompanying it may be remarkably normal, with preservation of muscle blood flow being at the expense of increased vasoconstriction in other vascular beds. Exercise tends to stop abruptly quite frequently with the respiratory exchange ratio (ratio of CO_2 produced to O_2 consumed) being not much above 1.0, indicating true maximal cardiopulmonary reserve has not been reached. Further evidence of this comes from the observation that the addition of arm exercise to maximal leg exercise increased observed peak O_2 uptake in heart failure patients but not in normal controls. This suggest that the heart had the capacity to increase its output and therefore at maximal leg exercise the limiting factor must have been based either on an intolerable symptom, or on the inability of the leg to accept a greater blood supply, or in the muscles of the leg to utilise the oxygen delivered any further.[6] This suggests that the limiting factor in the majority of patients with CHF may be peripheral.[7]

Correlates of exercise capacity in CHF

Much work has recently concentrated on noncardiac abnormalities in stable CHF. Abnormalities have been described in peripheral blood flow, endothelial function, skeletal muscle, and lung function.[8–11] These changes acting alone, or in combination, may lead to early muscle fatigue and dyspnoea. Better correlations with exercise tolerance are seen with these peripheral abnormalities than for haemodynamic measurements.[12] Patients with heart failure exhibit a subnormal peripheral blood flow response to both exercise and pharmacological vasodilatation, caused by a combination
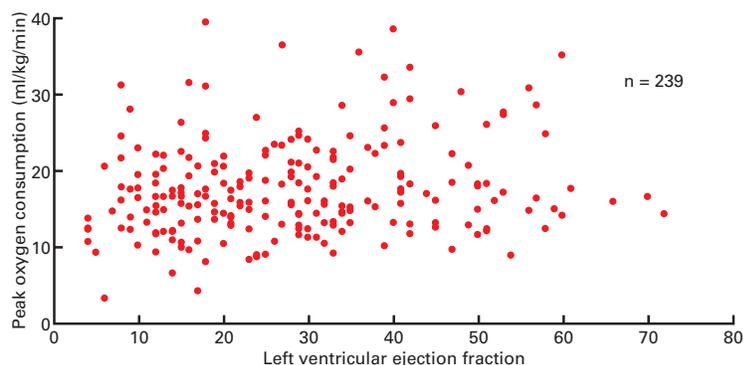

Figure 1. Lack of correlation between exercise capacity and resting left ventricular ejection fraction in 239 patients attending the cardiopulmonary exercise laboratory of the Royal Brompton Hospital, London, UK.

of persistent vasoconstrictor drive, a relative paucity of peripheral blood vessels, a deficient nitric oxide vasodilator system, and an enhancement of the vasoconstrictor endothelin system. CHF patients can demonstrate evidence of early muscular lactate release despite normal skeletal muscle blood flow. An inherent defect in skeletal muscle metabolism independent of blood flow has been described in this condition. There are abnormalities in histology, mitochondrial structure and function, oxidative enzymes, and a shift in fibre type distribution with predominance of type IIb over IIa fibres and many of reduced fibre dimension.[13]

Skeletal muscle changes

Skeletal muscle is abnormal in CHF in many ways (fig 2). There is impaired gross function, substantial wasting, impaired intrinsic blood flow, and a limited ability to accept a blood flow. This limitation can be seen independent of reduced blood flow, and intrinsic metabolic function is abnormal.[14] Metabolic abnormalities have also been described, including early dependence on anaerobic metabolism, excessive early depletion of high energy phosphate bonds, and excessive early intramuscular acidification. Biopsy studies have confirmed defects in oxidative and lipolytic enzymes, succinate dehydrogenase and citrate synthetase, and β hydroxyacyl dehydrogenase. Muscle is also abnormal in gross function, showing in particular early fatigue, and maximal strength. The changes seen are at least partially similar to those seen in physical deconditioning and are at least partially correctable by exercise training indicating a degree of plasticity.[15]

The abnormalities of muscle and even the degree of wasting show a better correlation with exercise tolerance than do measures of left ventricular function. This is because fatigue is a common symptom interrupting exercise in patients with CHF. Less clear is the aetiology of the muscle changes. Although deconditioning contributes, there are suggestions of a distinct phenotype in CHF muscle not explained by
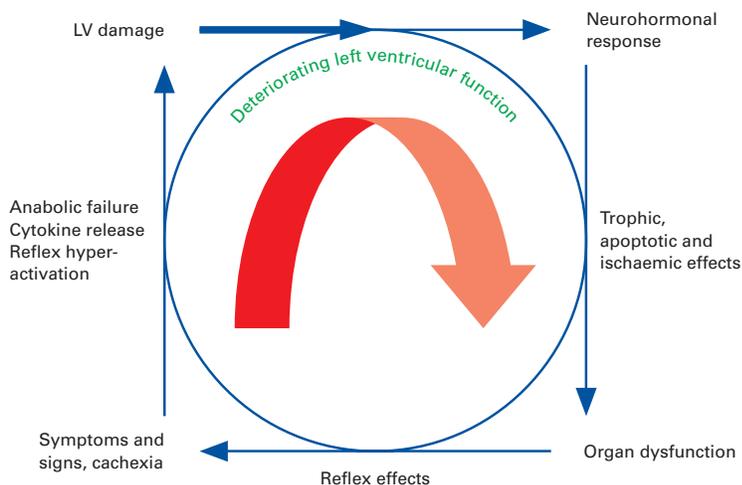
> ### Abnormalities of skeletal muscle in CHF
>
> - Loss of bulk
> - Impaired perfusion
> - Increased fatigue
> - Abnormal histology
> - Abnormal metabolism

deconditioning.[16] Major abnormalities in catabolic and anabolic function have been described in those CHF patients with substantial wasting of skeletal muscle,[17] and these patients have been identified as having in particular an exaggerated release of catabolic cytokines,[18] and resistance to the effects of growth hormone.[19] The cause, progress, and most appropriate management of these abnormalities in muscle structure and function remain unknown. Physical inactivity is likely to play a role in some cases, along with activation of catabolic processes, and loss of normal anabolic function, such as insulin resistance,[20] raised concentrations of tumour necrosis factor α, and excessive noradrenaline (norepinephrine) concentrations. Anorexia and intestinal malabsorption may also play a role in some patients. When seen, these changes are also markers of an extremely poor prognosis.[21]

Endothelial dysfunction

Recent research has demonstrated the importance of the endothelium to the development and progression of a number of cardiovascular conditions, including hypertension, diabetes, heart failure, and atherosclerosis. Endothelial dysfunction is associated with deficiency of the natural endothelial nitric oxide vasodilator system, with exaggerated activity of the vasoconstrictor endothelin system. Both abnormalities are now considered hallmarks of human CHF. When present they lead to a further impairment of nutritive blood flow to already stressed and metabolically abnormal skeletal muscle, and they therefore contribute to exercise intolerance in patients with CHF. Interventions which improve endothelial function, such as exercise training, also increase exercise tolerance and appear to do so by improving the sensation of fatigue within skeletal muscle. All these features make it likely that muscle dysfunction, either intrinsic or caused by impaired blood flow, contributes to exercise intolerance and symptoms in CHF.

Lung and ventilatory abnormalities

It is easy to see how major alterations in skeletal muscle and endothelial function could contribute to fatigue. Major changes have been described within the lung and in two major ventilatory control reflexes (the muscle ergo- or metaboreflexes and the arterial chemoreflexes).[22–24] These appear to be in a better position to explain the dyspnoea which is so common in CHF even when haemodynamics are relatively well controlled. These may

Figure 2. The muscle hypothesis of chronic heart failure, in which it is proposed that alterations in skeletal muscle contribute not only to symptom generation but also, via reflex effects, to further neurohormonal activation and progression of the syndrome of CHF.

575

also be important pathophysiological mechanisms as abnormalities of ventilatory control have consistently been shown to predict accurately a poor prognosis in CHF.[25 26] These may be more important in predicting symptomatic limitation than even the underlying cause of the heart failure.[27] More recent research has shown that both exercise tolerance per se, even if measured in simple corridor tests,[28] and the physiological ventilatory response to exercise are important and independent prognostic markers in CHF.[29]

Respiratory muscle is also abnormal in CHF. Early muscle deoxygenation, respiratory muscle fatigue, and histological changes have all been described.[30] These may also contribute to the sensation of dyspnoea. Whether these abnormalities can explain the excessive ventilatory response to exercise seen frequently in CHF remains unknown. The relation between minute ventilation (VE) and CO_2 production (VCO_2) during progressive exercise—the VE/VCO_2 slope—is characteristically raised in patients with non-oedematous CHF (figs 3 and 4).[31] Possible causes include ventilation–perfusion mismatch within the lung causing excessive, but non-contributory ventilation,[32] along with enhanced sensitivity of ventilatory control mechanisms described above. The ergoreflex system senses the metabolic state of exercising skeletal muscle and reflexly increases ventilation. It is sensed by small work sensitive afferents and carried by small myelinated or unmyelinated nerve fibres. An overactivity of these fibres and the resultant reflex responses have recently been described in CHF; it was also shown that the overactivity could be partially reduced by localised muscle training, highlighting the possible importance of muscle deconditioning in this abnormal response. The second overactive ventilatory control system in CHF is the chemoreceptor system. We have recently described augmentation of peripheral hypoxic and central CO_2 sensitivity in CHF patients.[33] These alterations could explain the heightened ventilatory responses and also lead to excessive sympathetic excitation. The cause of the heightened chemosensitivity itself remains undetermined, but it is possible that there is a direct interaction between the ergoreflex and chemoreflex systems.

Features of the CHF syndrome

The haemodynamic profile of patients limited by fatigue differs in no substantial measure from those patients limited predominantly by dyspnoea.[34] Ambulatory pulmonary arterial pressure monitoring has shown virtually no correlation between the haemodynamic disturbances and the symptoms noted by the patients at the time of the disturbance. No measure of haemodynamics (with the possible exception of measures of right ventricular performance) has demonstrated a convincing capacity to predict variations in exercise capacity between patients as well as do measures of peripheral function,
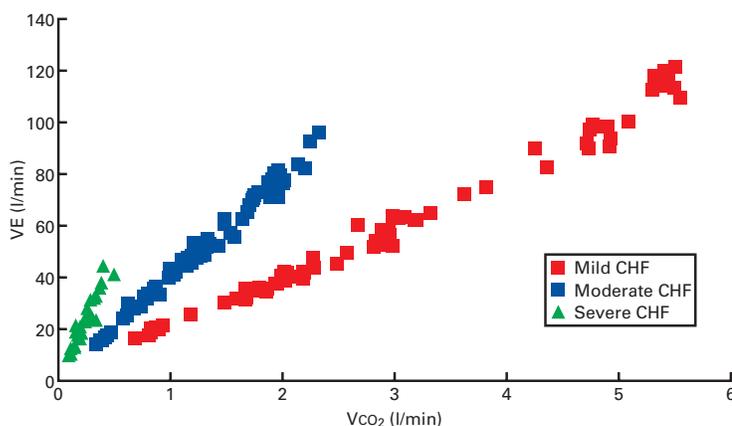

Figure 3. Plot of minute ventilation (VE) versus the rate of carbon dioxide production (VCO_2) in three patients with chronic heart failure. You can see that the ventilation needed for the same carbon dioxide elimination rate increases with the increasing severity of heart failure. This is associated with a greater sensation of dyspnoea despite preservation of arterial blood gases in these patients.

such as skeletal muscle strength, endothelial function or ventilatory abnormalities. Whatever treatments are used (with a few exceptions in selected patients), there is a delay between haemodynamic effect and any objective change in exercise tolerance.[35] Treatments such as angiotensin converting enzyme (ACE) inhibitors and cardiac transplantation require weeks or months to improve exercise tolerance. The delay may be caused by the need to reverse some of the peripheral pathophysiological changes that have become the weakest link in the chain of oxygen delivery and utilisation necessary for muscular exercise. CHF is, we now realise, a systemic disorder with major neurohormonal,[36] cytokine, metabolic, and inflammatory consequences[37] that affect a myriad of organ systems in the body. The new treatments might come from any of these non-traditional targets for intervention for heart failure sufferers.

Exercise training in CHF

Exercise training in carefully selected patients with stable mild to moderate CHF can increase exercise capacity and lessen dyspnoea and fatigue.[38] These improvements have been seen mainly in peripheral pathophysiology, with no
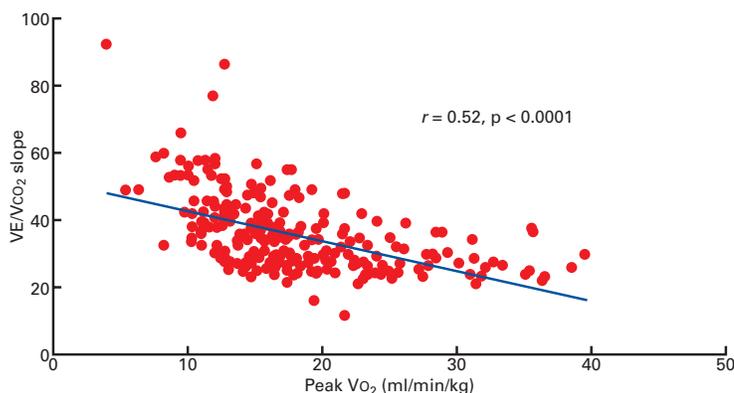

Figure 4. Relation between the minute ventilation to carbon dioxide production slope and exercise capacity in 248 patients with chronic heart failure.

consistent effect on left ventricular ejection fraction, either beneficial or detrimental. Most of the beneficial effects seem to depend on training induced adaptations in the periphery, correcting many of the pathophysiological changes described above, and giving further credence to their original importance in mediating symptomatic exercise limitation.

Sullivan and colleagues demonstrated both an increased blood flow to exercising muscle and an increased ability of skeletal muscle to extract oxygen from the nutritive blood flow associated with improved symptoms and exercise tolerance. Ventilatory function was also improved, with a reduction in the respiratory exchange ratio at submaximal exercise and a delay in the anaerobic threshold.[39] The first controlled study was published soon after.[40] After baseline evaluation and familiarisation with laboratory procedures all patients performed eight weeks of exercise training and eight weeks of exercise avoidance in a randomised crossover study. The training regimen led to a 20–25% increase in exercise tolerance and peak oxygen consumption. There was also a significant reduction in questionnaire rated symptoms attributable to heart failure, and a coincident increase in both the extent and ease of performing daily activities. In a study involving 16 women with heart failure, Tyni-Lenne and colleagues[41] showed that eight weeks knee extensor endurance training could increase skeletal muscle citrate synthase activity by 44% ($p < 0.0001$) and lactate dehydrogenase activity by 23% ($p < 0.002$). There was an increase in oxidative capacity in relation to the glycolytic capacity of 23% ($p < 0.002$), showing plasticity of the skeletal muscle abnormalities described as accompanying CHF. In addition peak oxygen uptake increased 14% ($p < 0.0005$), peak work rate increased 43% ($p < 0.0001$), and physical ($p < 0.05$), psychosocial ($p < 0.03$), and overall ($p < 0.01$) health related quality of life improved.[41]

Hambrecht and colleagues showed biopsy derived skeletal muscle mitochondrial volume density increased significantly after training in CHF, a finding later shown to correlate well with the training induced improvement in exercise capacity.[42]

Wielanger and associates compared 41 trained and 39 control patients.[43] Training was supervised for 12 weeks. They showed "feelings of being disabled" decreased, while "self-assessment of general well-being" and exercise time increased (+21.4%, $p < 0.0001$), as did anaerobic threshold (+12.5%, $p < 0.05$).[43] A summary of trials performed by one collaborative European group[44] and an overview of all trials published to 1998[45] have both shown a consistent increase in exercise capacity across a broad range of heart failure patients of approximately 15–20%. Beneficial changes produced by training have included improvements in haemodynamic responses, myocardial perfusion, diastolic function, skeletal muscle function, histological and biochemical responses, ventilatory control, peripheral vascular and endothelial function, and neurohormonal and autonomic improvements,

> **Symptoms of heart failure: key points**
>
> - Symptoms are poorly correlated with resting haemodynamics in non-oedematous chronic heart failure (CHF)
> - Fatigue relates to muscle changes in the periphery
> - Dyspnoea in CHF is related to increased ventilation during exercise
> - Ventilatory reflexes are exaggerated in CHF
> - Blood gases remain near normal during exercise in stable CHF
> - Training can improve symptoms in CHF mainly by correcting peripheral non-cardiac pathophysiological changes
> - Conventional treatments—apart from diuretics—poorly control symptoms in CHF
> - Endothelial dysfunction in CHF contributes to fatigue
> - Muscle wasting is associated with a particularly poor prognosis in CHF

577

further reinforcing the close correlation between the systemic pathophysiology of CHF and the symptoms limiting exercise.

Conclusions

In understanding the physiological basis of symptoms of patients with CHF, and in designing optimal strategies to improve these symptoms, we must now begin to unravel the complex physiological processes determining exercise capacity. It appears that the periphery, including muscle endothelium, the lung, and ventilatory control reflexes, play a central role in the factors limiting exercise, in contrast to the more haemodynamic basis of symptom generation in acute heart failure with pulmonary oedema. This introduces a new era in the treatment of heart failure in which antineurohormonal and metabolic[46] treatments might be of increasing importance as we target the pathophysiology limiting our CHF patients.

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578

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