Mechanisms of exercise limitation in chronic heart failure and the role of rehabilitation

Exercise limitation is a cardinal clinical feature in patients with chronic heart failure, and is often the reason these patients seek medical attention. Breathlessness and fatigue are the two main symptoms that cause heart failure patients to stop exercising. It was initially thought that dyspnoea was largely due to pulmonary congestion, and fatigue due to reduced skeletal muscle perfusion. However, there appear to be no distinguishing clinical characteristics that determine which symptom will cause a patient to terminate exercise. Indeed, the same patient may stop exercising because of dyspnoea or fatigue, depending upon what type of exercise is being performed. Treadmill exercise and fast exercise protocols are more likely to result in breathlessness, whereas cycle exercise and slow exercise protocols more often cause fatigue.

A number of factors may contribute to exercise intolerance in heart failure including patient motivation, central perception of breathlessness, increased work of breathing, decreased oxygen supply to exercising skeletal muscles, intrinsic skeletal muscle changes and impaired substrate utilization. It appears likely that all of these factors may be important to varying degrees.

Exercise capacity may be assessed by measuring the duration of exercise that can be performed according to a specific cycle or treadmill protocol, or alternatively by measuring the distance achieved within a specified time period. These tests provide different information, and indeed the latter gives an assessment of sub-maximal exercise capacity, which may be more relevant to everyday life. In addition, gas exchange may be monitored to allow determination of oxygen consumption achieved either at the time of anaerobic threshold or when exercise is terminated because of fatigue or dyspnoea. This allows accurate quantification of exercise capacity, and aids in the identification of individuals limited by non-cardiac factors. Maximal oxygen consumption is an important prognostic variable which is often employed in selecting patients for cardiac transplantation.

Given that maximal oxygen consumption is a function of both cardiac output and peripheral oxygen extraction by the tissues, it is not surprising that the ability to augment cardiac output is an important determinant of maximum exercise capacity, both in healthy subjects and those with heart disease.

Because of reduced contractile reserve, cardiac output augmentation, in patients with chronic heart failure, relies on Frank-Starling mechanisms and on the ability to increase heart rate. Chronotropic incompetence is common in patients with severe heart failure, and contributes to exercise limitation. Impaired ventricular filling, by preventing use of the Frank-Starling mechanism, is an important contributor to exercise limitation, not only in patients with primarily diastolic dysfunction, but also in those with systolic impairment. Indeed, exercise capacity does not relate to left ventricular ejection fraction in patients with chronic heart failure, but in a recent study of patients with mild to moderate left ventricular systolic dysfunction, was strongly related to parameters of diastolic filling measured on exercise. Impaired left ventricular filling may be a consequence of delayed relaxation, or in severe heart failure, of constraint to filling caused by the surrounding pericardium and right ventricle.

It has traditionally been assumed that pulmonary venous congestion contributes importantly to exercise limitation in chronic heart failure, either by reducing lung compliance, impairing gas exchange, or activating juxtapulmonary capillary receptors. Studies have reported either no correlation or a weak correlation between maximum oxygen consumption and resting or exercise pulmonary capillary wedge pressure. Nevertheless, pulmonary vascular factors may be important. In one study, right ventricular ejection fraction (the major determinant of which is right ventricular afterload) was related to maximum oxygen consumption. This may in part be because pulmonary hypertension, by causing right ventricular dilatation, is a major factor leading to pericardial constraint, thereby limiting stroke volume augmentation.
Although cardiac output is a major determinant of exercise capacity, peripheral factors are equally important in heart failure. Whereas in normal subjects, maximal exercise capacity appears to be limited primarily by cardiac output, in patients with severe chronic heart failure, the addition of arm to maximal leg exercise causes a further increase in oxygen consumption. This suggests that peripheral factors may limit maximal exercise performance in at least some heart failure patients. These factors include maldistribution of blood flow to exercising skeletal muscle, reduced skeletal muscle mass, and changes in skeletal muscle function.

Maldistribution of skeletal muscle blood flow is a consequence of sympathoexcitation, increased sodium content in the vessel wall, and endothelial dysfunction. However, whilst chronic hypoperfusion may contribute to skeletal muscle structural and functional changes, there is no correlation between blood flow to exercising muscle and exercise capacity in patients with chronic heart failure. This suggests that overall skeletal muscle blood flow is not a limiting factor acutely, but does not exclude inhomogeneity of flow as a consequence of microvascular endothelial dysfunction as a contributory mechanism.

Several studies have reported skeletal muscle ultrastructural, histochemical and functional disturbances in heart failure patients. Muscle wasting occurs even in mild heart failure, and exercise capacity correlates with muscle mass and strength. Myocyte atrophy, with an increase in the percentage of type IIB fibres, and a reduction in mitochondrial density, with reduced cristae surface density, are reported. Oxidative enzymic capacity is reduced, causing a premature switch to anaerobic metabolism. Phosphorus-31 magnetic resonance spectroscopy demonstrates rapid depletion of phosphocreatine during exercise, resulting in an exaggerated increase in the inorganic phosphate/phosphocreatine ratio. Important factors leading to these skeletal muscle changes include deconditioning, malnutrition, and cytokine activation (especially TNF-α), leading to expression of iNOS in skeletal muscle.

Reduced vital capacity, increased airways resistance, decreased lung compliance and ventilation-perfusion mismatching have all been documented in patients with chronic heart failure. Hypoxaemia does not usually occur during exercise in patients with chronic heart failure. However, these pulmonary abnormalities may contribute to the work of breathing and thereby influence exercise capacity. Reduced respiratory muscle strength has been demonstrated in patients with chronic heart failure, and correlates with ratings of perceived dyspnoea. However, another study reported no correlation between respiratory muscle strength and exercise time or breathlessness. There is an increased ventilatory cost of CO₂ elimination in heart failure, which may contribute to the work of breathing. The mechanism is unproven, but it has been suggested that endothelial dysfunction may impair ventilation-perfusion matching during exercise.

Chemosensitivity (i.e. the ventilatory response to hypoxaemia or hypercapnia) is increased in patients with chronic heart failure. Mechanisms may include the effects of increased circulating catecholamines, decreased baroreceptor activity, and decreased chemoreceptor blood flow. The ergoreflex contribution to ventilation is also increased in heart failure. These factors may contribute to the perception of breathlessness. Finally, the breathing pattern during exercise is abnormal in chronic heart failure. Tidal volume does not increase normally, and increased ventilation is achieved principally by increased ventilatory rate, at the cost of greater anatomical deadspace.

Breathlessness and fatigue are subjective sensations. The demonstration of improved breathlessness scores and exercise capacity following the administration of synthetic opiates in patients with chronic heart failure underscores the importance of central factors in the perception of breathlessness. Traditionally, heart failure patients have been advised to rest and avoid undue physical exertion, because of the potential adverse consequences.

There is however, increasing evidence that exercise training should be encouraged in patients with stable chronic heart failure. A number of studies have demonstrated beneficial effects of training in heart failure patients including improvements in exercise time, maximal oxygen consumption, symptom scores and quality of life. Perhaps more importantly, exercise training appears possible without major complications or ill-effects on left ventricular function. The benefit derived from training occurs despite there being little or no effect on haemodynamics. Sullivan et al. demonstrated an increase in both peak exercise leg blood flow and arteriovenous oxygen difference in association with an increase in maximal oxygen consumption during training in heart failure patients. Other studies have reported enhanced oxidative metabolism in exercising skeletal muscle, improved autonomic function, and reduced ergoreflex contribution to ventilation following training.

Patient selection is important, in that patients should be stabilized on adequate medical therapy prior to undertaking exercise training. The exercise programme should be geared to the individual patient. Patients are usually advised to exercise at 70% to 80% of their maximum heart rate or oxygen uptake, for 20 to 45 min three to five times a week. Most studies have used aerobic exercise such as walking or cycling. However, it appears that muscle
strength training and specific respiratory muscle training may also benefit heart failure patients.\(^{28,29}\) It is likely therefore that training programmes which combine all of these aspects will provide the greatest benefit to patients with chronic heart failure. Future studies will be required to assess the influence of training on morbidity and mortality.

J.J. Atherton  
A.C. Tweddell  
M.P. Frenneaux  
Department of Cardiology  
University of Wales College of Medicine  
Cardiff

References


