

Editorial

The role of exercise testing in chronic heart failure

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The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure (Sir Thomas Lewis, 1933).¹

Exercise testing is often used by clinicians to diagnose and follow patients with coronary artery disease, because myocardial ischaemia during exercise produces haemodynamic and electrocardiographic changes that can be quantitatively and qualitatively defined by safe, accurate, reliable techniques. The role of exercise testing in this context is well established: its potential in the management of patients with heart failure remains to be fully exploited.²⁻⁴ Adequacy of peripheral tissue perfusion during exercise depends upon cardiovascular performance, but exercise testing to assess overall functional capacity has been used primarily by exercise physiologists and relatively little by clinicians. Nevertheless, symptoms in chronic heart failure are manifest on exertion.

Until recently patients with heart failure were assessed solely by a questionnaire about symptoms (usually the criteria of the New York Heart Association)⁵ and by clinical examination. With the appearance of new drugs it became important to document objectively the effects of treatment on cardiorespiratory fitness so that a scientific basis for treatment could be established. The limitations of the assessment of functional state by the New York Heart Association criteria are obvious. The criteria are by their nature subjective and reproducibility between observers is poor.⁶ The New York Heart Association functional classification is unlikely to reflect small but clinically important changes in functional status because the categories are too broad. Because there are only four grades, it is possible that the functional class will not alter despite a clinically important change in functional status after

a therapeutic intervention. Symptomatic assessment by the criteria of the Specific Activity Scale may be better than the New York Heart Association system because it is more reproducible; however, the other criticisms of the New York Heart Association assessment still apply.⁶

Why perform an exercise test?

An objective assessment should mirror the general wellbeing and exercise capacity of the patient with precision and reproducibility such that small, yet significant changes in functional state are detected in response to drug intervention, cardiac transplantation, and rehabilitation. Ideally, the assessment should provide a guide to the severity and hence prognosis of the condition. Unfortunately, there is no gold standard. General wellbeing is difficult to assess objectively, so attention has been directed to indices that can reflect changes in exercise capacity. Though a chest x ray is a part of the routine investigation of a patient with heart failure, two studies have demonstrated either a poor correlation or no correlation between cardiothoracic ratio and exercise capacity.^{7,8} As left ventricular dysfunction is presumably the primary event that initiates the clinical syndrome of heart failure, it has been presumed that indices of left ventricular performance are related to exercise capacity. Several studies have shown that estimates of resting or peak exercise left ventricular ejection fraction or resting left ventricular end diastolic dimensions do not correlate with exercise capacity.⁹⁻¹¹ It is perhaps not surprising that these measurements fail to predict exercise capacity in a miscellaneous population of patients with severe heart failure. The mechanism by which these patients increase cardiac output on exercise varies with the aetiology of the heart failure.¹² Patients with idiopathic dilated cardio-

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myopathy increase stroke volume by increasing the ejection fraction and with little change in left ventricular end diastolic dimensions, whereas patients with poor left ventricular function secondary to ischaemic heart disease have larger increases in left ventricular end diastolic and end systolic dimensions with the result that there is no change in ejection fraction.

Attention has recently been directed to the importance of the right ventricle in heart failure in determining exercise capacity.⁷⁻¹⁰ Exercise capacity appears to correlate with pulmonary vascular resistance¹³ and resting right ventricular ejection fraction.¹⁰ Pulmonary vascular resistance in heart failure does not fall, as it does in normal subjects during exercise. Since the right ventricle may not be as extensively affected as the left ventricle by the underlying pathological process, right ventricular function is predominantly afterload dependent. So it is interesting to note that only drugs that cause dilatation of the pulmonary vascular bed can significantly increase exercise capacity in controlled trials of heart failure. Other predominantly arterial vasodilators have failed to improve exercise capacity despite producing a pronounced improvement in systemic haemodynamic and left ventricular function.¹⁴⁻¹⁵ It would be optimistic, however, to expect minor changes in exercise capacity to be reflected closely by changes in right ventricular function and the pulmonary circulation. Thus it is clear that if we wish to detect an improvement in exercise capacity this has to be measured directly by some form of exercise test.

Methods of exercise testing

The choice of exercise protocol has not been satisfactorily evaluated, though recent studies provide guidelines. The bicycle ergometer is probably the best method of exercising normal volunteers.¹⁶ The technique is simple and energy output can be predicted with greater accuracy than with other forms of exercise because the mechanical efficiency is independent of body weight. A bicycle exercise test may be undesirable as a method of assessing exercise capacity in people who have never ridden a bicycle before because the motivation and stimulation of the subject are particularly important during this form of exercise. The treadmill is preferable to the bicycle for testing middle aged and elderly subjects, though some individuals find it difficult to walk on the treadmill and view the experience as frightening. The major disadvantage of treadmill exercise is that it is difficult to standardise the workload, as factors other than treadmill speed and gradient can affect the final workload achieved. The workload can be

affected by the subject holding on to the rail or walking with long or short strides.

To date most studies have reported data from maximal exercise tests, that is, an incremental test which is terminated by dyspnoea or fatigue. The safety of a graded maximal exercise test has recently been established in a group of 607 stable patients from the Veterans Administration Cooperative Heart Failure Trial.¹⁷ At least two exercise tests were performed in all patients. Arrhythmias were the end point in <1.8%. Hypotension occurred in 0.2% of baseline tests. There were no major complications in a total of 2892 exercise tests. Ventricular tachycardia was unmasked during exercise and in the immediate recovery period in only 3.2% of patients.

Exercise protocols have usually been modified to accommodate a reduced exercise capacity. This is necessary to permit patients to exercise long enough for sufficient data to be acquired for the discrimination of different grades of exercise limitation. Haemodynamic and metabolic responses to exercise may be delayed when the cardiac output is reduced; therefore it is essential when designing a multistage exercise test, to ensure that stages are sufficiently long to permit equilibrium at each exercise stage. In our laboratory we use a modified Naughton protocol with exercise stages of three minutes because we have demonstrated that metabolic and respiratory gas exchanges have reached a plateau for each workload in that time.³

Reliance on symptomatic end points alone can be unsatisfactory as they are clearly subjective and easily affected by observer encouragement. Recent studies have suggested that coupling respiratory gas analysis with maximal exercise testing provides a more objective assessment.^{2-4, 18} During muscular work there is a complex interplay of diverse physiological mechanisms that ensures that oxygen delivery is commensurate with oxygen demand. The heart, lungs, and oxygen capacity of the blood participate in these adjustments. Measurement of maximal oxygen consumption during exercise is thus an index of total cardiorespiratory function and is a measure of the maximal capacity to transfer oxygen to the tissues of the body. Although exercise duration correlates significantly with oxygen consumption, the relation between the two variables is not sufficiently strong to permit accurate estimates of oxygen consumption.³ Furthermore, repeated exercise testing in the same individual increases exercise duration (as the subject learns to walk more "efficiently" on the treadmill) without a corresponding increase in workload as shown by an increase in maximal oxygen consumption.^{3, 19} This is why measurement of oxygen consumption is a better measure

of exercise capacity in patients with heart failure.

Many factors (genetic, age, sex, and previous level of physical activity) affect symptom limited maximum oxygen consumption in normal individuals.¹⁶ These effects are much less important than the gross changes in symptom limited maximum oxygen consumption seen in patients with heart failure. Many studies have claimed that as a person exercises at increasing workloads maximal oxygen consumption increases to a plateau.^{2 20 21} As this is the physiological limit of the aerobic capacity of the body it is an objective assessment of individual exercise capacity. It is now clear that a physiological limit to maximal oxygen is rarely reached in patients with heart failure.^{3 4 22} Nevertheless, the measurement of oxygen consumption at peak exercise, so-called "maximal" oxygen consumption, is reproducible and permits categorisation of patients into subgroups according to the severity of functional impairment.^{2-4 18} Thus in one study there were significant differences in maximal oxygen consumption between patients in different New York Heart Association functional classes.³ Two other studies did not show significant differences in maximal oxygen consumption between New York Heart Association classes II and III,^{2 18} but this may have related to the definition of New York Heart Association class II in the different reports.

The ideal index of exercise capacity is one that is totally independent of patient motivation and thus completely objective. In normal individuals the oxygen consumption/heart rate response to asymptomatic submaximal exercise may provide an approximate yet objective index of maximal exercise capacity.¹⁶ Unfortunately, in patients with heart failure the heart rate response to submaximal exercise has no predictive value,²³ perhaps because in this condition the heart rate response is affected by fear and altered baroreceptor reflexes²⁴ and β adrenergic function.²⁵ In an attempt to achieve the goal of an objective assessment there has been renewed interest in the measurement of the anaerobic threshold.^{2 3 26} In the early part of this century it was found that increased workloads could be achieved without any change in blood lactate concentration from the resting value.²⁷ As the work rate increased beyond a certain level, the blood lactate concentration increased. The carbon dioxide combining power of the blood (essentially the bicarbonate concentration) fell with an increase in blood lactate and breathing was "stimulated to expel the carbon dioxide set free" as the bicarbonate concentration in the blood diminished.²⁸ Hill *et al* postulated that during muscular exercise if the oxygen supply to contracting muscle became inadequate lactate production increased. The stage at which this increase

occurred reflected the limits of cardiorespiratory function.²⁹ Thus during exercise patients with severe heart failure develop a metabolic acidosis more quickly than those with mild heart failure. Because the onset of the acidosis is presumably independent of patient motivation its detection gives an objective assessment of cardiorespiratory fitness. Wasserman and McIlroy introduced the term "anaerobic threshold" and elaborated on the concept that pulmonary gas exchange measured at the mouth could be used to detect the onset of a metabolic (lactate) acidosis.³⁰ The respiratory anaerobic "threshold" can be determined by several methods, the most common being a non-linear increase in minute ventilation or carbon dioxide production relative to oxygen consumption.

Recently the concept of an anaerobic threshold has been challenged for the following reasons.³¹ Firstly, plasma lactate concentration is the net result of lactate production and removal. The rate of lactate production can be three times higher than during rest while blood lactate remains at resting values. Secondly, training increases lactate clearance but not lactate production. Thirdly, and arguably the most important challenge, lactate production may occur in fully oxygenated conditions with activation of fast twitch skeletal muscle fibres. Furthermore, there is debate about whether a rise in plasma lactate is linked with the ventilatory anaerobic threshold.³¹ The postulated association between an increase in lactate and the ventilatory stimulus is supported by evidence from individuals who have had surgical resection of the carotid bodies.³² These individuals have a smaller ventilatory response to exercise above the anaerobic threshold. None the less, patients with McArdle's syndrome also have a ventilatory anaerobic threshold despite an inability to produce lactate,³³ but because exercise induces pain in this disease the disproportionate increase in ventilation during exercise is likely to be caused by hyperventilation in response to pain.³⁴ Some investigators have found a close association between the ventilatory anaerobic threshold in patients with heart failure and the rise in blood lactate²⁶; others have not.⁴ The confusion has in part occurred because of the different methods of determining the anaerobic threshold and detecting where, if at all, there is a sharp rise in plasma lactate or in fact a discrete ventilatory threshold. Computerised analysis, using a curve fitting model, of the oxygen consumption/carbon dioxide production relation during exercise appears to avoid the problem of defining a discrete ventilatory threshold. This promising new technique provides a refinement to the concept of anaerobic threshold and, it is hoped, greater objectivity.³⁵

The anaerobic "threshold" is in part determined by a lactate acidosis during exercise, but other factors may be important. Measurement of the ventilatory anaerobic threshold has two potential uses. First, it can be used as a general index of patient motivation. Failure to achieve the ventilatory anaerobic threshold suggests poor patient motivation. Secondly, changes in maximum oxygen consumption in the absence of change in the anaerobic threshold suggest an alteration in patient motivation rather than a change in functional capacity. Assessment of maximum oxygen consumption alone can be misleading, but linked with knowledge of the anaerobic threshold these measurements provide an objective and accurate means of classifying and following patients with heart failure.²

The equipment required to measure respiratory gas exchange is expensive and some patients find it difficult to exercise on a treadmill. High workloads are not typical of activities performed by these patients in daily life. In patients with moderate to severe disability it may be more reasonable to measure exercise capacity at constant submaximal workloads, for example 60–70% of symptom limited maximal oxygen consumption. Unfortunately these tests may be difficult to perform as the duration of exercise may be considerable and boredom may be a limiting factor. Various groups have used a 2, 6, and 12 minute walking test to monitor exercise capacity in normal subjects and patients with obstructive lung disease. Recently, a test which simply measures the distance walked in six minutes has been used to assess patients with heart failure.³⁶ Patients preferred the six minute walking test to the treadmill, finding it easier and more closely related to their daily level of physical activity. There were wide ranges of six minute distances walked among those patients with a very low maximal oxygen consumption. Some of these individuals may have been poor treadmill performers who produced a better account of their abilities during the walking test. Conversely, there was little variation in the six minute distance in normal subjects and in patients with mild heart failure despite noticeable differences in their maximal exercise capacities. In those with mild heart failure the maximal rather than the submaximal test may be a more suitable method of assessing exercise capacity, as exercise is performed at workloads sufficient to cause symptoms.³⁶

To summarise, the choice of exercise protocol used to assess patients with heart failure is partly determined by available facilities. Maximal exercise testing is conventional, and should if possible be linked with respiratory gas analysis. Submaximal exercise tests may be more appropriate in patients with severe failure, and may gain popularity

especially in centres that do not have access to gas analysis equipment.

Symptoms limiting exercise tolerance

The symptoms limiting exercise in patients with heart failure are difficult to evaluate.³⁷ Exercise testing linked with analysis of respiratory gas exchange and haemodynamic assessment has permitted insight into the problem. Classic teaching suggests that breathlessness in patients with heart disease is caused by pulmonary venous hypertension and fatigue by an inadequate increase in cardiac output on exercise. Though this may be the case in acute heart failure, the situation is less clear once chronic heart failure is established. The feeling of breathlessness appears to be independent of changes in left atrial pressure (as estimated from the pulmonary capillary wedge pressure). There is no correlation between the wedge pressure at rest or during maximal exercise and maximal oxygen consumption reached at the end of symptom limited exercise.^{8 9 38 39} The symptom which terminates exercise depends on the type of exercise performed rather than peak wedge pressure. Slow exercise is usually terminated by fatigue whereas rapid exercise is terminated by dyspnoea despite a similar peak pulmonary capillary wedge pressure at the end of each form of exercise.³⁹ Furthermore, when submaximal and maximal exercise tests are compared, both forms of exercise are terminated at identical ventilatory levels and peak exercise pulmonary capillary wedge pressures.⁴⁰ If the primary stimulus to excessive ventilation during exercise was an acute increase in pulmonary venous pressure then the increase in ventilation would be greater during more prolonged submaximal exercise. In addition, long term drug studies have shown that an improvement in exercise capacity is often, but not invariably, associated with an improvement in haemodynamic function and a fall in pulmonary capillary wedge pressure during exercise. Short term vasodilators and inotropic agents almost always improve the haemodynamic indices and lower the pulmonary capillary wedge pressure, but usually do not increase exercise capacity in the long term.¹⁴ An alternative explanation relates the many complex metabolic changes that occur during exercise.³⁹ Blood flow through skeletal muscle is reduced in patients with heart failure.⁴¹ A lactic acidosis develops during rapid forms of exercise and may stimulate peripheral chemoreceptors which contribute to the hyperventilatory response and feeling of breathlessness.³⁹

The mechanisms of fatigue in heart failure are elusive. Fatigue is associated with inadequate oxy-

gen supply to skeletal muscle. During maximal exercise testing, the oxygen content of blood in the femoral vein is negligible.⁴² Wilson *et al* showed that patients with chronic heart failure became fatigued when underperfusion of skeletal muscle reached a critical level; they concluded that fatigue in patients with heart failure was caused by impaired nutrient flow to skeletal muscle.⁴³ The mechanisms may be intracellular acidosis, caused by accumulation of lactate, or depletion of phosphocreatine.⁴³ Alternatively, there may be persistent changes in skeletal muscle function in chronic heart failure caused by deconditioning which also contribute to exercise limitation in these patients.⁴⁴ After cardiac transplantation, despite virtually immediate restoration of a normal resting cardiac output, the expected increase in exercise capacity is delayed over several months.⁴⁵ This response may relate to a gradual reduction in those factors that limit skeletal muscle blood flow or to a gradual improvement in the function of skeletal muscle.⁴⁴ What these research findings show, then, is that the limitation of exercise and the feelings of breathlessness or fatigue in patients with chronic heart failure have multifactorial mechanisms. Their symptoms should not be related solely to an altered haemodynamic response to exercise. The symptom that limits an individual patient will depend on the different mechanisms influencing neural and metabolic signals from exercising muscle and the response of more central receptors.

Rehabilitation in heart failure

Surprisingly, the effect of regular exercise testing per se on exercise capacity has not been extensively studied. There are only two published reports.^{46 47} Regular exercise (30 minutes, three times per week at 60–70% of maximal oxygen consumption for 15 weeks) improves cardiac output and reduces pulmonary capillary wedge pressure at submaximal exercise workloads and increases symptom limited maximal oxygen consumption by 25%.⁴⁷ It has been suggested that the improvement in maximal exercise capacity is related to an improvement in skeletal muscle blood flow,⁴⁷ yet the same group also showed that short term treatment with dobutamine increases blood flow to skeletal muscle during submaximal exercise but does not augment maximal oxygen consumption.⁴⁸ Regular training probably improves exercise capacity partly because of the cardiovascular training effect, but also perhaps because of a direct peripheral effect, presumably on skeletal muscle function. Further longitudinal studies are required to evaluate the effect of treatment and rehabilitation on the performance of skeletal muscle

in heart failure.

Prognosis in heart failure

Prolonged survival remains the major goal of treatment. From the time of initial diagnosis of heart failure, overall mortality exceeds 50% within five years.⁴⁹ In patients who remain symptomatic despite treatment with diuretics, the mortality rate is approximately 75% over three years.^{50 51} Until recently there was no evidence that treatment, with the presumed exception of cardiac transplantation, altered this terrible prognosis.^{50 52} The detection of any possible positive association between survival and treatment has been delayed by a tendency to perform small drug studies with an inadequate duration of follow up. Combined data from the trials of angiotensin converting enzyme inhibitors appear promising and the published results of large trials are awaited.⁵⁰ The results of a large trial of the effects of enalapril in heart failure have now been published. Enalapril reduced mortality at six months and one year by 40% and 31% respectively when compared with placebo.⁵³ The data from the Veterans Administration Cooperative Heart Failure Trial study demonstrate a 28% reduction in long term mortality with hydralazine and isosorbide dinitrate compared with placebo.⁵² To alter significantly the course of the disease, it is essential to recognise indicators of outcome. Data relating to haemodynamic function are conflicting.^{54 55} Though the left ventricular ejection fraction does not correlate with exercise capacity, it is an important predictor of survival.⁵⁶ The importance of non-sustained ventricular tachycardia is less clear. Though the presence of ventricular tachycardia correlates with mortality it is not clear whether it predicts sudden death.⁵⁷ Concentrations of plasma noradrenaline⁵⁸ and serum sodium⁵⁹ determined from a single blood sample may provide a guide to prognosis in heart failure. The cynic might say that the obvious conclusion from all these studies is that the sicker the patients, the quicker they will die.

Most of the indices of prognosis are not independent predictors of survival. Because the known predictors of survival do not relate to exercise capacity, it is pertinent to assess the prognostic significance of exercise testing. It is clear that the more severe the functional disability at the time of presentation with heart failure, the worse the prognosis.^{55 56} As previously stated, however, New York Heart Association assessment is unreliable. Exercise capacity as assessed by maximal oxygen consumption may provide a simple non-invasive prognostic index. But in a relatively small study maximal oxygen consumption was found to be reduced to the same ex-

tent in survivors and non-survivors.⁶⁰ Other studies show a relation between maximal oxygen consumption and prognosis. One investigation divided patients into two groups: group 1 had maximal oxygen consumption of <10 ml/kg/min and group 2 had maximal oxygen consumption >10 ml/kg/min. The one year mortality for group 1 and group 2 was 21% and 77% respectively ($p < 0.001$).⁶¹ Two larger studies, of 136 and 637 patients respectively,^{62 63} showed that maximal oxygen consumption was a highly independent predictor of survival ($p < 0.005$), which in turn was a better predictor than exercise duration or left ventricular ejection fraction. Thus quantitative exercise tolerance also provides an important guide to prognosis in heart failure.

Conclusions

The clinical syndrome of heart failure is disabling and has a high mortality with a prognosis that is worse than many cancers. Exercise testing is a useful tool for assessing the severity of the disease. Measurement of functional capacity based on respiratory gas exchange during exercise permits greater understanding of the pathophysiology of symptoms and provides an objective method of assessing responses to pharmacological and rehabilitative interventions. The major aim of treatment in this condition is to reduce mortality. It is unlikely that we can have a major impact on survival once heart failure is established. Surely it would be more rewarding to develop strategies aimed at early intervention? Perhaps an ability to perceive early deterioration will permit a more logical approach to treatment and optimise the timing of cardiac transplantation. A scientific approach to understanding the pathophysiology and treatment of heart failure can no longer rely on subjective or crude measurements of left ventricular function.

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