The role of exercise testing in the evaluation and management of heart failure

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Exercise testing is routinely performed to assess patients with chronic heart failure (CHF) in specialist centres. Combined respiratory gas analysis ensures that physiological parameters are more thoroughly explored and improves test reproducibility. Resting haemodynamics, eg, ejection fraction, correlate poorly with exercise capacity in heart failure patients and subjective profiles such as the 6-minute walk test are relatively insensitive. Whilst exercise tests are readily available and non-invasive, they are not without limitations and must not be relied upon excessively in the evaluation of therapeutic interventions.

In order to maximise the information available from an exercise test it is necessary to consider both the patient response and the nature of the test undertaken. At present no single exercise test is able to provide complete evaluation of the patient with cardiac failure. The search for such an investigative tool intensifies with the increasing incidence of heart failure, despite advances in cardiac management. The objectives of exercise testing in patients with CHF are to improve our understanding of pathophysiological mechanisms, to confirm and quantify symptoms/severity, to predict prognosis and to assess therapeutic success (box 1). We will discuss each of these points in broad context and more specifically with regard to cardiac reserve, which represents the pumping capability of the heart and measures the difference between cardiac function at rest and during maximal stimulation.

Interpretation

When interpreting the results from an exercise test it is essential to consider the variables illustrated in box 2. Exercise tests are conducted either on a treadmill or bicycle ergometer. There are considerable variations in national and international opinion as to which is the most appropriate for patients with CHF. Treadmill testing produces a higher peak oxygen consumption in ml/kg/min (VO2) and ventilation threshold due to the greater mass of skeletal muscle used. However, superior correlation between exercise time and oxygen consumption exists for bicycle testing. Submaximal tests such as the 6-minute walk test more accurately reflect daily activity yet have inferior reproducibility and quantitative value. Some investigators support dual maximal and sub-maximal testing. Whichever test is adopted, standardisation of the procedure is essential with regard to ambient temperature, humidity, time of day, and time span from last meal. A preliminary test for familiarisation is also mandatory.

Protocol selection affects the results obtained. Peak VO2 varies considerably whilst VO2 at the anaerobic threshold remains reproducible when the same patients complete different protocols. Variations in metabolite levels, eg, catecholamines, have similarly been reported during interval exercise of differing intensity. It is generally accepted that patients with CHF should be investigated using gentle protocols with small increments in speed and incline.

In selecting an end-point achieved during exercise it is necessary to consider both the value of the information obtained and its reliability. Peak VO2 is recognised as the best criteria of exercise capacity in patients with CHF. As an objective measure of maximal exertion it is used in the selection of patients for cardiac transplantation, as a prognostic indicator, and as a marker of success of medical intervention. Motivational inconsistency and patient distress during maximal testing reduce the efficacy of VO2 as an end-point during exercise. Anaerobic threshold has thus been considered as an alternative. The sub-maximal testing required is less stressful and independent of patient motivation. Good correlation with VO2 ensures that exercise capacity is still represented. Unfortunately, problems with validation and reproducibility have been elicited by several investigators. This is thought to be due to erratic

Summary

The clinical syndrome of heart failure has been investigated so extensively that it may now almost be regarded as a metabolic disorder. Although an initial insult reduces cardiac pump efficacy, the resultant physiological response culminates in complex neurohormonal dysfunction. This has created confusion and prevented the acceptance of a universal definition of cardiac failure. With much current research concentrating on the pharmacological modification of neuroendocrine imbalance, it is easy to lose sight of the fundamental principles behind heart failure management, namely, to improve cardiac function. In attempting to achieve this, the issues of morbidity and mortality must be addressed jointly; they are not mutually exclusive entities. Discrepant results between mortality studies and changes in exercise capacity have undermined the value of exercise testing. Because a treatment enhances longevity we should not ignore its effect on symptomatic status, and likewise we should not discard a therapy, which improves function because adverse events result in occasional premature deaths. Informed patient choice must exist.

Historically, exercise testing has been quintessential in our understanding and evaluation of heart failure. Peak oxygen consumption remains the best overall indicator of symptomatic status, exercise capacity, prognosis and hospitalisation. Unfortunately, muddling of surrogate and true end-points has confused many of these issues. Improved comprehension may be gained by applying the concept of cardiac reserve which has been described in a variety of heart conditions and used in cardiac failure patients to provide an indication of prognosis and functional capacity.
Objectives of exercise testing in patients with cardiac failure

- understand pathophysiology
- confirm and quantify symptoms
- predict prognosis
- assess treatment

Considerations during exercise testing

- exercise type
- protocol
- standardisation
- maximal/sub-maximal
- end points
- sensitivity/reproducibility
- terminating symptoms
- familiarity
- motivation
- supervisor experience

Mechanisms by which dyspnoea is perceived

- vascular receptor stimuli
- mechanical stimuli, eg, respiratory muscle stretch
- hypoxaemia, hypercapnia and acidosis
- movement of extremities
- psychogenic factors

Pathophysiology

The morbidity experienced by patients with CHF is due to a reduction in functional capacity. The pathophysiological basis for this has been investigated by observing their response to exercise. Alteration in central haemodynamics, ventilation, peripheral circulation, neurohormonal activity and skeletal muscle all contribute to the impaired clinical status. Heart failure has been variously defined in terms of such abnormalities and therefore eliciting them during exercise can be of diagnostic value. Despite our incomplete knowledge, it is the modification of physiological adaptations which forms the fundamental basis for symptomatic treatment in heart failure.

The contribution of central haemodynamics to the physical limitation of CHF patients remains a contentious subject. Although resting and exercise left ventricular ejection fraction (LVEF) do not correlate with peak VO₂, it is naive to conclude that abnormalities in cardiac function are not important in determining exercise tolerance. Attenuation of stroke volume increments during exercise in patients with CHF without alteration in LVEF, leads to a relative reduction in exercise cardiac output, which is exaggerated by chronotropic incompetence and the effect of mitral regurgitation. Accordingly, significant ‘pump failure’ during exertion has been proposed as the basis for exercise intolerance in heart failure.

Significant correlation between maximal exercise cardiac output and peak VO₂ demonstrated by several investigators adds credence to such a theory. It also explains the increase in arteriovenous oxygen difference during exercise in patients with CHF, the reduced cardiac output being responsible for decreased perfusion of working skeletal muscle resulting in premature anaerobic metabolism. Structural and biochemical changes in skeletal muscle also occur independently from blood flow limitation. An alternative theory, whereby peak VO₂ correlates with peripheral functional and vascular responses, has thus been proposed. Such changes are not uniform throughout muscle groups or during different types of exercise and further evaluation is required before conclusions can be made.

During physical activity, patients with CHF often experience disproportionate dyspnoea. This phenomenon is mediated by a multitude of mechanisms. According to Wasserman and Casaburi these can be classified as shown in box 3. In the context of reduced functional capacity in CHF, the relationship between abnormal respiratory physiological parameters is extremely complex. Ventilatory equivalents for oxygen (VE/VO₂) and carbon dioxide (VE/VCO₂) are consistently elevated during exercise. Reasons for this include an elevation in respiratory rate and a reduction in tidal volume resulting in a
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Independent prognostic indicators by multivariate analysis in patients with CHF

- peak oxygen consumption
- ejection fraction
- serum sodium concentration
- ventricular arrhythmia
- norepinephrine level
- urea/creatinine concentration
- NYHA classification
- pulmonary artery pressure
- exercise duration
- ventilatory equivalent for CO₂
- furosemide dose

Prognosis

Because of the high mortality associated with CHF, an indication of prognosis may be the most appropriate measure of disease severity. Assessment of the impact of numerous variables on mortality should help to establish the relative importance of these clinical markers. Since death in these patients can occur suddenly or from progressive heart failure, therapeutic approaches could potentially be targeted at specific mechanisms of death.

Independent prognostic indicators for patients with CHF have been determined from multivariate analysis (box 4). This list is not exhaustive and it must be emphasised that some indicators are significantly predictive in one study but not in another. Despite the diverse choice, peak VO₂ is one of the most extensively studied and hence clinically applicable. This patients with a peak VO₂ > 20 ml/kg/min have a good prognosis and those with a peak VO₂ < 10 ml/kg/min have a severe prognosis. For those patients with an intermediate peak VO₂, more integrated approaches incorporating measurement of exercise haemodynamics has thus been proposed.
VO₂, other indices should be combined to provide a predictive profile. Monitoring of respiratory response to exercise⁷⁷ and resting haemodynamics⁷⁸ have been used in just this way.

Measurement of exercise haemodynamics is less frequently performed. In one study by Griynet al.,⁷⁹ peak exercise stroke work index actually proved superior to peak VO₂ as a prognostic indicator in patients with ischaemic heart failure and idiopathic dilated cardiomyopathy. Exertional cardiac output response is also an independent predictor in the selection of transplant candidates and is currently being used in combination with peak VO₂.⁷² Independent work showed cardiac reserve to be of significant prognostic value during pharmacological stress in ambulatory CHF patients,⁸⁰–⁸¹ and patients with cardiogenic shock.⁸² This represents patients with end-stage cardiac failure in whom exercise testing is inappropriate.

**Treatment**

The treatment of CHF has huge implications regarding cost and resources. Patients require frequent out-patient follow-up, occasional hospital admission, and complex drug prescriptions. Treatment is aimed at improving both mortality and morbidity. Unfortunately, the results from several large studies assessing the impact of angiotensin-converting enzyme (ACE) inhibitors have created discrepancy regarding these principles. Mortality has been significantly reduced without consistent enhancement of exertional capacity and morbidity.⁵⁵–⁵⁶. Swedberg thus questioned the value of exercise testing in assessing the changes that occur as a result of drug therapy.⁵⁷ Clinical practice adopted from the V-HeFT II study highlighted this point, as the improved exercise capacity sustained due to the hydralazine–isosorbide dinitrate combination was overshadowed by the superior effect of enalapril on mortality.⁸⁶ Studies purporting similar alterations in exercise capacity have actually been prematurely terminated due to excess deaths in the treatment groups.⁸⁶–⁸⁸ An ethical dilemma thus confronts clinicians treating CHF: should we solely aim to reduce mortality at the expense of patient quality of life? Preliminary data suggest that beta-blockers enhance survival in CHF patients,⁹⁸ yet given in sufficient doses such drugs can actually impede exertional performance.

In order to resolve such issues it is essential to understand the pathophysiologic effects of intervention on the heart and to relate these to functional capability. The heart is a pump, which must impart sufficient hydraulic energy to maintain the requisite level of circulation demanded by the body. Intrinsic myocardial contractility and vascular tone are integral in this, as emphasised by the improvement in functional status brought about by the positive inotropic effect of digoxin in patients with CHF.⁹⁷ Myocardial fibrosis and ventricular dilatation result in reduced pump efficacy and consequently clinical heart failure. Increased cardiac myocyte necrosis due to angiotensin II⁹⁸ and catecholamines⁹⁹ can thus explain the cardioprotective action of ACE inhibitors and the adverse effect on mortality exhibited by milrinone and enoximone (sympathomimetics). Conversely, the positive inotropic component of the latter two drugs augments the cardiac pump and increases functional capacity. The treatment of end-stage CHF and cardiogenic shock depend on such mechanisms and it is therefore inappropriate to disregard the effect on exercise capacity of drug therapies.

In the evaluation of individual therapies it is essential to standardise patient status prior to randomisation. The objective nature of exercise tests ensures that this is achieved and also allows monitoring of patient morbidity. The inclusion of exercise testing is thus mandatory when designing any study to evaluate treatment of CHF.¹⁰⁰

Although treatment of CHF relies heavily on pharmacological therapy, the benefits of physical training should not be overlooked. Mortality studies are at present very sparse; however, the effects of physical training on functional and symptomatic status are well established. Exercise testing has been integral in eliciting the improvement in functional capacity with high-¹⁰¹–¹⁰³ and low-intensity¹⁰⁴ training programmes. Investigation of the pathophysiological basis for such clinical enhancement has relied almost entirely upon exercise testing. A combination of central haemodynamic,¹⁰² peripheral,¹⁰³ and metabolic changes,¹⁰²–¹⁰⁴,¹⁰⁵ act together to improve physical performance, whilst respiratory effort is also reduced at a given work load.¹⁰⁵

**Conclusions**

Exercise testing plays an essential and integral role in the evaluation and treatment of chronic heart failure. The concept of cardiac reserve provides further
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45. Calvin BP, Mathier PT, Semigran MJ, De GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in...