EXERCISE TESTING IN THE ASSESSMENT OF CHRONIC CONGESTIVE HEART FAILURE

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Despite advances in treatment which have resulted in reductions in morbidity and mortality, heart failure remains a common condition often associated with a poor outcome. In most patients with chronic congestive heart failure, symptoms are not present at rest but become limiting with exertion. Despite this, the majority of measures used to characterise the severity of heart failure and prognosis are obtained at rest.

The New York Heart Association (NYHA) classification attempts to stratify patients according to their exercise limitation, but has a limited relation to objective measures of exercise tolerance and is a very subjective measure of disability. Self administered questionnaires which attempt to assess activity and exercise limitation are unable to measure functional capacity accurately and have only modest correlation with objective parameters such as peak oxygen uptake ($\dot{V}O_2$).

Making the diagnosis of heart failure can be difficult. Signs and symptoms lack both sensitivity and specificity. Although objective resting measures, such as left ventricular ejection fraction, can define structural cardiac abnormality, they are by no means synonymous with the diagnosis of heart failure. A further issue is the increased recognition of heart failure in subjects with normal left ventricular ejection fraction, and the difficulty of diagnosis in this patient group.

Exercise testing of patients, in combination with assessment of gas exchange parameters, is an attractive and practical method of obtaining accurate information which can aid in the diagnosis of heart failure as well as the assessment of functional limitation and prognosis.

Directly measured maximum oxygen uptake (more correctly $\dot{V}O_2$ in heart failure patients) has been shown to be a reproducible marker of exercise tolerance in heart failure and provide objective and additional information regarding patients clinical status and prognosis. Facilities for exercise testing with continuous measurement of gas exchange parameters are increasingly available.

PRACTICAL ISSUES IN EXERCISE TESTING

Exercise testing with concurrent measurement of gas exchange parameters can be undertaken using either treadmill or bicycle exercise protocols (table 1). Peak $\dot{V}O_2$ has been found to be 10–20% higher on treadmill exercise compared to bicycle exercise. Patient familiarity is important and subjects who are unaccustomed to riding bicycles may be unable to sustain bicycle exercise for as long because of leg fatigue. It is important that patients are given time to become accustomed to the requirements of the exercise test in order to obtain peak exercise capacity. This involves practising getting on and off the treadmill or adjusting bicycle pedals to an appropriate height, as well as becoming familiar with the mask or mouthpiece and nose clip.

In order to obtain valid data with regard to peak exercise parameters in patients with cardiac disease, it is important that subjects exceed the anaerobic threshold or that the respiratory exchange ratio (the ratio of carbon dioxide production to oxygen consumption) is greater than 1 to indicate adequate effort. With regard to this, peak exercise parameters are affected by patient motivation and perceived symptoms as well as patient familiarity, and experienced medical and technical personnel are required when performing these tests to obtain adequate data.

Ideally the exercise protocol should be individualised for each patient. Small increments in exercise load and total duration of around 8–12 minutes are ideal. Ramp protocols, where workload increases continuously, are available for both bicycle and treadmill exercise.

There may be concerns about the safety of exercise testing of patients with significant heart failure. Available data suggest a very low incidence of serious adverse events such as arrhythmias or significant hypotension. In a study of 607 patients with a history of heart failure and average left ventricular ejection fraction of 30% who underwent symptom limited exercise testing, only 10 patients' exercise tests were stopped because of arrhythmia, and only one of these subjects had ventricular tachycardia.¹ Only one exercise test was stopped because of hypotension. Commonsense precautions, such as avoiding exercising patients with unstable symptoms, active arrhythmia or critical valvar stenosis, should be taken.

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Table 1 Suggestions for obtaining an adequate exercise test

- ▶ Avoid unstable patients
- ▶ Ensure patient familiarity with equipment and requirements of the test
- ▶ Individualise the protocol (ramp protocol preferred)
- ▶ Optimal duration 8–12 minutes
- ▶ Consider using submaximal data in those unable to perform maximal test—for example, early slope of ventilation versus CO_2 production, six minute walk

EXERCISE TESTING IN THE DIAGNOSIS OF HEART FAILURE

A normal exercise test with gas exchange monitoring virtually excludes congestive heart failure as a cause for patient symptoms.²

Easily obtained variables help to distinguish between cardiac and pulmonary causes of breathlessness and exercise limitation. For example, subjects with pulmonary disease often experience a decrease in oxygen saturation with exercise, while in subjects with cardiac disease oxygen saturation remains unchanged or increases (table 2, fig 1).

This ability to differentiate the cause of shortness of breath may be useful in subjects with heart failure caused by diastolic dysfunction where differentiation from other causes of shortness of breath may be very difficult.

EXERCISE TESTING IN DEFINING PROGNOSIS IN HEART FAILURE

Most investigators have found that $\dot{V}\text{O}_2$ is the best indicator of prognosis in patients with heart failure. This well established variable can be thought of as integrating a number of factors which determine the severity of heart failure and the degree of functional limitation including cardiac reserve, skeletal muscle function, pulmonary abnormalities, and endothelial dysfunction.³

Peak $\dot{V}\text{O}_2$ correlates poorly with haemodynamic factors measured at rest which is consistent with the fact that these resting parameters do not reflect functional reserve. There is, however, a good correlation between maximum cardiac output and $\dot{V}\text{O}_2$.⁴

The factors that appear to be important in determining $\dot{V}\text{O}_2$ are outlined in table 3.

The measurement of $\dot{V}\text{O}_2$ was first described by Webber and colleagues as a method for characterising cardiac reserve and functional status in heart failure.⁵ Subsequently $\dot{V}\text{O}_2$ has been shown by a number of investigators to be of prognostic significance, with lower $\dot{V}\text{O}_2$ predicting mortality and the need for cardiac transplantation. For example, Szlachcic and

colleagues studied 27 patients with heart failure and reported a 77% one year mortality rate in those with $\dot{V}\text{O}_2 < 10 \text{ ml/kg/min}$ and 21% mortality rate in those with $\dot{V}\text{O}_2$ between 10–18 ml/kg/min.⁶ A further study of 201 heart failure patients found that $\dot{V}\text{O}_2$ was an independent predictor of mortality.⁷ Many other studies have confirmed these findings.

Cardiac transplantation is an important and successful treatment for end stage heart failure but its major limitation continues to be a shortage of appropriate donors. Therefore, accurate selection of those patients who will benefit most from transplantation is important. In this regard exercise parameters, in particular $\dot{V}\text{O}_2$, have been found to be very important. Measurement of $\dot{V}\text{O}_2$ in the assessment of subjects for cardiac transplantation is now endorsed within guidelines.⁸

In a widely quoted study Mancini and colleagues reported on 116 patients who were referred for assessment for cardiac transplantation (fig 2).⁹ Thirty five of the patients had a $\dot{V}\text{O}_2$ of $< 14 \text{ ml/kg/min}$; these patients were accepted for cardiac transplantation. A further 52 patients had a $\dot{V}\text{O}_2 > 14 \text{ ml/kg/min}$ and in these subjects transplantation was deferred. In addition to these two groups, a further 27 patients had $\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$ but had other comorbidities which meant that they were not suitable for cardiac transplantation. One year survival in those with $\dot{V}\text{O}_2 > 14 \text{ ml/kg/min}$ was 94%, while in those with $\dot{V}\text{O}_2$ below this cut-off in whom transplantation was not carried out because of comorbidities, survival at one year was only 47%. In the subjects with $\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$ accepted for transplantation, one year survival while waiting for transplantation was 70%, and if urgent transplantation was counted as death one year survival was reduced to 48%. One year survival of 24 patients with a $\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$ after transplantation was 83%. These results clearly demonstrate that low $\dot{V}\text{O}_2$ identified a group of heart failure patients at high risk of death or need for urgent transplantation and that those subjects with higher $\dot{V}\text{O}_2$ could have transplantation deferred.

Attempts have been made to use percentage of predicted $\dot{V}\text{O}_2$ to improve the prognostic power of this measure. Percentage of predicted $\dot{V}\text{O}_2$ may account for factors such as age, sex, and muscle mass which may have a significant impact on $\dot{V}\text{O}_2$. In a study of 272 patients referred for transplantation, subjects were divided by strata of $\dot{V}\text{O}_2$ uptake and percentage of predicted $\dot{V}\text{O}_2$.¹⁰ These strata were designed to be of similar size. In this study survival curves were found to be similar whether the strata were classified by $\dot{V}\text{O}_2$ or percentage of predicted $\dot{V}\text{O}_2$. Others have found that percentage of $\dot{V}\text{O}_2$ is a better prognostic marker than $\dot{V}\text{O}_2$, with 50% of predicted $\dot{V}\text{O}_2$ the most significant predictor of death.¹¹ It is likely that in some patients, percentage of $\dot{V}\text{O}_2$ would be more useful—for example, at the extremes of age and possibly in women.

Table 2 Response to exercise in cardiac versus pulmonary disease

Variable	Cardiac disease	Pulmonary disease
Peak $\dot{V}\text{O}_2$	Reduced	Reduced
Heart rate reserve	Usually none	Increased
Anaerobic threshold	Reduced ($< 40\%$ predicted)	Normal or not achieved
Oxygen pulse	Reduced	Normal
$\dot{V}\text{O}_2$ workload ratio	Reduced	Normal
Peak PaO_2 or O_2 saturation	Normal	Decreased

Peak $\dot{V}\text{O}_2$, peak oxygen uptake; Heart rate reserve, difference between predicted maximum heart rate and attained heart rate with maximum exercise; Oxygen pulse, O_2 uptake divided by heart rate, represents O_2 extracted by the tissues from O_2 carried in each stroke volume; $\dot{V}\text{O}_2$ workload ratio, represents the efficiency of muscular work; PaO_2 , arterial oxygen tension.

Figure 1 Representative cardiopulmonary exercise test data from a patient with a dilated cardiomyopathy (left ventricular ejection fraction 30%). Heart rate accelerates quickly and there is no heart rate reserve (difference between predicted maximum heart rate and attained heart rate with maximum exercise), maximum oxygen uptake is reduced, oxygen pulse (O_2 uptake divided by heart rate) is reduced, and the respiratory quotient data demonstrate the patient reached anaerobic threshold (point where the respiratory quotient (ratio of $\dot{V}\text{CO}_2$ to $\dot{V}\text{O}_2$) exceeds 1) and that this occurred early in exercise. Parallel lines in top left panel represent predicted values.

Table 3 Factors determining exercise capacity

- ▶ Central factors: resting ventricular function, chronotropic response, stroke volume response
- ▶ Peripheral factors: skeletal muscle mass, skeletal muscle vascular function, endothelial function, autocrine/paracrine factors
- ▶ Pulmonary function and pulmonary response to exercise
- ▶ Neurohormonal systems including sympathetic nervous system, other vasodilator and vasoconstrictor systems

Although a $\dot{p}\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$ is well known as a measure for deciding on eligibility for cardiac transplantation, it has been clearly shown that there is no absolute threshold for adverse prognosis and that $\dot{p}\dot{V}\text{O}_2$ uptake should be considered as a continuous variable. In terms of discriminating survivors from non-survivors, it appears that a $\dot{p}\dot{V}\text{O}_2 < 10 \text{ ml/kg/min}$ definitely defines high risk, while a value $> 18 \text{ ml/kg/min}$ defines low risk; those values in between may represent a grey zone. Attempts have been made to stratify further the group with a $\dot{p}\dot{V}\text{O}_2$ uptake of $< 14 \text{ ml/kg/min}$. In a study of 500 patients, 154 had $\dot{p}\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$.¹² Using all the non-invasive parameters measured during exercise testing in a multivariate analysis including peak heart rate, systolic blood pressure, respiratory quotient, minute ventilation, $\dot{p}\dot{V}\text{O}_2$, percentage of predicted $\dot{p}\dot{V}\text{O}_2$, and anaerobic threshold it was found that a peak systolic blood pressure $< 120 \text{ mm Hg}$ and percentage of predicted $\dot{p}\dot{V}\text{O}_2$ were significant prognostic indicators. Three year survival in those with a $\dot{p}\dot{V}\text{O}_2 < 14 \text{ ml/kg/min}$ but $> 50\%$ of the predicted maximal value was similar to those with a $\dot{p}\dot{V}\text{O}_2 > 14 \text{ ml/kg/min}$. Survival was 55% if peak exercise blood pressure was $< 120 \text{ mm Hg}$, while it was 83% with a peak systolic blood pressure of $> 120 \text{ mm Hg}$.

A number of investigators have attempted to combine $\dot{p}\dot{V}\text{O}_2$ and haemodynamic variables in an effort to improve prognostic power. Chomsky and colleagues, in a study of 185 ambulatory heart failure patients with an average $\dot{p}\dot{V}\text{O}_2$ uptake of 12.9 ml/kg/min , calculated cardiac output from the $\dot{V}\text{O}_2$ data.¹³ In multivariate analysis a $\dot{p}\dot{V}\text{O}_2 < 10 \text{ ml/kg/min}$ and a reduced cardiac output response to exercise were predictive of one year survival. Directly measured haemodynamics can be added but

may considerably increase the risk and difficulty of exercise testing, and may be of limited additional benefit. End systolic stroke work index has been shown to add to the prognostic power of $\dot{p}\dot{V}\text{O}_2$.¹⁴ However, in addition to requiring invasive measurements this variable is not accurate in the presence of significant mitral regurgitation.

There has been recent interest in using the slope of the relation between minute ventilation ($\dot{V}\text{E}$) and carbon dioxide production ($\dot{V}\text{CO}_2$) in assessing the prognosis of subjects with heart failure. There is a linear correlation between minute ventilation and carbon dioxide production until anaerobic threshold is reached. Subjects with a steeper response have decreased cardiac output, increased pulmonary pressures, and increased dead space to tidal volume ratio as well as possibly augmented chemoreceptor sensitivity. The slope of the relation between $\dot{V}\text{E}$ and $\dot{V}\text{CO}_2$ has been shown to be predictive of survival in addition to $\dot{p}\dot{V}\text{O}_2$.¹⁵ Others have looked at the slope of the relation between $\dot{V}\text{E}$ and $\dot{V}\text{CO}_2$ within the first six minutes of exercise, and while this was predictive of survival it was not as strong a prognostic indicator as $\dot{p}\dot{V}\text{O}_2$.¹⁶ However, this measure may be useful if maximum exercise is not obtained. $\dot{V}\text{O}_2$ at anaerobic threshold has been considered as a prognostic marker, but it does not outperform $\dot{p}\dot{V}\text{O}_2$ and problems exist with defining and determining this variable.

There are a large number of other well recognised prognostic markers in heart failure which are not exercise related. An attempt to combine these variables along with exercise data in pretransplant risk stratification has been reported.¹⁷ A heart failure survival score was developed using 268 ambulatory patients from the University of Pennsylvania Hospital from July 1986 to January 1993. The model was subsequently validated in a group of 199 patients at Colombia Presbyterian Hospital who were followed from July 1993 to October 1995. The model contained 80 clinical variables from each patient that were derived from history, laboratory data, exercise data, catheterisation data, and physical examination. Significant univariate predictors were subsequently analysed using multivariate techniques where the variables were grouped and prognostic factors thought to represent different aspects of heart failure were incorporated into the model. One statistical model incorporated seven non-invasive parameters which

Figure 2 (A) Survival curves for patients with heart failure. Group 1 ($n = 35$) represents survival while waiting for transplantation in patients accepted for transplantation with $\dot{p}\dot{V}O_2 < 14$ ml/kg/min. Group 2 ($n = 52$) comprises patients with $\dot{p}\dot{V}O_2 > 14$ ml/kg/min in whom transplantation was deferred. Group 3 ($n = 27$) comprises patients with $\dot{p}\dot{V}O_2 < 14$ ml/kg/min rejected for transplantation because of non-cardiac problems. Survival of groups 1 and 3 are similar but significantly reduced compared to group 2. Numbers in parentheses represent number of subjects at risk. (B) Survival curves for group 1 patients after transplantation ($n = 24$) and for medically treated patients (group 2). Difference in survival is not significant. Reproduced from Mancini et al⁹ with permission.

included the presence of ischaemic heart disease, resting heart rate, left ventricular ejection fraction, mean arterial pressure, presence of intraventricular conduction defect on ECG, serum sodium, and $\dot{p}\dot{V}O_2$. This model (the heart failure survival score, HFSS) provided excellent ability to predict survival, and in the validation group the model performed better than $\dot{p}\dot{V}O_2$ alone. Interestingly, in the sample used to derive the model $\dot{p}\dot{V}O_2$ alone performed as well as the model.

Limited data are available on serial exercise testing and prognosis. It has been suggested that increases in $\dot{p}\dot{V}O_2$ on serial tests are predictive of better survival, although this has not been supported in other studies.^{18, 19}

As mentioned above, measuring the slope of the relation between $\dot{V}E$ and $\dot{V}CO_2$ in the initial stages of exercise may provide useful prognostic information in those unable to obtain maximum exercise, or if maximum exercise is contraindicated. Others have attempted to predict $\dot{p}\dot{V}O_2$ from the initial stages of exercise testing. In general these measures are

less predictive of prognosis than $\dot{p}\dot{V}O_2$ but may be useful when maximum exercise is not possible.

The six minute walk test has been used as a submaximal exercise test in heart failure subjects. There are some conflicting data about the value of the six minute walk test. It may be useful in discriminating high risk from low risk. In a recent study of 315 patients with moderate to severe heart failure, six minute walk distance was not related to central haemodynamics and only moderately related to exercise capacity.²⁰ In that study six minute walk distance was not an independent predictor of prognosis in models that contained either NYHA class or $\dot{p}\dot{V}O_2$.

COMBINING EXERCISE PARAMETERS WITH OTHER NOVEL PREDICTORS OF PROGNOSIS IN HEART FAILURE

Functional reserve as defined by an increase in left ventricular ejection fraction during dobutamine infusion has been shown to be a multivariate predictor of survival in heart failure. This may be helpful in those with intermediate values of $\dot{p}\dot{V}O_2$. The ability of dobutamine assessed cardiac reserve to stratify prognosis in subjects with non-ischaemic dilated cardiomyopathy has been assessed in a study of 27 patients with $\dot{p}\dot{V}O_2$ between 10–14 ml/kg/min.²¹ Dobutamine was infused at 10 μ g/kg/min and the increase in ejection fraction measured. This particular range of $\dot{p}\dot{V}O_2$ was chosen as it was felt to represent a grey zone in which further risk stratification in terms of selection for transplantation may be useful. After a mean follow up of 18 months, changes in left ventricular end systolic dimension and end systolic wall stress were found to be significantly different between those who died of cardiac causes ($n = 9$) and those who survived ($n = 18$). This finding suggests that dobutamine echocardiography may be a useful prognostic indicator in addition to $\dot{p}\dot{V}O_2$ in those being considered for cardiac transplantation who have a low $\dot{p}\dot{V}O_2$ uptake.

It is known that the restrictive left ventricular filling pattern defined by transmitral Doppler echocardiography is a predictor of mortality in heart failure in those with impaired left ventricular function. This parameter has been compared to $\dot{p}\dot{V}O_2$ uptake.²² While a restrictive filling pattern was shown to be a better predictor than ejection fraction, it did not perform as well as $\dot{p}\dot{V}O_2$ in the assessment of prognosis.

It has been known for some time that neurohormonal factors are predictive of survival in heart failure when measured at rest. Measurement of plasma natriuretic peptides in particular has often been shown to perform better as a prognostic marker than other established rest parameters such as left ventricular ejection fraction. There has been some interest in the use of these factors in combination with exercise testing in prediction of prognosis in heart failure. In a study of 264 patients with moderate heart failure, atrial natriuretic peptide (ANP), noradrenaline (norepinephrine), and endothelin-1 were measured at rest and a maximum exercise test was undertaken.²³ It was found that ANP, left ventricular ejection fraction, and noradrenaline predicted death or transplantation. In this study $\dot{p}\dot{V}O_2$ was not predictive. In a further study in which maximum exercise workload was measured, endothelin-1 and ANP measured at rest were again shown to convey independent prognostic power.²⁴ One study has reported both rest and peak exercise neurohormonal data.²⁵ Fifty five consecutive ambulatory patients with stable, moderate congestive heart failure (NYHA functional class II–III) underwent maximum symptom limited cardiopulmonary

Exercise testing in assessing CHF: key points

- ▶ Exercise testing with monitoring of gas exchange parameters provides useful information on exercise capacity and prognosis in heart failure; in addition it is helpful in establishing the cause of exercise limitation
- ▶ Both treadmill and bicycle protocols are acceptable, but attention to technical aspects of exercise testing are important in order to obtain maximum exercise data
- ▶ Peak $\dot{V}O_2$ is probably the strongest predictor of prognosis in heart failure but other exercise, clinical, and hormonal data must be taken into account in arriving at an assessment of prognosis.
- ▶ In subjects unable to perform a maximal exercise test submaximal data such as the slope of the relation between $\dot{V}E$ and $\dot{V}CO_2$ may be useful
- ▶ Further studies of the response of neurohormones to exercise may add to the utility of exercise tests in assessing prognosis

exercise testing with determination of peak oxygen consumption, and measurement of plasma ANP, aldosterone, and plasma renin activity at rest and peak exercise. There was no correlation between exercise parameters and hormone values either at rest or at peak exercise. At a median follow up of 724 days the most significant independent prognostic marker was the plasma concentration of ANP at peak exercise.

We have undertaken a study in 68 patients with NYHA class III–IV heart failure and average $p\dot{V}O_2$ of 13.6 ml/kg/min. Natriuretic peptide plasma concentrations were measured at rest and with peak exercise. In multivariate analysis which included $p\dot{V}O_2$, only change in brain natriuretic peptide (BNP) with exercise or a fall versus an increase in BNP with exercise added prognostic power for survival in addition to left ventricular ejection fraction at rest. Fifteen subjects had a decrease in plasma BNP with exercise and over an average follow up of two years seven (45%) of these patients died, compared with only eight out of 53 (15%) in those with a rise in BNP during exercise ($p < 0.01$).²⁶

From the limited information available, the addition of neurohormonal data, in particular measurement of natriuretic peptide plasma concentrations and their response to exercise, offer promise in the assessment of subjects with heart failure.

CONCLUSIONS

Congestive heart failure is characterised by symptoms with activity. Exercise testing is useful in the diagnosis of heart failure, assessing functional capacity objectively, and in determining prognosis. It appears that if maximum exercise is possible, measurement of $p\dot{V}O_2$ or percentage predicted $\dot{V}O_2$ is the most useful exercise parameter. It may be that other measures are useful if maximal exercise cannot be undertaken. Prognosis should not be assessed from exercise data in isolation but other clinical factors should be also taken into account. Peak $\dot{V}O_2$ is known to be a continuous variable in terms of its ability to predict prognosis and, although much remains to be learned, it is likely that further assessment of subjects with intermediate level $p\dot{V}O_2$ will prove useful. Finally, preliminary data suggest combining maximum exercise testing with assessment of neurohormones (particularly the natriuretic peptides both at rest and at peak exercise) may be valuable.

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