EXERCISE AND HEART FAILURE: ASSESSMENT AND TREATMENT

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Older textbooks of cardiology cite the presence of heart failure as a contraindication to exercise testing. However, the heart failure syndrome is characterised by the presence of symptoms, and these are principally symptoms of exercise limitation caused by breathlessness and/or fatigue. Some form of exercise testing is essential to evaluate these symptoms. Similarly, textbooks until recently specified “rest” as one of the mainstays of heart failure management, but it is now clear that exercise training has some important benefits for heart failure patients. In this article, I will be discussing patients with chronic stable heart failure; there is no role for exercise in the management of patients admitted to hospital with acute heart failure.

Exercise has a number of possible uses in patients with chronic heart failure. Exercise testing can help: (1) establish the diagnosis and the underlying cause of heart failure; (2) assess severity of heart failure and stratify risk; (3) monitor the response to treatment; and (4) explore the pathophysiology of exercise limitation in heart failure. Finally, exercise can be used as a prescription for some heart failure patients to help reduce symptoms and possibly improve outcome.

EXERCISE TESTS

In assessing patients complaining of exercise-induced symptoms, it is usually helpful to watch the patient exercising. Simple tests include a walk up and down the outpatient department corridor while watching for changes in ventilation and heart rate, and the development of symptoms. Simply adding pulse oximetry before and after the walk can help—patients who desaturate are highly likely to have pulmonary pathology underlying their breathlessness.

More formal exercise testing can be done using a large number of different exercise protocols. These can be broadly classed as maximal or submaximal tests. Maximal tests characteristically use incremental protocols on either a treadmill or a cycle, with encouragement to exercise to exhaustion. Which protocol to use is debatable, but broadly speaking, a test that lasts around 10 minutes elicits the highest peak oxygen consumption in heart failure patients. Among treadmill protocols, the modified Bruce and Naughton protocols are widely used. Cycle protocols are also widely used and have the merit of having precisely controllable workloads and well defined normal ranges for oxygen consumption at specific workloads.

Maximal tests poorly reflect daily activity, and an estimate of submaximal activity might more accurately assess patients' symptoms. The six minute walk test, during which subjects walk as far as possible during six minutes at their own pace, is widely used.¹ Variations are common. The shuttle test is also advocated, with subjects moving between two points in time to a signal which gradually increases in frequency.

Despite concerns that exercise testing might be dangerous in patients with chronic heart failure, it has repeatedly been found to be safe.^{2,3} Blood pressure and pulse should be continually monitored, and there should be full resuscitation facilities available.

GENERAL MEASUREMENTS

Much of what follows will be a consideration of metabolic gas exchange variables, but it is important not to lose sight of simpler descriptors of the exercise response. Exercise duration is an excellent marker of exercise capacity. Heart rate at rest and during exercise can help pick up patients limited by, for example, an excessive ventricular rate response in atrial fibrillation; or patients with an inadequate chronotropic response to exercise. Monitoring the blood pressure response to exercise is vital in heart failure patients. A fall in blood pressure is an indication of deteriorating left ventricular function and an indication to stop the test.

Bearing in mind that most patients with heart failure have underlying coronary heart disease, the usual 12 lead ECG monitoring is important. A test characterised by pronounced ST segment changes is suggestive of underlying coronary disease. Monitoring rhythm during exercise is essential for safety.

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Figure 1 Metabolic gas exchange during an incremental exercise test in a normal subject (Bruce treadmill protocol). The exercise period is lightly shaded. $\dot{V}O_2$ and $\dot{V}CO_2$ are shown on the left hand axis. Note that at around two thirds of the test, $\dot{V}CO_2$ "overtakes" $\dot{V}O_2$, and the respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$) rises above 1.0 (to reach 1.26 at peak). Peak ventilation is over 150 litres/min and peak $\dot{V}O_2$ averaged over the last 30 seconds of exercise was 49 ml/kg/min.

Symptoms induced by exercise are also important, and we record symptom score at each stage of an incremental test. The development of angina or altered consciousness is also important for safety and diagnosis.

Contraindications to exercise testing include symptoms at rest and significant fluid retention and oedema. Left bundle branch block is not a contraindication.

MEASUREMENT OF METABOLIC GAS EXCHANGE

Inspired air contains approximately 20.9% molecular oxygen and almost no carbon dioxide. The difference between this and expired air (containing less oxygen and around 5% carbon dioxide) can be measured, and from these measurements, indices of metabolic gas exchange derived. Originally, Douglas bags were used to collect all expired air over a measured time interval with precise volumes and gas concentrations then measured, but the method is cumbersome and difficult in practice, particularly during exercise.

Modern metabolic gas exchange measurements use rapid analysers. A subject has to breathe through a tightly fitting mask (or mouthpiece with nasal grips) to prevent any leakage of expired air. One way valves ensure that normal room air is breathed in, but all the expired air is collected for analysis.

GAS MEASUREMENTS

Most metabolic carts use rapid gas analysers with continuous instantaneous measurements of expired oxygen and carbon dioxide. Air flow is measured separately with a pneumotachograph, and oxygen consumption and carbon dioxide production are calculated breath-by-breath. The results can be time averaged to account for the phasic nature of breathing. Three separate devices and three separate calibrations are usually necessary for this system: the flow meter and each of the gas sensors. Breath-by-breath measurements are subject to a lot of measurement noise.

A second approach is to use a mixing box. Here, all the expired gas is collected and mixed with a tracer gas (such as helium, not otherwise present in air) introduced into the mixing chamber at a known flow rate. The mixing is helped with a system of baffles, and equates closely to the use of

Douglas bags. The mixed gas is sampled at regular intervals to measure concentrations of metabolic and tracer gases. The dilution of the tracer gas gives flow. Typically, a respiratory mass spectrometer is used to measure gas concentrations. There is less noise in a mixing box system, but there is a time delay between expiration and measurement due to the need for mixing, and the system is much less sensitive to rapid changes.

METABOLIC GAS EXCHANGE VARIABLES

The principle measurements made are of oxygen consumption, $\dot{V}O_2$, and carbon dioxide production, $\dot{V}CO_2$. The results are usually expressed either as litres/min or corrected for body weight as ml/min/kg. Expired minute ventilation, $\dot{V}_E$, is measured in litres/min. From the ventilatory frequency, tidal volume can be calculated.

During incremental exercise, $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ increase as a function of exercise load and duration (fig 1). Peak oxygen consumption is usually taken as a measure of the maximum exercise tolerance of the patient. Physiologists often make reference to " $\dot{V}O_2$ max", the maximum possible level of oxygen consumption that an individual's cardiopulmonary system can attain. This is defined as the oxygen consumption reached during an incremental test when there is no further increase in $\dot{V}O_2$ despite an increase in exercise load. In practice, $\dot{V}O_2$ max is very rarely achieved in patients with chronic heart failure, and the term "peak $\dot{V}O_2$ " is preferable. Typically, the readings for the last 20–30 seconds of an exercise test will be averaged to give peak $\dot{V}O_2$.

Minute ventilation increases approximately linearly with exercise, so to record peak ventilation is largely a measurement of exercise duration. However, it also increases linearly with carbon dioxide production, and the slope of that relation can be used as an index of the ventilatory response to exercise (the $\dot{V}_E/\dot{V}CO_2$ slope).

The respiratory exchange ratio (RER) is the ratio of carbon dioxide production to oxygen consumption. It reflects the tissue respiratory quotient (RQ), and depends upon the cellular energy substrate. If glucose is being burned, the respiratory quotient is 1.0 (one molecule of carbon dioxide is evolved for each molecule of oxygen consumed). For lipid

oxidation, RQ is lower as lipid is more highly reduced. Less carbon dioxide is produced per molecule of oxygen consumed.

RER reflects RQ, but is also influenced by body carbon dioxide stores. During hyperventilation, for example, carbon dioxide is blown off, resulting in a higher RER than RQ. At rest, RER is typically 0.7–0.8. Towards peak exercise during an incremental test, lactic acid is produced (see “Anaerobic threshold” below) which causes carbon dioxide to be blown off, resulting in an increase in RER above 1.0. The RER at peak exercise can be used as a measure of whether truly maximal exercise has been performed. Normal subjects will often reach an RER in excess of 1.2, and a peak RER much less than 1.1 suggests that a test has been submaximal.

Anaerobic threshold is measured as the level of oxygen consumption at which anaerobic metabolism becomes necessary to maintain energy production. During an incremental test, there comes a point where the oxygen supply is no longer sufficient to meet the energy demands of the exercising muscle, and anaerobic metabolism is required to supplement the supply of high energy phosphate. In turn, this results in lactic acid accumulation. The lactate is buffered in blood by bicarbonate; bicarbonate is converted to water and carbon dioxide, and the carbon dioxide is blown off. At this point, there is a non-linear increase in $\dot{V}_{CO_2}$ relative to $\dot{V}_{O_2}$, measured as the anaerobic threshold.

The anaerobic threshold can be measured by several different methods. With the “v-slope” method, $\dot{V}_{CO_2}$ is plotted as a function of $\dot{V}_{O_2}$, and the anaerobic threshold is measured as the point where $\dot{V}_{CO_2}$ increases non-linearly with respect to $\dot{V}_{O_2}$ (fig 2). In the “ventilatory equivalent” method, the instantaneous ratio of $\dot{V}_E$ to $\dot{V}_{CO_2}$ (ventilatory equivalent for carbon dioxide) and of $\dot{V}_E$ to $\dot{V}_{O_2}$ (ventilatory equivalent for oxygen) are plotted, and the anaerobic threshold is the point at which $\dot{V}_E/\dot{V}_{O_2}$ starts to increase. Anaerobic threshold is typically 60% of peak $\dot{V}_{O_2}$.

Other useful variables measured from gas exchange data include the end tidal carbon dioxide. This falls towards the end of a maximal test, representing hyperventilation induced

by a falling pH; if end tidal carbon dioxide falls early in exercise, it can represent hyperventilation. The ratio of $\dot{V}_{O_2}$ to heart rate, termed the oxygen pulse, is dependent on stroke volume and the arterial–mixed venous oxygen difference. It is sometimes used to characterise the exercise response: if the increase in stroke volume is limited by disease, then oxygen pulse reaches an early plateau with increases in oxygen uptake being dependent upon increase in heart rate.

Pulmonary ventilation-perfusion matching can be assessed with metabolic gas exchange data. Physiological dead space, representing areas of lung that are ventilated but not perfused, can be calculated from $\dot{V}_E$, $\dot{V}_{CO_2}$ and the arterial oxygen tension. The alveolar–arterial oxygen difference ($A-aDO_2$) is an estimate of shunt—that is, areas of lung that are perfused but not ventilated. Accurate derivation of these variables requires arterial blood gas sampling.

EXERCISE IN CHRONIC HEART FAILURE

Exercise capacity is reduced in chronic heart failure. This translates to a lesser distance covered in a six minute walk test, and reduced performance in shuttle tests. During incremental tests, exercise time is reduced, as is peak $\dot{V}_{O_2}$. In anticipation of this, the exercise protocol used should be chosen to last around 10 minutes to maximise peak $\dot{V}_{O_2}$. In parallel with the reduction in peak $\dot{V}_{O_2}$, anaerobic threshold is reduced, but is still approximately the same proportion of peak $\dot{V}_{O_2}$ as in normal subjects.

Heart rate response is difficult to predict, particularly as many patients are on β blockers. Typically, patients have a low oxygen pulse (oxygen uptake per heart beat) and poor blood pressure responses to exercise.

The ventilatory response to exercise in patients with chronic heart failure is increased, and correlates inversely with peak $\dot{V}_{O_2}$. Thus, the slope of the $\dot{V}_E/\dot{V}_{CO_2}$ relation increases, so that at any particular level of carbon dioxide production, the ventilatory response is greater (fig 3). Peak minute ventilation is, however, notably less than normal. In normal subjects, a typical peak ventilation is around 120 litres/min, but heart failure patients usually stop with a peak ventilation of around 50–60 litres/min. At any given ventilation, tidal volume tends to be smaller and respiratory frequency greater. The sensation of breathlessness is greater at any given ventilation than normal.

Dead space ventilation is increased in chronic heart failure. Quite how this arises and what it means is not clear. Dead space is usually expressed as a fraction of tidal volume, V_D/V_T , and is derived from the alveolar ventilation equation.* As V_D/V_T is calculated from the $\dot{V}_E/\dot{V}_{CO_2}$ relation, the two variables necessarily correlate closely with each other. Many commentators have assumed that the cause of the increased $\dot{V}_E/\dot{V}_{CO_2}$ slope is an increase in V_D/V_T .⁴ Other abnormalities on exercise in chronic heart failure include impaired diffusion at the level of the alveolar–capillary membrane.⁵

An important observation is that arterial blood gas tensions are normal, or even supra-normal, in heart failure, with a rise in P_{aO_2} towards peak exercise, and fall in P_{aCO_2} . Any abnormality of blood gases (including a fall in arterial oxygen saturation) should prompt a search for other pathology.⁶

Figure 2 The anaerobic threshold. As anaerobic metabolism is needed to keep up the supply of high energy phosphate, lactate starts to accumulate. Buffering lactate with bicarbonate produces carbon dioxide (and water) which is blown off at the lungs. $\dot{V}_{CO_2}$ thus increases at a faster rate than $\dot{V}_{O_2}$ after the threshold. The threshold is defined by the intersection between two regression lines of $\dot{V}_{CO_2}$ as a function of $\dot{V}_{O_2}$ as shown.

* $\dot{V}_E/\dot{V}_{CO_2} = 863/P_{aCO_2} \times (1 - V_D/V_T)$, where 863 is a constant to standardise volume measurements, P_{aCO_2} is the arterial tension of carbon dioxide and V_D/V_T is dead space as a fraction of tidal volume.

Figure 3 The $\dot{V}_E/\dot{V}_{CO_2}$ slope in heart failure. Note that the relation between ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}_{CO_2}$) remains linear, but that the slope increases with worsening heart failure. Thus, for a $\dot{V}_{CO_2}$ of 1 litre/min, a normal subject has to ventilate at 22 litres/min, the patient with moderate heart failure ventilates at 42 litres/min. Reproduced from Clark,¹⁶ with permission of the BMJ Publishing Group.

Typically, patients are less able to exercise to a high RER at peak exercise than control subjects, but this is quite variable. A test with a peak RER less than 1.0 is usually submaximal.

Response to fixed submaximal workload is also of some interest in chronic heart failure patients. $\dot{V}_{O_2}$ should reach a plateau at a given workload which is the same for both patients and control subjects. However, heart failure patients reach their plateau, and at the end of exercise return to baseline, more slowly. The oxygen deficit at exercise onset, and debt at the end, are thus greater in heart failure.⁷

USES OF EXERCISE TESTING

Diagnosis, assessment and prognosis

It seems common sense when a patient complains of exercise-induced symptoms to test their exercise response objectively. In the case of heart failure, this can have several functions. Firstly, it gives a picture of the exercise capacity of the patient and the degree of his or her limitation. Typically, the New York Heart Association (NYHA) classification of symptoms is used, but this is a wholly subjective description. One patient's NYHA class I could be another's NYHA III. The peak $\dot{V}_{O_2}$ describes actual exercise capacity. Secondly, it gives an assessment of performance during exercise. Is the ventilatory response normal, or is there hyperventilation? Is the patient able to exercise beyond anaerobic threshold and to an RER of greater than 1.1? Thirdly, there is some diagnostic use from any ECG changes there might be, any symptoms that develop or for any change in arterial oxygen saturation.

Many of the exercise variables are prognostic indicators. In the very many studies of predictors of prognosis, increasing peak $\dot{V}_{O_2}$ (where it has been measured) is one of the most powerful predictors of survival. The $\dot{V}_E/\dot{V}_{CO_2}$ slope adds further predictive value (the steeper the slope, the worse the outcome) as do some other variables, such as failure to increase blood pressure.⁸

One of the most valuable roles for metabolic gas exchange measurements is in selecting patients for heart transplantation. The value of 14 ml/kg/min is generally taken as the cut-off point below which patients should be considered for transplantation.⁹

A peak $\dot{V}_{O_2}$ of 14 ml/kg/min is very low, and yet much above this value, patients have little to gain in terms of prognosis from transplantation. (Typical peak $\dot{V}_{O_2}$ in well adults is in the order of 30–50 ml/kg/min depending upon age, sex, height and weight; 14 ml/kg/min is approximately the oxygen consumption required to perform 50 W exercise).

The worth of the particular cut-off of 14 ml/kg/min has been challenged. Modern medical treatment of chronic heart failure with angiotensin converting enzyme (ACE) inhibitors, β blockers and aldosterone antagonists is now so effective that patients with a peak $\dot{V}_{O_2}$ as low as 10 are probably best treated medically rather than with transplantation.¹⁰

Assessing response to treatment

Exercise tests of some sort are commonly used to assess the effects of new interventions for chronic heart failure with some support from regulatory authorities. However, exercise testing is remarkably insensitive to changes in drug treatment. Treatments that improve prognosis, such as ACE inhibitors and β blockers, have little effect on peak oxygen uptake,¹¹ although these medications also appear to improve symptoms as reflected in decreases in hospitalisation. By contrast, drugs such as positive inotropic agents do improve exercise performance, but reduce prognosis.

However, in trial work, even if the intervention is not destined to improve exercise capacity, peak $\dot{V}_{O_2}$ is useful for defining severity of heart failure.

Device therapy, particularly with biventricular pacing, can improve exercise performance.¹² At present, device optimisation is done (predominantly) using echocardiography at rest, but is designed to help patients during exercise. Formal exercise testing may become a useful tool in programming devices to optimise performance.

Exploring mechanisms of exercise intolerance

One of the greatest uses of metabolic gas exchange measurements is in exploring the pathophysiology of exercise impairment. In turn, this leads (potentially) to better treatment strategies for exercise-induced symptoms. Thus, there is little relation between either peak $\dot{V}_{O_2}$ or $\dot{V}_E/\dot{V}_{CO_2}$ slope and indices of left ventricular function. Manoeuvres to increase cardiac output acutely do not increase exercise performance.¹³ If, at peak leg exercise additional arm exercise is imposed, unlike with normal subjects, oxygen consumption and cardiac output increase further.¹⁴ These observations suggest that exercise tolerance in heart failure is not limited by cardiac function.

By contrast, exercise capacity correlates better with indices that reflect peripheral adaptations to heart failure, such as chemoreflex activity and skeletal muscle mass. In particular, the activity of the ergoreflex, a reflex originating from muscle in response to work and causing increased ventilation, is enhanced in heart failure and potentially causes breathlessness and fatigue as well as increasing sympathetic activity.¹⁵ For a review, see Clark.¹⁶

This understanding leads to work exploring the possible role of interventions aimed specifically at modifying the periphery as treatments for heart failure symptoms.

EXERCISE TRAINING

Many of the features of the heart failure syndrome are similar to the changes that occur in normal subjects who become de-trained. Thus, for example, peripheral muscle atrophies, and decreases in strength. There is activation of the

renin-angiotensin and sympathetic systems accompanied by a rise in resting heart rate and a decrease in heart rate variability. Exercise training offers the possibility of reversing some of these changes.

In one of the earliest randomised trials of training, Coats and colleagues¹⁷ showed that home-based unsupervised cycling at 60–80% of previously determined maximal heart rate for 20 minutes, five days per week for eight weeks, led to an improvement in exercise capacity, reduction in norepinephrine (noradrenaline) spillover and improvement in the abnormal sympathovagal balance.¹⁷ These general findings have been confirmed in many subsequent studies. The overall finding is that a training regimen will produce an increase in exercise capacity of around 15% with benefits on quality of life.¹⁸

Training in most studies has little effect on central haemodynamic function, although by improving exercise performance it causes an increase in peak cardiac output. Note that this does not imply an increase in cardiac performance per se; cardiac output at a given workload is unchanged. What does increase is muscle strength together with an improvement in muscle metabolism; skeletal muscle becomes acidotic less quickly after training. At the same time, ergoreflex activation is reduced, perhaps mediating a reduction in sympathetic activation and improvement in symptoms.¹⁹

Whether the training benefits translate into an improvement in outcome is not known. No single study has shown such an effect, but meta-analysis of the available data¹⁹ suggests that exercise training can reduce mortality by approximately 35%. The result, that the number needed to treat to prevent one death in two years is 17, is remarkable. Were this a drug intervention, there is no doubt that randomised long term studies would be in progress, but it is difficult to mount such studies where the intervention is more complex. Funding remains a major issue for proposed trials of exercise training.

The logistics of providing exercise training to most patients with chronic heart failure remain formidable. Most patients are elderly and often have substantial co-morbidity limiting compliance. Trials of rehabilitation in other fields suggest that those most likely to comply and benefit were younger males with less co-morbidity, and most of the heart failure trials have been conducted in just such populations. The training benefit is proportional to compliance to training. Which training regimen (or which components of a training regimen) confer most benefit remains controversial; supervision is difficult; and training probably needs to last indefinitely.

Other methods of training are being assessed, such as electrical muscle stimulation,²⁰ which may be useful in a broader group of patients than formal training programmes.

CONCLUSION

The chronic heart failure syndrome is defined in part by the presence of symptoms, and the dominant symptom is exercise limitation. Exercise testing has a crucial role in defining that limitation objectively and for assessing the possible contributing causes for exercise limitation. Exercise testing is a vital tool for exploring the pathophysiology of exercise limitation. As a therapy, exercise training is something of an orphan at present. It undoubtedly benefits selected patients, but its widespread uptake depends upon resources, both equipment and personnel, and perhaps on the possibility of commercial exploitation.

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