The clinical importance of cardiopulmonary exercise testing and aerobic training in patients with heart failure

A importância clínica de testes de exercícios cardiopulmonares e treinamento aeróbico em pacientes com insuficiência cardíaca

Arena R1, Myers J2, Guazzi M3

Abstract

Introduction: The appropriate physiological response to an acute bout of progressive aerobic exercise requires proper functioning of the pulmonary, cardiovascular and skeletal muscle systems. Unfortunately, these systems are all negatively impacted in patients with heart failure (HF), resulting in significantly diminished aerobic capacity compared with apparently healthy individuals. Cardiopulmonary exercise testing (CPX) is a noninvasive assessment technique that provides valuable insight into the health and functioning of the physiological systems that dictate an individual’s aerobic capacity. The values of several key variables obtained from CPX, such as peak oxygen consumption and ventilatory efficiency, are often found to be abnormal in patients with HF. In addition to the ability of CPX variables to acutely reflect varying degrees of pathophysiology, they also possess strong prognostic significance, further bolstering their clinical value. Once thought to be contraindicated in patients with HF, participation in a chronic aerobic exercise program is now an accepted lifestyle intervention. Following several weeks/months of aerobic exercise training, an abundance of evidence now demonstrates an improvement in several pathophysiological phenomena contributing to the abnormalities frequently observed during CPX in the HF population. These exercise-induced adaptations to physiological function result in a significant improvement in aerobic capacity and quality of life. Conclusion: Furthermore, there is initial evidence to suggest that aerobic exercise training improves morbidity and mortality in patients with HF. This paper provides a review of the literature highlighting the clinical significance of aerobic exercise testing and training in this unique cardiac population.

Key words: ventilatory expired gas; cardiac output; skeletal muscle; survival.

Resumo

Introdução: A resposta fisiológica aguda ao exercício aeróbio progressivo demanda funcionamento adequado dos sistemas pulmonares, cardiovasculares e músculo-esquelético. Infelizmente, todos estes sistemas estão negativamente afetados em pacientes com insuficiência cardíaca (IC), resultando numa redução significativa da capacidade aeróbia comparada com indivíduos aparentemente saudáveis. O teste de exercício cardiopulmonar (TCP) representa uma técnica não-invasiva de avaliação que fornece compreensão valiosa sobre a saúde e funcionamento dos sistemas fisiológicos que ditam a capacidade aeróbia de um indivíduo. Os valores de várias variáveis-chave obtidas através do TCP, como consumo pico de oxigênio e eficiência ventilatória são encontrados frequentemente como anormais em pacientes com IC. Além da capacidade das variáveis do TCP refletir de maneira aguda os graus variáveis da fisiopatologia, também possuem forte significância prognóstica, aumentando ainda mais o seu valor clínico. A participação num programa de exercícios aeróbios crônicos, anteriormente era contra-indicada em pacientes com IC. Agora é uma intervenção aceitável de estilo de vida. Após um período de treinamento com exercícios aeróbios, durante várias semanas/meses, tem sido evidenciada uma melhora em vários fenômenos fisiopatológicos que contribuem às anormalidades constatadas frequentemente durante TCP na população com IC. Conclusões: As adaptações fisiológicas induzidas por exercícios aeróbios resultam em uma melhora significativa de capacidade aeróbia e de qualidade de vida. Além disso, há evidências sugerindo que treinamento com exercícios aeróbios melhora a morbidade e a mortalidade em pacientes com IC. Este artigo fornece uma revisão da literatura que destaca a significância clínica dos testes de exercícios aeróbicos e treinamento nesta população cardíaca única.

Palavras-chave: gás expirado ventilatório; rendimento cardíaco; músculo esquelético; sobrevivência.

Received: 15/01/2008 – Revisado: 17/01/2008 – Aceito: 04/02/2008

1 Departments of Internal Medicine, Physiology and Physical Therapy, Virginia Commonwealth University, Health Sciences Campus, Richmond, Virginia, United States
2 VA Palo Alto Health Care System, Cardiology Division, Stanford University, Palo Alto, California, United States
3 Cardiopulmonary Laboratory, Cardiology Division, University of Milan, San Paolo Hospital, Milan, Italy

Correspondence to: Ross Arena, PT, PhD, Associate Professor, Department of Physical Therapy, Box 980224, Virginia Commonwealth University, Health Sciences Campus, Richmond, VA, USA 23298-0224, e-mail: raarena@vcu.edu
Introduction

Systems influencing the physiological response to normal exercise

An individual’s capacity to perform aerobic exercise is dependent upon pulmonary, cardiovascular and skeletal muscle function. While proper physiological functioning of these three systems is important, cardiac output (Q), i.e. the product of heart rate and stroke volume, is the primary determinant of peak or maximal oxygen consumption (VO$_2$). Cardiac output is approximately five liters/minute at rest and increases to approximately 20-25 and 30-35 liters/minute at maximal exercise in apparently healthy sedentary subjects and elite athletes, respectively. The ability of skeletal muscle to increase oxygen extraction during aerobic exercise plays a lesser but still important role in determining aerobic capacity. In apparently healthy subjects, the difference in oxygen (O$_2$) concentration between arterial and venous blood (a-vO$_2$ diff) increases from approximately 5 mlO$_2$/100 ml at rest to 16 mlO$_2$/100 ml at maximal exercise. The Fick equation, defined as the product of Q and a-vO$_2$ diff, is used to describe VO$_2$. While pulmonary function is not included in the Fick equation, the ability to increase gas exchange (oxygen intake and carbon dioxide removal) is of paramount importance to aerobic exercise capacity. Minute ventilation (VE), the product of respiratory rate and tidal volume, normally increases 10-20 fold at maximal aerobic exercise compared with resting values. It should be noted that pulmonary function is not typically the primary limiter of aerobic capacity, either in apparently healthy individuals or among patients diagnosed with cardiovascular disease. Even when the pulmonary, cardiovascular and skeletal muscle systems are all functioning properly, maximal aerobic capacity remains a rather heterogeneous phenomenon, since it is also influenced by age, sex, genetic predisposition and exercise habits. Considering these factors, the approximate range for maximal VO$_2$ in the apparently healthy population is between 20-55 mlO$_2$.kg$^{-1}$.min$^{-1}$.

Pathophysiological abnormalities associated with diminished aerobic capacity in patients with heart failure

Severely compromised cardiac function is a primary pathophysiological component in heart failure (HF), and previous investigations have demonstrated a significant relationship between cardiac output during exercise and peak VO$_2$ in this population$^{26}$. It has furthermore been well established that patients with HF frequently present reduced capillary density$^6$ and intrinsic skeletal muscle abnormalities, primarily in the form of diminished aerobic (mitochondrial) function$^{6-13}$. Given that aerobic capacity is reliant primarily on Q and secondarily on the a-vO$_2$ diff, as defined by the Fick equation, the significant reduction in peak VO$_2$, frequently observed in patients with HF should be of no surprise. On average, peak VO$_2$ is approximately 50% lower in this patient population, compared with values observed in apparently healthy individuals matched according to age and sex. Moreover, peak VO$_2$ is approximately 25% lower in patients with HF, compared with patients diagnosed with coronary artery disease$^{14}$. A relationship between pulmonary abnormalities and peak VO$_2$ has also been demonstrated in patients with HF$^{15-17}$. Both resting$^9$ and maximal$^{18}$ measures of pulmonary function (i.e. inspiratory capacity), as well as diffusion capacity$^{17}$, have all demonstrated significant correlations with peak VO$_2$. The degree to which these pulmonary abnormalities contribute towards the diminished aerobic capacity observed in HF, after accounting for the contributions of cardiovascular and skeletal muscle dysfunction, is unknown. Figure 1 illustrates the systems involved in the physiological response to aerobic exercise and how HF affects these systems.

The clinical applications of cardiopulmonary exercise testing in patients with heart failure

Cardiopulmonary exercise testing (CPX) is a highly reliable$^{18}$, well-accepted assessment technique in the HF population. American$^{19-21}$ and European$^{22-24}$ associations have endorsed its use. CPX is most often performed on a treadmill or lower-limb ergometer using highly conservative ramping protocols, which are appropriate given the severely diminished exercise tolerance often observed in this population$^{25-28}$. The addition of ventilatory expired gas analysis to the standard exercise test enables measurement of VO$_2$, carbon dioxide production (VCO$_2$) and minute ventilation (VE) over time. In addition to aerobic capacity, several other variables generated from CPX data have demonstrated clinical value with regard to exercise prescription, prognosis and response to a given intervention. Table 1 highlights key considerations for several CPX variables in patients with HF, which are described in greater detail in the following sections. It should be noted that the overwhelming majority of the literature cited in subsequent sections consists of studies performed on systolic HF cohorts. While the initial evidence indicates that CPX is also prognostic in patients with diastolic HF$^{29}$, much more work is required in this area. Therefore, with regard to the prognostic applications of CPX, the following information and recommendations primarily apply to patients diagnosed with systolic HF at this time.

Table 1 highlights key considerations for several CPX variables in patients with HF, which are described in greater detail in the following sections. It should be noted that the overwhelming majority of the literature cited in subsequent sections consists of studies performed on systolic HF cohorts. While the initial evidence indicates that CPX is also prognostic in patients with diastolic HF$^{29}$, much more work is required in this area. Therefore, with regard to the prognostic applications of CPX, the following information and recommendations primarily apply to patients diagnosed with systolic HF at this time.
Resting state VO\textsubscript{2}≈ 3.5 mlO\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1}

### Aerobic exercise progression to maximum tolerance

**Palmonary**
- Increased respiratory rate
- Increased tidal volume
- Increased oxygen intake and carbon dioxide removal

**Cardiac**
- Increased heart rate
- Increased stroke volume
- Increased cardiac output

**Peripheral**
- Increased oxygen extraction for energy production within mitochondria
- Widening of a-vO\textsubscript{2} diff

### HF pathophysiology
- Decreased inspiratory capacity and diffusion capacity
- Decreased stroke volume and cardiac output
- Decreased capillary density and aerobic characteristics of skeletal muscle

- Peak aerobic exercise tolerance diminished: ≈50% of predicted on average
- Peak VO\textsubscript{2} ≈ 6-25 mlO\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1} in the HF population
- Value achieved dependent upon HF etiology, sex, disease severity and activity pattern
- Negative correlation between age and peak VO\textsubscript{2} diminished in patients with HF

### Figure 1. Illustration of central and peripheral physiological adaptations from rest to maximal aerobic exercise and the impact of heart failure.

### Table 1. Key considerations for cardiopulmonary exercise testing variables in patients with heart failure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prognostic value</th>
<th>Prognostic thresholds</th>
<th>Response to interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VO\textsubscript{2} Slope*</td>
<td>Well established; &gt;20 papers</td>
<td>( \geq 34 ) as dichotomous threshold; prognosis appears to progressively worsen as slope increases into 40s (VC-IV ( \geq 45.0 ))</td>
<td>Significant reduction with multiple interventions; should be assessed with interventional trials</td>
</tr>
<tr>
<td>Peak VO\textsubscript{2} ( ^\circ )</td>
<td>Well established; &gt;20 papers</td>
<td>( \leq 10 ) mlO\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1} in patients prescribed a beta-blocker; ( \leq 14 ) mlO\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1} in patients not prescribed a beta-blocker</td>
<td>Significant reduction with multiple interventions; should be assessed with interventional trials</td>
</tr>
<tr>
<td>EOV*</td>
<td>Consistent results; 4 papers</td>
<td>Defined as oscillatory pattern in VE that occurs for ( \geq 60% ) of the exercise test at an amplitude ( \geq 15% ) of average amplitude observed at rest</td>
<td>Not well investigated; significant reduction in occurrence of EOV following milrinone treatment and respiratory muscle training</td>
</tr>
<tr>
<td>OUES</td>
<td>Compelling results; 2 papers</td>
<td>Not well established at this time; lower = worse prognosis</td>
<td>Not well investigated; significantly improved following exercise training</td>
</tr>
<tr>
<td>( P_{\text{CO}_2} ) Rest and exercise</td>
<td>Compelling results; 2 papers</td>
<td>Not well established at this time; lower = worse prognosis</td>
<td>Response to interventions not investigated at this time</td>
</tr>
<tr>
<td>HRR</td>
<td>Compelling results; 3 papers with small cohorts</td>
<td>Not well established at this time; lower = worse prognosis</td>
<td>Not well investigated; significantly improved following exercise training</td>
</tr>
</tbody>
</table>

Abbreviations: EOV= Exercise oscillatory ventilation; OUES= Oxygen uptake efficiency slope; \( P_{\text{CO}_2} \)= Partial pressure of end-tidal carbon dioxide; HRR= Heart rate recovery.

* Combination of high VE/VO\textsubscript{2} slope plus the presence of EOV and/or low peak VO\textsubscript{2} may be highly indicative of poor prognosis; \( \circ \) Use of peak VO\textsubscript{2} for prognostic purposes not recommended if peak RER <1.0 and test terminated at subject’s request. Similar peak RER values between/among exercise tests during interventional trials is indicative of consistent subject effort.
Peak oxygen consumption

Oxygen consumption at peak exercise remains the most frequently assessed variable obtained from CPX in the HF population and is often significantly reduced, compared with normal predicted values for a given age. It is usually referred to as "peak VO₂" in patients with HF, since a plateau in oxygen uptake is uncommon. Although ventilatory expired gas systems provide absolute peak VO₂ data (ml/min or l/min), it is most often reported clinically as a relative value (mlO₂·kg⁻¹·min⁻¹). Figure 2 illustrates a comparison of VO₂ responses during symptom-limited CPX between an apparently healthy individual and a patient diagnosed with HF. Both subjects were 55-year-old males. A plateau in VO₂ is observed in the apparently healthy individual (VO₂max) but is absent in the patient with HF (peak VO₂). Values of 37.8 and 11.2 mlO₂·kg⁻¹·min⁻¹ place the apparently healthy individual and patient with HF in the 50th and below the 10th percentile for their age, respectively.

Numerous investigations have reported relationships between peak VO₂ and the pathophysiological abnormalities associated with HF. Lower cardiac output during exercise, decreased alveolar-capillary membrane conductance, decreased heart rate variability, increased pulmonary vascular pressures, and increased brain natriuretic peptide have all been significantly correlated with lower peak VO₂ in patients with HF. Furthermore, several interventions have been shown to significantly improve peak VO₂, including aerobic exercise training, inspiratory muscle training, left ventricular assistance device implantation, cardiac resynchronization therapy, ACE inhibition, and sildenafil. Beta-blockade, however, has consistently been shown to have no effect on peak VO₂.

Given the ability of peak VO₂ to reflect varying degrees of disease severity, the consistently demonstrated prognostic value of this CPX variable should be of no surprise. In fact, peak VO₂ remains the most frequently analyzed variable in clinical practice with regard to prognostic assessment. A peak VO₂ threshold of ≤ 14 mlO₂·kg⁻¹·min⁻¹ was established for prognostic purposes by Mancini et al. in 1991 and is still used today. More recently, O’Neil et al. found that this threshold might be too high in patients with HF who have been prescribed beta-blocking agents, a pharmacological class that improves survival but does not significantly improve peak VO₂. Given these findings, a peak VO₂ threshold of ≤ 10 mlO₂·kg⁻¹·min⁻¹ may be more appropriate for present-day practice, particularly given the large percentage of patients with HF who are prescribed beta-blockers.

Although peak VO₂ is clearly an important prognostic variable, it does have limitations. The central limitation is dependence on maximal effort by the subject to attain a valid measurement. Mezzani et al. demonstrated that the prognostic value of peak VO₂ ≤ 10 mlO₂·kg⁻¹·min⁻¹ was significantly diminished in subjects who attained peak respiratory exchange ratio (RER) ≤ 1.15 (clinical significance of peak RER is discussed in the following section). For this reason, the prognostic veracity of peak VO₂ should be questioned among subjects who voluntarily terminate the exercise test and do not demonstrate objective signs of maximal effort (i.e. high peak RER).

Peak respiratory exchange ratio

Achievement of at least 85% of age-predicted maximal heart rate is a classic indicator of maximal effort during the exercise test. The maximal heart rate response to exercise, however, has wide variability (± 12 beats per minute) in the general population and this has a negative impact on the ability to use heart rate to accurately gauge subject effort. Furthermore, the use of beta-blocking agents, now commonplace in the HF population, dramatically and heterogeneously blunts the heart rate response at maximal
exercise, thus negating the validity of age-predicted maximal heart rate. The RER, defined as the ratio between VCO\(_2\) and VO\(_2\), is the most accurate way to assess subject effort during CPX. As exercise progresses to higher intensities, lactic acid buffering contributes towards VCO\(_2\), thereby increasing the numerator of this expression at a faster rate than the denominator. This physiological response to exercise is consistent across all individuals, making peak RER a reliable method for determining subject effort. Peak RER ≥ 1.10 is an indication of excellent subject effort during CPX. As a minimal threshold, peak RER < 1.00 during CPX that is terminated at the subject’s request, with the absence of electrocardiographic and/or hemodynamic abnormalities (ST segment changes, ventricular arrhythmias, drop in systolic blood pressure, etc.), may be indicative of poor subject effort. Caution should therefore be applied in using peak VO\(_2\) for prognostic purposes when coinciding with a low peak RER. Assessment of peak RER is also important during interventional trials, to ensure comparable subject effort from one test to the next. A significant increase in aerobic capacity following a given intervention, with similar peak RER values, strongly supports the assertion that observed improvements are secondary to physiological adaptation.

Oxygen consumption at ventilatory threshold

Minute ventilation, VO\(_2\) and VCO\(_2\) all increase in a similar linear fashion during the initial stages of progressive exercise tests, because of increased aerobic metabolism. At a given submaximal level of exercise unique to each individual, anaerobic metabolism begins to increase. From this point to maximal exercise, there are two significant sources of CO\(_2\), consisting of byproducts from metabolism and lactic acid buffering. This causes a nonlinear rise in VCO\(_2\) in relation to VO\(_2\). Ventilation is driven by VCO\(_2\), thus causing a simultaneous nonlinear break in VE. The ability to detect this break point through ventilatory expired gas (ventilatory threshold) enables noninvasive estimation of the anaerobic threshold. The VO\(_2\), VCO\(_2\) and VE responses to progressive CPX are illustrated in Figure 3.

The v-slope, ventilatory equivalents and end-tidal O\(_2\)/CO\(_2\) methods have all been used to determine the ventilatory threshold. Techniques for these calculations are described elsewhere\(^{49,50}\). Because of the significantly reduced aerobic capacity and/or oscillations in exercise ventilation among patients with HF, accurate determination of the ventilatory threshold is not always possible. When detectable, VO\(_2\) at ventilatory threshold, like peak VO\(_2\), is often significantly reduced in patients with HF. Although there is some evidence to indicate that VO\(_2\) at the ventilatory threshold is prognostically significant\(^{41}\), its analysis is at present more important as a core component of exercise prescription, with regard to the overload principle (discussed in a subsequent section).

Figure 3. Detecting ventilatory threshold using oxygen consumption, carbon dioxide production and the minute ventilation response to exercise.

The minute ventilation – carbon dioxide production relationship

Minute ventilation and VCO\(_2\) are tightly coupled during exercise, since the former is driven by the metabolic and anaerobic production of the latter. The VE-VCO\(_2\) relationship is most often expressed as a slope value, calculated by linear regression
(y = mx + b, b = slope). A VE/VCO₂ slope < 30 is considered normal, while the range observed in HF is < 30 to > 70. Figure 4 illustrates normal and elevated VE/VCO₂ slope responses to progressive exercise tests on two patients diagnosed with HF.

The pathophysiological mechanism behind an abnormally elevated VE/VCO₂ slope in HF patients appears to be multifactorial. Centrally, an elevated VE/VCO₂ slope has been linked to ventilation-perfusion abnormalities (adequate ventilation and poor perfusion)⁵²,⁵³. Additionally, elevated VE/VCO₂ slopes have demonstrated significant correlations with abnormally increased chemo and ergoreceptor sensitivity⁵⁴-⁵⁶, both contributing towards exaggerated ventilatory response to exercise. Like peak VO₂, the VE/VCO₂ slope has been significantly correlated with decreased cardiac output⁵⁰,⁵¹,⁵², increased pulmonary pressures⁴⁸, decreased alveolar-capillary membrane conductance⁵⁸ and decreased heart rate variability⁵⁰,⁵¹. Also consistent with peak VO₂, several interventions have been shown to significantly improve the VE-VCO₂ relationship, including aerobic exercise training⁵⁰, inspiratory muscle training⁵⁰, left ventricular assistance device implantation⁵⁷, cardiac resynchronization therapy⁴⁸, ACE inhibition⁵⁰ and Sildenafil⁴⁸. In contrast to peak VO₂, beta-blockade has also been shown to significantly improve the VE-VCO₂ relationship⁴¹-⁴³.

Given the link between the VE-VCO₂ relationship and pathophysiology, considerable attention has been given to the prognostic value of this CPX variable. The VE-VCO₂ relationship, again most often expressed as a slope, has consistently been shown to have high prognostic value in patients with HF.⁵¹,⁵²,⁵³,⁵⁴. For prognostic purposes, the most frequently used dichotomous VE/VCO₂ slope threshold is ≤ ≥ 34⁴⁹,⁶². A four-level ventilatory classification (VC) scheme based upon the VE/VCO₂ slope (VC-I: < 29.9, VC-II: 30.0-35.9, VC-III: 36.0-4.9, VC-IV: ≥ 45.0) may, however, better identify varying levels of risk of adverse events⁶¹. Irrespective of the VE/VCO₂ slope threshold that is used, this variable should be calculated using all the exercise data (beginning of exercise to peak exertion), as opposed to submaximal calculations. Using all the exercise data to calculate the VE/VCO₂ slope has consistently been shown to provide stronger prognostic information⁶⁰,⁶¹. Furthermore, the VE-VCO₂ relationship appears to be prognostically superior to peak VO₂⁶². One of the primary reasons for the consistent prognostic superiority of the VE-VCO₂ relationship over peak VO₂ is its independence from subject effort. Furthermore, diagnostic studies have shown that, while both the VE-VCO₂ relationship and peak VO₂ are correlated with the same pathophysiological markers (reduced cardiac output, elevated neurohormonal markers, etc), the relationship with the former CPX variable and these pathophysiological markers is stronger⁶². The body of evidence in this area supports the use of the VE/VCO₂ slope as the primary variable assessed when CPX is performed for prognostic purposes in HF populations. It should be noted that, while the VE/VCO₂ slope has consistently been the strongest prognostic marker in previous investigations, peak VO₂ was retained in multivariate regression analyses in approximately half of the studies comparing these CPX variables⁶². For this

Figure 4. VE/VCO₂ slope comparison during symptom-limited CPX: normal vs. heart failure.
Aerobic exercise and heart failure

reason, we recommend the analysis of both the VE/VCO₂ slope and peak VO₂ in clinical practice.

Exercise oscillatory ventilation

Minute ventilation generally increases linearly during progressive exercise tests. In HF populations, however, a number of patients present a waxing/waning VE pattern than has been defined as exercise oscillatory ventilation (EOV). The body of research investigating this phenomenon in patients with HF is not as robust as the work done in the areas of peak VO₂ and the VE-VCO₂ relationship. The analysis of EOV in HF does, however, rather convincingly indicate that disease severity is significantly increased when this ventilatory abnormality is present64,65. Although there is at present no universal definition of EOV, an oscillatory VE pattern at rest that persists for ≥ 60% of the exercise test at an amplitude ≥ 15% of the average resting value has been proposed66,67. Figure 5 illustrates the VE pattern at rest and during a progressive exercise test in two patients diagnosed with HF: one with a normal pattern and the other with EOV.

Like elevated VE/VCO₂ slopes, EOV has been linked to increased chemosensitivity in patients with HF68. In addition, oscillations in cardiac function have been reported in patients with EOV69. Using quantitative algebraic analysis of dynamic cardiorespiratory physiology, Francis et al.70 concluded that the primary pathophysiological factors resulting in EOV are circulatory delay and an increased chemoreflex gain. While the impact of interventions on EOV are limited, both milrinone64 and respiratory muscle training36 have been shown to reduce the occurrence of EOV.

Like peak VO₂ and the VE/VCO₂ slope, the presence of EOV appears to be a significant predictor of adverse events66,67,71,72. Furthermore, combined assessment of EOV and both peak VO₂67 and the VE/VCO₂ slope67 appears to enhance prognostic significance, thus warranting their inclusion when using CPX data to assess prognosis. The combination of the independence of EOV from subject effort and its ability to reflect cardiac pathophysiology may help to account for the strong prognostic value observed in previous investigations.

Other noteworthy cardiopulmonary exercise testing variables

Several other CPX variables have been assessed for their prognostic value in patients with HF. The oxygen uptake efficiency slope (OUES), defined as the linear relationship between VO₂ and the logarithmic transformation of VE73,74, the partial pressure of end-tidal carbon-dioxide production at rest75 and during exercise76, and heart rate recovery (HRR)77-79 have all demonstrated prognostic value among patients with HF. Furthermore, both the OUES80 and HRR81 have been shown to significantly increase (improve) following an aerobic exercise training program among patients with HF. The additive prognostic value of these variables to peak VO₂, the VE/VCO₂ slope and EOV is unclear at this time. Future investigations are needed in order to determine whether one or more of the variables mentioned should be added to multivariate modeling. Lastly, although not central to the prognostic assessment of patients with HF, monitoring of the hemodynamic and electrocardiographic response to CPX should be performed, particularly to identify potentially life-threatening situations that warrant test termination. A fall in systolic blood pressure during exercise compared with baseline measurements is a test termination criterion80,82 that potentially reflects worsening left ventricular performance.
Aerobic exercise training considerations in patients with heart failure

General principles of aerobic exercise training

The overload, specificity and reversibility principles are key considerations in developing an effective aerobic exercise program. The overload principle relates to the fact that the training stimulus must be greater than what the physiological systems (i.e., cardiovascular and skeletal muscle) are accustomed to, for a positive adaptation to occur. The mode, intensity, duration and frequency of aerobic exercise are considered in combination, in order to safely use the overload principle for a given training program. Among patients with HF, overload can typically be achieved at a lower training level, particularly during the initial phases of the exercise program, compared with apparently healthy subjects. The specificity principle states that physiological improvements are unique to the mode of exercise performed. For example, walking performance will be optimized with a training program primarily focusing on treadmill training as opposed to lower-limb ergometry or swimming. However, the positive health-related adaptations observed in patients with HF who participate in aerobic exercise training (discussed in a subsequent section) are achieved with any type of exercise using large muscle groups on a continuous basis (walking/running, lower-limb ergometry, elliptical devices, etc.). For the overwhelming majority of patients with HF, the specificity principle is less important than the fact that moderate aerobic activity of any type has numerous health benefits. The type of exercise should therefore be driven by individual preference and the availability of necessary equipment. Lastly, the reversibility principle states that positive training adaptations are not maintained if an individual returns to a sedentary behavior pattern. Life-long participation in the prescribed aerobic exercise program should therefore be a primary goal.

Specific recommendations for aerobic exercise prescription

Once contraindicated, aerobic exercise training is now a well-accepted lifestyle intervention for patients with compensated HF. The general frequency, duration and intensity recommendations for aerobic exercise in this population are 3-5 days/weeks, 30-60 minutes and 50-80% of maximal aerobic capacity, respectively. Walking (treadmill, track or other measured course), lower-limb cycle ergometry (mobile or stationary) or elliptical units enable physical stressing of larger muscle groups and are therefore acceptable types of exercise. Patients with HF should be guided to progress in frequency, duration and intensity towards the upper end of these aerobic exercise recommendations (i.e., 5 days per week, ~60 minutes per session, 70-80% of maximal aerobic capacity) over several weeks/months. While all patients should strive to ultimately achieve these recommendations, it should be recognized that some level of physical activity is always preferable to a sedentary lifestyle.

While continuous aerobic exercise is the ultimate goal, some debilitated patients with HF will not be able to sustain an exercise session for the entire time period at a given intensity, particularly during the initial stages of the training program. In these instances, interval training, i.e., periods consisting of 1-2 minutes of exercise at the desired intensity followed by a lower intensity recovery period, should be used. Progression for patients performing interval training entails a gradual increase in the training duration at a given exercise intensity (1-2 to 2-4 to 4-6 minutes, etc.) before it becomes necessary to start the lower intensity recovery period. The goal is to guide these patients to progress to continuous bouts of aerobic activity (i.e., 30-60 minutes) over several weeks/months of training.

Titration of exercise intensity is the exercise prescription component most frequently used to optimize the overload principle. Irrespective of the method used to set exercise intensity, it should be established by an exercise test, preferably in conjunction with ventilatory expired gas analysis, performed at the start of the training program. Because peak VO<sub>2</sub> is significantly improved as a result of certain pharmacologic interventions and cardiac resynchronization therapy, the ideal is to perform the baseline exercise test after these treatment options have been implemented. Identification of the ventilatory threshold via CPX is the preferred method for setting exercise intensity, since it enables identification of a specific heart rate and workload at which anaerobic metabolism begins to increase during exercise. Setting the training intensity at the heart rate or workload corresponding to the ventilatory threshold ensures the overload principle is correctly used, since the typical patient with HF is not accustomed to exercising at levels that correspond to an initial increase in anaerobic metabolism. When the ventilatory threshold is undetectable, prescribing an exercise intensity of between 50% and 80% of peak VO<sub>2</sub> is appropriate. If the peak VO<sub>2</sub> range method is used to prescribe exercise intensity, it is recommended that HF patients begin the training program at the...
lower end of this range (50%) and gradually progress to ~80% of the baseline peak VO\textsubscript{2} over several weeks or months of aerobic exercise training. The heart rate associated with this peak VO\textsubscript{2} range can be used to monitor compliance with the prescribed exercise intensity during individual training sessions. Because of the potential day-to-day variability associated with heart failure medical management and/or stability, setting an individual exercise session at ± 5% of the specific target intensity is recommended\textsuperscript{84}. For example, for a patient with a target exercise heart rate of 120 beats per minute, a ± 5% range would be 114-126 beats per minute. Alternatively, a perceived exertion level of 12-14 (on the Borg scale from 6 to 20) may be used to set the exercise intensity for patients who rate their exertion appropriately during the baseline exercise test.

The level of supervision, particularly at the initial stages of the exercise program, is an important consideration for this high-risk patient population. It is no longer considered necessary to recommend that all patients with HF undergo supervised exercise training with continuous electrocardiographic monitoring. This advanced level of supervision should, however, be strongly considered for patients with a history of cardiac arrhythmias, documented coronary artery disease that has not been surgically addressed or a low ejection fraction (≤ 25%), or whose characteristics resemble those of patients who suffered sudden cardiac death\textsuperscript{85}. Furthermore, irrespective of past medical history, patients who demonstrate an abnormal hemodynamic (hypertensive/hypotensive) response and/or electrocardiographic (ischemia/ventricular arrhythmias) abnormalities during the baseline exercise test should undergo supervised exercise training for some period of time. The duration and number of supervised exercise sessions is at the discretion of the health professional responsible for the training program. As a general guideline, patients should demonstrate an ability to appropriately self-monitor the exercise session and not have any abnormal physiological responses for several weeks before progressing to unmonitored exercise.

Documented benefits of aerobic exercise training

There is now a rather impressive body of research demonstrating numerous health-related benefits associated with aerobic exercise training among patients with HF\textsuperscript{7,31,62,85,86}. The benefits that have been documented are listed in Table 2. Furthermore, the adverse event rate with exercise training appears to be low\textsuperscript{14}.

While one large trial examining the impact of aerobic exercise training on survival and hospitalization among patients with HF is ongoing\textsuperscript{86}, no findings have been published to date. A meta-analysis on this topic, pooling together a number of smaller exercise trials (combined n= 801), demonstrated a significant increase in survival and significant reduction in hospitalization in the exercise training group, compared with controls. These results need to be confirmed by future prospective investigations. Lastly, the work cited in this section was exclusively performed on patients diagnosed with systolic HF. The initial evidence indicates that the improvements in peak VO\textsubscript{2} and quality of life following exercise training are similar in patients with systolic and diastolic HF\textsuperscript{86}. Despite these initial findings, caution should be applied in extrapolating the documented benefits of exercising training listed in Table 2 to the diastolic HF population.

Complementary interventions also shown to improve aerobic capacity

Several other interventions within allied health professionals’ scope of practice have been shown to improve peak VO\textsubscript{2} and should be considered as potential complements to the aerobic exercise training program on an individual basis. Unlike in apparently healthy populations, resistance training programs have been shown to significantly improve peak VO\textsubscript{2} among patients with HF\textsuperscript{86}. In addition, resistance training improves bone mineral density, muscle mass and muscle force production to a greater extent than aerobic exercise programs do. In general, resistance training programs for patients with HF should focus on higher numbers of repetitions (1-3 sets of 10-12 repetitions) at a lower load (=50% of one-repetition maximum). Additional general recommendations include a training frequency of 1-3 days per week, targeting large muscle groups with 4-9 training stations. Cable or hydraulic resistance systems may be preferable to free weights, from a patient-safety perspective. Subjects with a greater level of HF severity (New York Heart Class I-II vs. Class II-III) should be set tasks at the lower range of these recommendations\textsuperscript{86}. As previously mentioned, subjects with HF may present varying levels of inspiratory capacity impairment that seems to be correlated with peak VO\textsubscript{2}\textsuperscript{10,16}. Inspiratory muscle training may improve respiratory muscle function and peak VO\textsubscript{2}\textsuperscript{10}. This treatment alternative should

### Table 2. Benefits of aerobic exercise training in patients with heart failure.

- Improvement in quality of life
- Increase in peak VO\textsubscript{2}
- Increase in VO\textsubscript{2} at ventilatory threshold
- Reduction in the VE/VCO\textsubscript{2} slope
- Increase in heart rate recovery
- Improvement in endothelial function
- Improvement in aerobic characteristics of skeletal muscle
- Improvement in autonomic tone
- Improvement in pulmonary diffusion capacity
- Improvement in resting indices of cardiac function
- Improvement in cardiac output at maximal exercise

be considered when an HF patient presents an inspiratory capacity that is below the normative values predicted for the age and sex. Lastly, chronic electrical myostimulation has been shown to significantly improve muscle force production\(^9\), VO\(_2\) at ventilatory threshold\(^9\) and peak VO\(_2\)\(^{\text{max}}\) in patients with HF. These programs typically consist of myostimulation to lower extremity muscle groups (bilateral quadriceps plus hamstring or calf muscles), for one to several hours most days of the week for several weeks. Implementation of a myostimulation program may be particularly advantageous for severely debilitated patients who initially are unable to perform continuous aerobic exercise sessions.

Summary

There is now a robust body of evidence demonstrating the clinical value of both CPX and aerobic exercise training for systolic HF populations. Cardiopulmonary exercise testing provides valuable prognostic information, is valuable in assessing the response to numerous interventions and is important in developing individualized exercise prescriptions. Participation in an aerobic exercise program is a safe means for improving functional capacity, quality of life and numerous physiological measurements. There is also promising evidence to indicate that aerobic exercise training improves morbidity and mortality in systolic HF populations. These findings need to be reproduced in patients with diastolic HF before concrete CPX and aerobic exercise training recommendations are made for this subgroup. Allied health professionals who are responsible for assessing and treating patients with HF should be aware of the importance of CPX, aerobic exercise training and complementary interventions and, when appropriate, advocate their implementation.

References


