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EXERCISE TESTING OF HEART FAILURE PATIENTS WITH RESPIRATORY BREATH ANALYSIS – A REVIEW OF CURRENT TRENDS

Stephen J. Brown

School of Health Sciences, University of Ballarat, Victoria, Australia

Abstract

Objective: To highlight current trends in cardio-respiratory exercise testing of patients diagnosed with heart failure.

Methods: Measures of cardio-respiratory performance, namely maximum oxygen uptake, ventilatory efficiency, and oxygen uptake efficiency, are compared. Their utility is discussed with reference to the routine assessment of patients. Selected articles which report the use of cardio-respiratory testing in clinical populations, and selected articles which clearly show the benefit of using respiratory gas analysis in determining prognosis of heart failure, were used to construct the review.

Results: Data indicating the improved survival of heart failure patients with preserved cardio-respiratory efficiency are reported. We also present data which report the prognostic superiority of measures of cardio-respiratory efficiency when compared to peak oxygen uptake.

Conclusions: The physiological determinants of the measures are briefly discussed. Based on the improved prognostic capacity of measures of cardio-respiratory efficiency, the review favours the inclusion of cardio-respiratory testing in the routine clinical assessment of heart failure patients.

Key words: *exercise; cardiorespiratory testing; heart failure; oxygen uptake; ventilatory efficiency*

Introduction

Intolerance of physical exertion is a debilitating characteristic of heart failure, and an exercise test can be used to quantify this intolerance. Cardiopulmonary exercise testing is regularly used in developed countries to determine the peak oxygen uptake of heart failure patients, and the test can yield important prognostic information regarding survival. Alternatively, pulmonary ventilation during the test may be modelled in conjunction with either oxygen uptake, or carbon dioxide output – both methods have been used to predict survival following heart failure, and perhaps, show prognostic superiority over peak oxygen uptake. Although specialist equipment and training of staff is necessary for the inclusion of gas analysis in routine testing of patients, it is suggested that appropriate on-line gas analysis data should be collected during exercise testing of all heart failure patients, and the utility of such data be included in their treatment.

Maintaining equality in health care delivery is complicated by both ethnic diversity, variability in demand, and geographical dispersion into small rural communities. A commitment of appropriate resources in terms of both personnel and equipment, can limit the widespread availability of cardiopulmonary exercise testing of heart failure patients in many countries, particularly small countries which provide universal, free at the point of delivery, publically funded health care. For example, a cardiology resource survey [1] from an ethnically diverse, small, developed country (New Zealand) with free, regional health care cited limitations in the availability of appropriately trained personnel and equipment as sources of inequality in the delivery of health care. However, a decrease in age-standardized coronary heart disease mortality occurred since 1970 (61% in men, 56% in women) [2] in New Zealand, attributable to both treatment and prevention. Despite this, heart disease killed more women than breast cancer, and males of Maori and Pacific Island ethnicity had a greater prevalence of heart disease than those of European origin [3]. It was further suggested [4] that the availability of exercise testing of all heart failure patients in New Zealand was important, yet only limited facilities for such testing were available. Problems in the delivery of cardiopulmonary exercise testing are common in countries with a growing burden of cardiovascular disease, and this may worsen if budgets for health care provision reduce.

An incremental exercise test has been used in many cardiology departments throughout the developed world to aid in both diagnosis and prognosis of heart failure. A controlled, supervised cardiopulmonary exercise test has been considered the 'gold standard' [5] for evaluating the causes of exercise intolerance in patients with heart failure. The testing is based on the principle that indices of system failure become apparent when the system is under stress. During a cardiopulmonary exercise test, systems which support the body's ability to perform physical activity may be expressed relative to an appropriate reference, for example, minute ventilation ($\dot{V}E$) expressed relative to carbon dioxide output ($\dot{V}CO_2$). Exercise testing with continuous respiratory gas exchange analysis is an important and objective means of assessing the functional capacity of heart failure patients [6]. In this review, a brief synopsis of the utility of three dependent variables currently used in the interpretation of a cardiopulmonary exercise test on heart failure patients, is considered.

Oxygen uptake

A cardiopulmonary exercise test incorporates continuous incremental exercise on either a treadmill or a stationary bicycle ergometer, with simultaneous analysis of cardiovascular, ventilatory, and respiratory variables. During the test, oxygen consumption ($\dot{V}O_2$) increases in direct proportion to work rate, reaching a peak ($\dot{V}O_{2PEAK}$) which is typically measured at the end of the test. When normalized for body mass (units: ml· Kg^{-1}·min^{-1}STPD), the $V'O_{2PEAK}$ may be used in the triage of patients with chronic heart failure awaiting heart transplantation [7,8], predict outcome in heart failure patients [9], and assess the response to therapy [10]. Patients with a $\dot{V}O_{2PEAK}$ >14 ml·Kg^{-1}·min^{-1} had a 1 year survival rate similar to that of patients receiving heart transplantation. However, $\dot{V}O_{2PEAK}$ is sensitive to a lack of patient motivation, and a falsely low peak may be recorded by a patient who 'gives up' during the test.

Alternatively, the $\dot{V}O_2$ at, or just below, the onset of a sustained metabolic acidosis (anaerobic threshold, AT) may be a preferable index of functional capacity as it represents an intensity of physical activity which may be sustained for longer periods than the exercise intensity at $\dot{V}O_{2PEAK}$. The $\dot{V}O_2$AT may be less sensitive to a lack of motivation during testing, is safer in higher risk patients, and is a good prognostic indicator of survival in heart failure patients [11]. Problems, however, may still arise with an accurate determination of the anaerobic threshold using methods based solely on analysis of exhaled breath such as the 'V-slope' method. Although oxygen uptake measures at peak and/or the AT are still commonly used to describe the physiological response to physical exertion in heart failure patients, there are alternatives.

Ventilatory efficiency

The ventilatory response ($\dot{V}E$) during cardiopulmonary exercise testing may also yield valuable diagnostic and prognostic information, particularly when

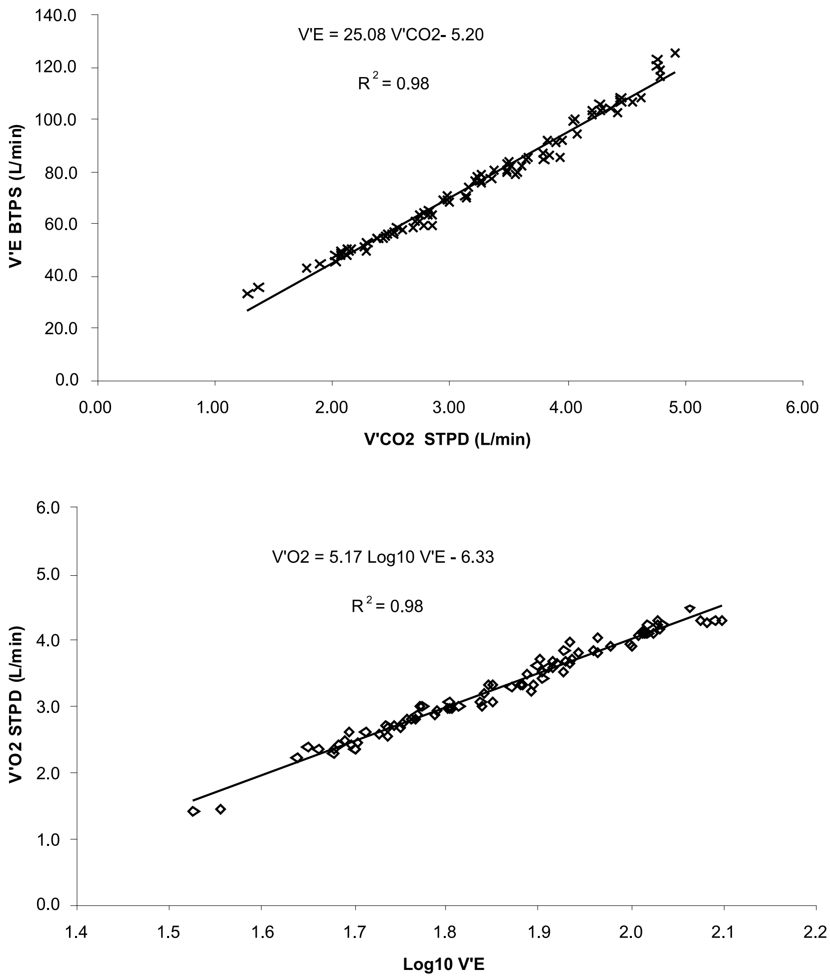

Fig. 1. *(Upper) The relation between carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) is linear for all exercise intensities up to maximal oxygen uptake, and can be closely modelled using linear regression whereby the slope of the regression line is the ventilatory efficiency. Alternatively, the slope of the linear relation between $\log_{10}$ $\dot{V}E$ and oxygen uptake ($\dot{V}O_2$) is the 'oxygen uptake efficiency slope' (Lower panel).*

expressed as a function of $\dot{V}CO_2$. As shown in Fig. 1, least squares linear regression yields a high correlation (usually $r > 0.95$) between $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise up to the anaerobic threshold, and in most cases, throughout the test to $\dot{V}O_{2PEAK}$ [12]. This linear relation between $\dot{V}E$ (units: $L{\cdot}min^{-1}$BTPS) and $\dot{V}CO_2$ (units: $L{\cdot}min^{-1}$STPD) during incremental exercise is often modelled by $\dot{V}E=a\dot{V}CO_2+b$, where a represents the $\dot{V}E$ vs. $\dot{V}CO_2$ slope. It has been suggested that the prognostic ability of the $\dot{V}E$ vs. $\dot{V}CO_2$ slope may be superior to traditional measures of $\dot{V}O_2$ [12–14]. In a Kaplan-Meier analysis of 341 heart failure patients, a $\dot{V}E$ vs. $\dot{V}CO_2$ slope of ≥ 34 [12] in 124 patients had 69.4% event free survival after 3 years, whereas a $\dot{V}E$ vs. $\dot{V}CO_2$ slope of < 34 in 217 patients had 95.9% event free survival after 3 years. Also, in a large (n = 355) group of heart failure patients with a 5 year follow-up, the majority of mortality prediction came from the V'E vs. $\dot{V}CO_2$ slope [15]. In a univariate analysis [15], the $\dot{V}E$ vs. $\dot{V}CO_2$ slope explained 11.1% of the mortality, whereas $\dot{V}O_{2PEAK}$ explained 5% of the mortality. In their multivariate analysis, 21% of the mortality prediction came from the $\dot{V}E$ vs. $\dot{V}CO_2$ slope (18% for $\dot{V}O_{2PEAK}$), and when $\dot{V}O_{2PEAK}$ and $\dot{V}E$ vs. $\dot{V}CO_2$ slope were combined, the explained mortality variation was the same as when they were both modelled independently [15]. When the $\dot{V}O_2$ at the anaerobic threshold was combined with the $\dot{V}E$ vs. $\dot{V}CO_2$ slope, values of <11 ml $Kg^{-1}min^{-1}$ and >34 respectively were better prognostic indicators than $\dot{V}O_{2PEAK}$ alone [16].

A possible deviation from linearity of the $\dot{V}E$ vs. $\dot{V}CO_2$ slope above the ventilatory threshold may cause an over-estimation of the slope. For example, slope calculation below the ventilatory threshold was 29.9 $\pm$ 6.8, whereas slope calculation inclusive of all data to $\dot{V}O_{2PEAK}$ was 32.5 $\pm$ 8, in 188 heart failure patients [17]. However, these authors concluded that using data from rest to peak exercise had the greatest prognostic power, a finding confirmed by others [11,18]. An excessive ventilatory response (determined using the $\dot{V}E$ vs. $\dot{V}CO_2$ slope) to a whole exercise test [33] was a predictor of poor outcome regardless of heart failure severity as assessed by NYHA class. Similarly, a high $\dot{V}E$ vs. $\dot{V}CO_2$ slope recorded during the first 3 minutes of an exercise test was related to increased mortality in patients all NYHA classes (I–IV). This excessive ventilation during the early stage of an exercise test may have increased validity as a clinical measure, as this is likely to more closely reflect the exercise intensities tolerated by patients .Thus it would appear that the cumulative evidence in favour of the use of the $\dot{V}E$ vs. $\dot{V}CO_2$ slope will dictate the incorporation of this index into the clinical management of a patients with heart failure.

The oxygen uptake efficiency slope

Alternatively, the $\dot{V}O_2$ (units: $ml{\cdot}min^{-1}$, or $L{\cdot}min^{-1}$) during cardiopulmonary exercise testing may also be expressed as a function of $\dot{V}E$ (units: $ml{\cdot}min^{-1}$, or $L{\cdot}min^{-1}$). As shown in Fig. 1, this yields a non-linear relation which can be modelled by $\dot{V}O_2=a \log_{10} \dot{V}E + b$, where a represents the Oxygen Uptake Efficiency Slope (OUES) [19]. A higher OUES indicates an improved oxygen uptake during exercise and it correlated well with $\dot{V}O_{2PEAK}$ [19,20]. The prognostic sensitivity of the OUES has received much less attention when compared to the $\dot{V}E$ vs. $\dot{V}CO_2$ slope, although early indications are that it is at least as good as the V'E vs. $\dot{V}CO_2$ slope. For example [12], in an initial group of 341 heart failure patients (mean $\dot{V}O_{2PEAK}$ 17.9 $\pm$ $ml{\cdot}Kg^{-1}{\cdot}min^{-1}$), the OUES was 1960 $\pm$ 910 and $\dot{V}E$ vs. $\dot{V}CO_2$ slope was 32.1 $\pm$ 8.5. Using a 3 year follow-up, patients who suffered a major cardiac event (n = 47) differed from those without event (n = 294) in their initial assessment of $\dot{V}O_{2PEAK}$ (18.7 $\pm$ 7.4 vs. 13.1 $\pm$ 4.7 $ml{\cdot}Kg^{-1}{\cdot}min^{-1}$), $\dot{V}E$ vs. $\dot{V}CO_2$ slope (30.7 $\pm$ 7.4 vs. 41.2 $\pm$ 9.5), and OUES (2060 $\pm$ 900 vs. 1320 $\pm$ 680). These authors concluded that the $\dot{V}E$ vs. $V'CO_2$ slope, when calculated from all the data up to $\dot{V}O_{2PEAK}$, was the superior prognostic indicator, but recognised the importance of the OUES in predicting survival [12]. In 45 patients with left ventricular dysfunction categorised by $\dot{V}O_{2PEAK}$ (group 1: $\dot{V}O_{2PEAK}$ <14 $ml{\cdot}Kg^{-1}{\cdot}min^{-1}$; group 2: $\dot{V}O_{2PEAK}$ >14 $ml{\cdot}Kg^{-1}{\cdot}min^{-1}$), a higher $\dot{V}E$ vs. $\dot{V}CO_2$ and lower OUES were recorded for group 1 (41.4 $\pm$ 9.9 and 977 $\pm$ 300 respectively) compared to group 2 (33.3 $\pm$ 5.2 and 1561 $\pm$ 405 respectively) [21]. Following 6 months of exercise training in 35 heart failure patients (initial $\dot{V}O_{2PEAK}$ 15.3 $\pm$ 3.7 $ml{\cdot}Kg^{-1}{\cdot}min^{-1}$), OUES improved from 1190 $\pm$ 341 to 1356 $\pm$ 376, and $\dot{V}E$ vs. $\dot{V}CO_2$ slope decreased from 36.9 $\pm$ 5.9 to 33.7 $\pm$ 6.0 [24]. Others [22] have suggested that OUES is superior as a prognostic indicator of major cardiac events when compared to both the $\dot{V}E$ vs. $\dot{V}CO_2$ slope and $\dot{V}O_{2PEAK}$ in a 6 year follow-up of 243 heart failure patients [22]. These authors also demonstrated that an OUES value obtained during only the first 50% of the exercise test was only 1% different from that obtained from all data up to $\dot{V}O_{2PEAK}$. This was evidence that the OUES was an improvement over $\dot{V}O_{2PEAK}$ as it did not require high levels of patient motivation to achieve an accurate result.

Ventilatory efficiency or OUES ?

The OUES and $\dot{V}E$ vs. $V'CO_2$ slope have different origins. The $\dot{V}E$ vs. $\dot{V}CO_2$ slope is an indicator of the efficiency of removal of CO_2 by the lung, whereas the OUES is an indicator of delivery, extraction, and O_2 use by the active tissue. Increased pulmonary vascular resistance [23], a decline in pulmonary perfusion [24], and a mismatching of pulmonary ventilation to perfusion [25], all contribute to a steeper $\dot{V}E$ vs. $\dot{V}CO_2$ slope in heart failure. In contrast, it has been suggested that the OUES incorporates, in a single index, cardiovascular and peripheral factors that determine oxygen uptake, as well as pulmonary factors that influence the ventilatory response to exercise [21]. However, both the OUES and $\dot{V}E$ vs. $\dot{V}CO_2$ slope show that heart failure patients have a greater need to ventilate the lungs for a given $\dot{V}O_2$ or $\dot{V}CO_2$ respectively, when compared to healthy controls. The distinction between the two slopes is that OUES is only affected by abnormalities that increase ventilation during exercise by a greater proportion than at rest. In other words, increases in $\dot{V}E$ by a constant proportion, either at rest or during exercise, will not directly affect the OUES [22].

Using data obtained during sub-maximal exercise [26], strong predictors of survival were $\dot{V}E$ vs. $\dot{V}CO_2$ slope, the ventilatory equivalent for CO_2, (termed $\dot{V}E$ / $\dot{V}CO_2$ ratio), end-tidal partial pressure of CO_2, OUES, and circulatory power. Using multivariate Cox regression analysis [26], the strongest predictive model for long term event- free survival from heart failure was obtained when demographic information, $\dot{V}O_{2PEAK}$, and sub-maximal $\dot{V}E$ vs. $\dot{V}CO_2$ slope were included. These authors further suggested that inclusion of maximal exercise gas exchange data may serve to further identify low- and medium-risk patients. In an interesting editorial comment [27] referring to the Davies et al paper [22], it was suggested that before the OUES became part of clinical practice, the potential influences of exercise modality, exercise duration, and familiarisation procedures on OUES, should be resolved. Recent reviews [15,28] which outline the utility of cardiopulmonary exercise testing in heart failure prognosis (and to a lesser extent, diagnosis) make little or no reference to the OUES measurement. There are no current clinical guidelines on the use of OUES in characterising patients.

Exertion oscillatory breathing during a cardiopulmonary exercise test

Increased ventilation during exercise is essential to regulate arterial partial pressure of CO_2, during increased CO_2 production and increased O_2 uptake. However, the appearance of oscillatory breathing patterns on physical exertion (Exertion Oscillatory Ventilation: EOV) is not unusual in patients with chronic heart failure [29- 31]. EOV is associated with poor clinical status, cardiac dysfunction, and reduced exercise capacity, and it is a powerful predictor of poor prognosis. The incidence of EOV during a cardiopulmonary exercise test was more frequent in non-survivors than in survivors [29], and a multivariate analysis [29] revealed $\dot{V}O_{2PEAK}$, left ventricular ejection fraction, and EOV were independent predictors of subsequent major cardiac events. Predictive algorithms based on cardiopulmonary exercise test measures including EOV may have utility in prognosis of heart failure [32], and inclusion of EOV instead of $\dot{V}E$ vs. $\dot{V}CO_2$ may prove beneficial. Combining the $\dot{V}E$ vs. $\dot{V}CO_2$ slope with systolic blood pressure [33], creates a novel index termed 'ventilatory power'. Ventilatory power attempts to link the combined physiology inherent in the $\dot{V}E$ vs. $\dot{V}CO_2$ slope to peripheral arterial pressure, and may provide greater prognostic discrimination than either $\dot{V}E$ vs. $\dot{V}CO_2$ slope or $\dot{V}O_{2PEAK}$. However, at present, ventilatory power coupled with EOV remains untested with regard to prognostic utility, but it is probable that this represents an undesirable combination.

Summary

The intolerance of physical exertion is very debilitating and is a characteristic of heart failure. The cardiopulmonary exercise test is a reproducible, robust, non-invasive method which can be used to quantify this intolerance. The exercise test is a suitable procedure to examine the underlying physiology [35,36] which supports a patient's ability to perform physical exercise. Indices which describe the responses of the cardiovascular and respiratory systems, whether derived during maximal or sub-maximal testing, have been shown to have utility in heart failure prognosis. When considering the financial cost of routine procedures used in medical practice, both start-up and on-going costs of cardiopulmonary exercise testing are modest. Therefore, exercise testing with appropriate gas analysis, should become increasingly prevalent in cardiology, and represent a useful additional tool in the treatment of heart failure.

Declaration of interest

The author reports no conflicts of interest.

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Address for correspondence:
Stephen J. Brown
School of Health Sciences,
University of Ballarat,
University Drive,
Mount Helen.
VIC 3350
Australia
Telephone: 61 3 5327 6258
Fax: 61 3 53279478
Email: brahrainstephen@gmail.com