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New Parameters of Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure: Practical Applications

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ABSTRACT

Cardiopulmonary exercise testing (CPX) has become the cornerstone of risk stratification for heart failure patients. Peak oxygen consumption (VO_2) was the first CPX variable to demonstrate prognostic value and is still the most frequently analyzed variable in clinical practice. More recently, several investigations have shown that ventilatory efficiency, typically expressed as the minute ventilation/carbon dioxide production (VE/VCO_2) slope, is a strong prognostic marker in patient with HF. The majority of studies report the VE/VCO_2 slope to be prognostically superior to peak VO_2 which underscore the clinical importance of assessing ventilatory efficiency in HF patients. Other expressions of ventilatory inefficiency like exercise oscillatory breathing (EOB), oxygen uptake efficiency slope (OUES), end-tidal carbon dioxide pressure (PET CO_2) at rest, and haemodynamic responses such as heart rate recovery (HRR) are strong predictors of outcomes in patients with heart failure (HF). So there is a need for simplified approaches that integrate the additive prognostic information from cardiopulmonary exercise testing.

Keywords: New Parameters; Cardiopulmonary Exercise Testing; Chronic Heart Failure

1. Introduction

The prognosis of patients diagnosed with heart failure (HF) remains poor despite recent advances in medical management.

Cardiopulmonary exercise testing (CPX) has become the cornerstone of risk stratification for HF patients. Peak oxygen consumption (VO_2) was the first CPX variable to demonstrate prognostic value [1] and is still the most frequently analyzed variable in clinical practice.

2. New Parameters of Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure

More recently, several investigations have shown that ventilatory efficiency, typically expressed as the minute ventilation/carbon dioxide production (VE/VCO_2) slope, is a strong prognostic marker in patients with HF [2-6].

The majority of studies report the VE/VCO_2 slope to be prognostically superior to peak VO_2, which underscores the clinical importance of assessing ventilatory efficiency in HF patients. The principal reasons are: first the dependence of peak VO_2 on subject effort for optimal value, whereas the VE/VO_2 slope is primarily effort independent. Second the VE/VCO_2 slope retains its prognostic significance across a range of clinical conditions, including the presence of sub maximal effort, in patient with HF secondary to diastolic left ventricular dysfunction and in patients prescribed a beta blocker.

The normal value is 20 to 30. A number of studies define a VE/VCO_2 slope of 34 as a threshold value for predicting a poor prognosis.

However the wide range of VE/VCO_2 slope values observed in the HF population indicates that a multilevel classification system may better define the increasing risk of adverse events:

Arena *et al.* [7] have studied four hundred forty eight subjects diagnosed with heart failure. In this study, 81 cardiac-related events (64 deaths, 10 heart transplants and 7 left ventricular assist device implantations) during 2 years tracking period. As one might expect, the VE/VCO_2 slope was the strongest predictor of major cardiac events in the multivariate analysis.

Receiver operating characteristic (ROC) curve analysis revealed the overall VE/VCO_2 slope classification scheme was significant (area under the curve: 0.78 [95% CI, 0.73

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to 0.83] $p < 0.001$).

On this basis of test sensitivity and specificity, the following ventilatory class system was developed:

Ventilatory class (VC)

1) ≤29;

2) 30.0 to 35.9;

3) 36.0 to 44.9;

4) ≥45.0.

Kaplan-Meier analysis revealed event-free survival for subjects in VC 1), 2), 3), 4) was 97.2%, 85.2%, 72.3%, 44.2% respectively (log-rank 86.8; $p < 0.001$).

Although the 4-level prognostic classification system-based peak VO_2 was significant, the VC system was superior, as indicated by difference in log-rank score (86.8 vs 35.0). For example, subjects with a VE/VCO_2 slope ≤ 29.9 demonstrated a favorable prognosis irrespective of peak VO_2. Furthermore, the trends for increasing event rates were more apparent as the VE/VCO_2 slope increased compared decreasing peak. Authors propose a ventilatory class clinical algorithm for optimal use of the VE/VCO_2 slope.

However the VE/VCO_2 slope is subject to transient hyperventilation early in exercise (from anxiety) and is affected by metabolic acidosis during high levels of exercise.

Sun *et al.* [8] recently studied the influence of age, gender, body, size, fitness, testing site and exercise mode on ventilatory efficiency in 474 Healthy adults and observed that the lowest VE/VCO_2 ratio (ventilatory equivalent for CO_2) during exercise represented the preferred non invasive index to estimate ventilatory inefficiency (more stable marker). Thus Myers *et al.* [9] demonstrated from a study of 847 HF patients followed 3 months that the lowest VE/VCO_2 ratio (higher ratio associated with greater risk) was similar to the VE/VCO_2 slope in predicting risk (Hazard Radio (HR) per unit increment 2.0 [95% CI: 1.1 - 3.4] and 2.2 [95% CI: 1.3 - 3.7] respectively; $p < 0.01$), followed by peak VO_2 (HR: 1.6 [95% CI: 1.1 - 2.4] $p = 0.01$).

The authors observed that adding the lowest VE/VCO_2 ratio to the more established markers of prognosis (peak VO_2 and the VE/VCO_2 slope) provided the highest prediction of risk for the composite outcome (mortality and transplantation). MEJHERT *et al.* [10] reported that patients with a heightened peak VE/VCO_2 ratio at the anaerobic threshold (analysis to the lowest VE/VCO_2 ratio) had a nearly 7 fold higher risk of mortality.

Thus higher VE/VCO_2 ratio reflects a more impaired cardiac output response to exercise. Other markers of ventilatory inefficiency have been shown to be independent prognostic markers: exercise oscillatory breathing (EOB), oxygen uptake efficiency slope, low resting or exercise end Tidal CO_2 pressure.

2.1. Exercise Oscillatory Breathing (EOB):

An important percentage of cases, patients with symptomatic HF display an abnormal ventilatory pattern consisting of EOB characterized by ventilatory waxing and waning that leads to an oscillatory kinetics in measured oxygen uptake (VO_2) and carbon dioxide production (VCO_2).

A pathophysiological interdependence has been described between exercise EOB and cyclic ventilatory abnormalities occurring during sleep disorders of central origin. The neuroautonomic abnormalities suggested as possible cause of EOB.

There is a wide variability of EOB pattern presentations, such as a variable length and amplitude of oscillations and persistence for the entire exercise or disappearance at early/intermediate stages. Different EOB classificatory criteria have been proposed. Independently of the criteria used across different studies, EOB provides independent prognostic power.

EOB was defined for LEITE [11] and GUAZZI [12] as 3 or more regular oscillatory fluctuation in VE, with minimal average amplitude of ventilatory oscillation of 5 L (peak value minus the average of 2 in-between consecutive nadir) and regular oscillation as defined by a standard deviation of 3 consecutives cycle lengths (time between 2 consecutive nadirs within 20% of the average). In this study 288 stable chronic HF patients who underwent cardiopulmonary exercise testing, the prognostic relevance of VE/VCO_2 slope, EOB, peak VO_2 was evaluated by multivariate CO_X regression.

During the mean interval of 28 ± 13 months, 62 patients died of cardiac reasons; 35% presented with EOB. Among patients exhibiting EOB, 54% had an elevated VE/VCO_2 slope. Univariate predictors of death included low left ventricular ejection fraction, low peak VO_2, high VE/VCO_2 slope and EOB presence. Multivariate analysis selected EOB as the strongest predictor (Chi^2: 46.5; $p < 0.001$).

KAPLAN-MEIER pilot relating survival to combination of VE/VCO_2 slope and EOB: four group.

Group A: No EOB and VE/VCO_2 slope < 36.2: 95.7% events free.

Group B: No EOB and VE/VCO_2 slope > 36.2: 75.5% events free.

Group C: EOB and VE/VCO_2 slope < 36.2: 63.6% events free.

Group D: EOB and VE/VCO_2 slope > 36.2: 50.9% events free.

So we can concluded that EOB, per se, holds a higher prognostic power than VE/VCO_2 slope; EOB documentation does not necessarily imply an association with a steep VE/VCO_2 slope and when EOB is associated with a steep VE/VCO_2 slope the burden risk for cardiac death is considerably elevated.

The main problem is that there is not an accepted EOB definition true incidence and prevalence are undefined. Its appears that the most important missing information is the absence of established criteria for EOB definition and classification.

2.2. Oxygen Uptake Efficiency Slope (OUES)

There has been interest in developing techniques to handle the problem of limited patient motivation which results in sub maximal exercise.

OUES is a non-linear measure of the ventilatory response to exercise. It is a relationship between VO_2 and VE during incremental exercise, via a logarithmic transformation of ventilation. OUES is defined as the regression slope "a" in VO_2 = a log10 VE + b. It has the advantage of using the whole of the exercise data, but also its log transformation reduces curvature, which gives a further potential opportunity for a measure resistant to disruption by early termination of exercise.

DAVIES *et al.* [13] studied 243 patients with CHF (mean age 59 + 12 years) underwent cardio pulmonary exercise testing. Mean peak VO_2 was 16.2 ± 6.7 ml/kg/min; VE/VCO_2 slope 38 ± 12.5; OUES 1.6 ± 0.7 l/min.

When only the first 50% of each exercise test was used to calculate the variables, the value obtained for OUES changed the least (peak VO_2 25% difference and OUES 1% difference).

After a median of 9 years of follow-up, 139 patients had died.

Each of the exercise variables was a significant univariate predictor of prognosis but in a multivariate model, only OUES was identified as the sole significant independent prognostic variable.

In this study the optimal cut-off value obtained from the Roc analysis was 1.47 l/min.

The value of OUES remains stable over the entire exercise duration. It might be useful in the assessment of patient unable to perform a maximal exercise.

The physiological meaning of OUES is that it represents the absolute rate increase in VO_2 per 10-fold increase in ventilation. Patient with CHF show a greater increase in ventilation per Unit increase in VO_2, because a various metabolic, reflex and gas exchange abnormalities.

According to Davies OUES differs in principle from measures such as VE/VCO_2 slope in that it considers changes in ventilation in term of scale factor (in multiples of the baseline value). Thus any abnormalities that raise ventilation by a constant proposition, both at rest and during exercise, will not directly affect OUES. Only abnormalities that increase ventilation during exercise by a greater proposition than at rest will be able to depress the OUES.

Thus OUES may quantify the specific pattern of ventilatory response to exercise.

2.3. Partial Pressure of Resting End-Tidal Carbon Dioxide (Resting PET CO_2)

The interest of the clinical value of resting ventilatory expired gas analysis is very important particularly in elderly patients. The resting PET CO_2 is one such variable that may provide important clinical information.

As matter of fact carbon dioxide elimination and therefore PET CO_2 decreases when blood flow to the lungs is reduced. Numerous studies have demonstrated a significant relationship between resting PET CO_2 and cardiac output [14-16].

SHIBUTAMI *et al.* [17] found PET CO_2 was significantly correlated with changes in cardiac output during surgery in patients undergoing abdominal aortic aneurysm repair.

The mechanism for the reduction in resting PET CO_2 observed in some patients with HF is multifactorial: reduced cardiac output, reduced partial pressure of carbon dioxide in arterial blood, and increased physiologic dead space ventilation.

ARENA *et al.* [18] studied 353 patients with systolic HF subjects were then followed for major cardiac events (mortality, left ventricular assist device implantation, urgent heart transplantation). There were 104 major cardiac events during the 23.6 ± 17.0 months tracking period.

Multivariate CO_X regression analysis revealed NYHA class (Chi^2: 28.7; $p < 0.001$), left ventricular ejection fraction (residual Chi^2: 21.7; $p < 0.01$) and resting PET CO_2 (residual Chi^2: 14.1; $p < 0.01$) were all prognostically significant and retained in the regression.

In the separate CO_X regression analysis, left ventricular ejection fraction (residual Chi^2: 8.8; $p = 0.003$), NYHA (residual Chi^2: 7.7; $p = 0.005$) and resting PET CO_2 (residual Chi^2: 5.7; $p = 0.02$) added prognostic value to the VE/VCO_2 slope (Chi^2: 26.0; $p < 0.001$), the strongest CPX predictor of adverse events but not to peak VO_2.

KAPLAN-MEIER analysis for resting PET CO_2 show 77.2% event free in patients with PET $CO_2 > 33$ mm Hg and 56.9% with PET $CO_2 \leq 33$ (log rank: 16.3; $p < 0.001$).

KAPLAN-MEIER analysis for combined LVEF, NYHA, resting PET CO_2 and VE/VCO_2 slope thresholds show for group:

Group A: patients with non negative resting value (resting PET $CO_2 > 33$; NYHA class I, II, LVEF > 25%) and positive VE/VCO_2 slope (<36.0) with 92.3%. event free.

Group B: patients with a negative resting value or negative VE/VCO_2 slope (≥36) with 74.0% event free.

Group C: patients with a 2 negative resting values and positive VE/VCO_2 slope or 1 negative resting value and negative VE/VCO_2 slope with 59.3% event free.

Group D: patients with 3 negative resting values and negative VE/VCO_2 slope with 43.3 event free.

So resting PET CO_2 appears to add prognostic value to variable that are well established and commonly collected in clinical practice (LVEF, NYHA, VE/VCO_2 slope). The fact that resting PET CO_2 is easily, cheaply, and non invasively obtained portends high clinical promise for this measurement. In fact, when PET CO_2 was assessed multivariate with the VE/VCO_2 slope, peak VO_2 was not a significant predictor of these out come.

Exercise test response not involve ventilatory gas exchange have also been shown to predict risk in patients with CHF. The most important seems to be heart rate recovery at 1 minute (HRR1).

The heart rate increase during exercise (delta HR) and heart rate recovery (HRR) have demonstrated prognostic value in several investigations.

Now its application in heart failure (HF) population is established particularly the HRR at 1 minute. The heart rate recovery at 1 minute was the difference between HR at peak exercise and 1 minute post (with an active cool-down).

ARENA *et al.* [19] studied five hundred and twenty subjects with HF underwent cardiopulmonary exercise testing to determine peak VO_2, the VE/VCO_2 slope, delta HR (increase in HR from rest to maximal exercise) and HRR at 1 minute. There were 79 cardiac-related deaths during the tracking period (50 months). A HRR1 threshold of < / ≥ 16 beats/minute was a significant prognostic marker in the overall group (HR: 4.6, 95% CI: 2.8 - 7.5; $p < 0.001$) as well as no betablockers (BB) (HR: 9.1, 95% CI: 4.1 - 20.2; $p < 0.001$) and BB (HF: 2.9, 95% CI: 1.6 - 5.4; $p < 0.001$) subgroup. The delta HR was a significant univariate predictor in the overall group and no BB subgroup only. Multivariate Cox regression analysis revealed HRR1 was the strongest prognostic marker (Chi^2: 39.9; $p < 0.001$). The VE/VCO_2 slope (residual Chi^2: 21.9; $p < 0.001$) and LVEF (residual Chi^2: 49.6, p < 0.002) were also retained in the regression.

Both the VE/VCO_2 slope and peak VO_2 were significantly correlated with delta HR and HRR1. These relationships were stronger between peak VO_2 and HR derived variables than they were for the VE/VCO_2 slope.

We can divide patients in 3 groups:

Group A: HRR1 > 16 beats/min; VE/VCO_2 slope < 36 with 95.8% event free.

Group B: HRR1 < 16 beats/min; or VE/VCO_2 slope > 36 with 83.1% event free.

Group C: HRR1 < 16 beats/min; and VE/VCO_2 slope ≥ 36 with 60.2% event free.

In fact HRR1 was the strongest prognostic marker in the overall group and in the no BB subgroup. In patients prescribed a BB, the VE/VCO_2 slope was the strongest predictor (Chi^2: 21.1) while HRR1 was retained in the regression (Chi^2: 7.5).

The synergistic prognostic value of HRR1 and the VE/VCO_2 slope is likely explained by the difference pathophysiologic mechanisms each variable represents: In one hand, the rate at which parasympathetic tone increases following the cessation of exercise appears to heavily influence the time course. A blunted HRR following the cessation of exercise reflects an abnormal autonomic balance favouring the sympathic system. In the other hand many investigations have linked an abnormal elevated VE/VCO_2 slope to poor pulmonary perfusion and decreased cardiac output, both at rest and during maximal exercise.

3. Synthesis

These new parameters are strong predictors of outcomes in patients with heart failure.

Beginning in the mid-1995, consensus guidelines recommended the application of the CPX to supplement other clinical data in the management of patients with HF.

However, these guidelines limited their recommendations to the application of peak VO_2 archived in the context of selecting patients for transplantation.

A growing body of studies over the last decade has demonstrated that among patients with CHF, the VE/VCO_2 slope more powerfully predicts mortality, hospitalization, or both, than peak VO_2. There have also been other expressions of ventilatory inefficiency associated with poor outcomes in CHF including OUES, PET CO_2 at rest and EOB. Exercise test responses not involving ventilatory gas exchange have also been shown to predict risk in patients with CHF particularly impaired heart rate recovery (HRR1).

However, there is a need for simplified approaches that integrate the additive prognostic information from CPX.

Myers *et al.* [20] have studied a multivariate score. They have studied 710 patients with HF (568 males/142 females, mean age 56 ± 13 years resting left ventricular ejection fraction 33% ± 14%) underwent CPX and were followed for cardiac related mortality and separately for major cardiac events (death, hospitalization for HF, transplantation, left ventricular assist device implantation) for a mean of 29 ± 25 months.

The age adjusted prognostic power of the peak VO_2, VE/VCO_2 slope, OUES, resting PET CO_2, HRR1 were determined using CO_x proportional hazards analysis, optimal end point were determined, the variables were weighted, and a multivariate score was derived.

So the VE/VCO_2 slope (>34) was the strongest predictor of risk and was attributed a relative weight of 7, with weighted scores for abnormal HRR (≤16 beats/minute), OUES (>1.4 l/min), PET CO_2 (<33 mmHg) and peak VO_2 (≤14 ml/kg/minute) having score of 5, 3, 3 and 2 respectively.

A summed score > 15 was associated with an annual mortality rate of 27% and a relative risk of 7.6, whereas a score < 5 was associated with a mortality rate of 0.4%. In this study, the composite score was the most accurate predictor of cardiovascular events among all CPX responses considered (concordance indexes: 0.77 for mortality and 0.75 for composite outcome). The summed score remained significantly associated with the increased risk after adjusting for age, gender, body mass index, ejection fraction and cardiomyopathy type.

In conclusion, several studies show the important role of the CPX for predicting outcomes in patients with HF.

Several easily obtained responses from the CPX can be used to more accurately describe the spectrum of risk for adverse events in these patients. We have to include indices that reflex abnormalities in several systems that are related to outcomes, including oxygen delivery and extraction (peak VO_2), ventilatory inefficiency (VE/VO_2 slope, OUES, EOB) and autonomic function (HRR1).

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Abbreviations and Acronyms

CPX: Cardiopulmonary exercise testing;
VO_2: Peak oxygen consumption ml/kg/min;
VE/VCO_2: Minute ventilation/carbon dioxide production;
VC: Ventilatory class;
EOB: Exercise oscillatory breathing;
OUES: Oxygen uptake efficiency slope;
PET CO_2: End-tidal carbon dioxide pressure;
HF: Heart failure;
BB: Betablockers.

