ECRONICON OPEN ACCESS

EC CARDIOLOGY
Case Report

A Theoretical CPX Paradigm for Assessment of Exercise Performance in Heart Failure

Jeffrey Dwyer*

Department of Cardiology, Kaiser Permanente Medical Center, Vallejo, CA, USA

***Corresponding Author:** Jeffrey Dwyer, Department of Cardiology, Kaiser Permanente Medical Center, Vallejo, CA, USA.

Received: June 05, 2021; **Published:** August 30, 2021

Abstract

Data derived from cardiopulmonary exercise tests (CPX) provide prognostic indicators that reliably distinguish heart failure (HF) patients who may benefit from medical therapy from those who are likely to require hospital admission in the near future or advanced therapies, including implanted left-ventricular assist devices (L-VAD) and heart transplant. CPX also provides indices a patient's progress toward an improved cardiac capacity for exercise. Currently, peakVO_2 and slope-Ve/VCO_2 provide the greatest prognostic power for risk-stratification of HF patients. Other CPX variables that may be affected by a dysfunctional cardiovascular system, resulting in a disparity between oxygen delivery and oxygen demand in active tissues, include PetCO_2 (end-tidal PCO_2) and Ve/VCO_2 (ventilation equivalent for volume of CO_2 eliminated). A theoretical analysis of trend-line intersections of these variables, plotted against %peakVO_2 in serial CPX, was conducted that revealed a new paradigm with the potential for enhanced prognosis and tracking of progressive impairment or improvement of circulatory adaptation to the demands of exercise as HF status changes. A case history is presented that demonstrates the sensitivity and theoretical utility of this paradigm as the clinical status of a HF patient declined from NYHA I to heart transplant.

Keywords: *Heart Failure; Respiratory Compensation; Cardiopulmonary Exercise Test; Ventilation; Heart Transplant; Anaerobic Threshold*

Introduction

Initial applications of cardiopulmonary exercise (CPX) test data to the assessment of patients with heart failure (HF) focused on the oxygen consumption rate (VO_2) at the anaerobic threshold, or AT [1-6]. Early researchers [7-10] argued that the AT, whether assessed by serial venous or arterial lactate measurements (L-AT) or ventilatory analogs (V-AT) of elevated blood lactate, reflected the onset of a disparity between oxygen demand in active tissues and oxygen delivery. In the context of evaluating HF patients, many clinicians [10-14] attributed this disparity to the abnormal hemodynamics of impaired left ventricular function and other elements of HF. Operational difficulties in the assessment of V-AT and L-AT in HF patients [1,15,16], challenges to the theory that an AT truly represents a disparity in oxygen delivery and oxygen demand in active tissues [17-19] and unclear prognostic power [15,20,21], prompted clinicians to focus on other variables, principally the maximal aerobic power (VO_2max), defined as the rate of oxygen consumption in maximally tolerated exercise.

Efforts to assess VO_2max in HF patients also faced several challenges, including the safety of exercise at intensities sufficient to reach the age-predicted heart rate maximum (HRmax) while off medications and inability of patients to satisfy the classic criteria for this vari-

able [13,22,23]. As an alternative, peakVO_2 became the prime prognostic variable used to identify patients who might benefit from medical management as opposed to those who may require advanced therapies including placement of a left-ventricular assist device (LVAD) and transplant.

In current practice, peakVO_2 is identified simply as the highest rate of oxygen consumption attained in graded exercise terminated by the patient for any reason [16,24,25] without indications that physiologic maxima had been achieved. In contrast to VO_2max, this variable is not encumbered by the strict criteria that include a HR within 10 beats of the age-predicted HRmax, a plateau in VO_2 over two consecutive work stages, and a respiratory exchange ratio above 1.1, presumed to reflect a blood lactate concentration above 70 - 80 mg/dl [23]. Due to the lack of physiologic end-points, peakVO_2 must be viewed as a transient event and not an index of the capacity of an impaired cardiovascular system.

Several authors have demonstrated the power of peakVO_2 to identify patients at high risk for cardiac-related hospitalization and major adverse cardiac events, including death [23,24,27-30]. Despite significant operational limitations, including dependence on the subject's effort, highly variable attenuation of heart rate response by medications, and a sensitivity that does not exceed 70%, peakVO_2 is currently an integral element in the assessment of heart failure patients [25,32,33]. It is widely recognized, however, that many assessments of peakVO_2 occur when patients choose to stop exercise due to gait disorders, balance deficits, oral discomfort from the mouthpiece, or leg muscle discomfort without chest symptoms and without achieving HRmax, or ECG or BP indications that exercise should be terminated [26].

In 2004, Arena., *et al*. [33] suggested that the vast array of data generated by CPX may provide additional variables that have prognostic value superior to peakVO_2. Specifically, they examined the rate of pulmonary ventilation (Ve) in L/min, in a graded exercise performance, referenced to the volume of exhaled CO_2 (VCO_2) in L/min, comprising the ventilation-equivalent for CO_2 (slope-Ve/VCO_2), and found it to be consistently elevated in HF patients above that of healthy controls. They, and several others, have reported that the prognostic power of slope-Ve/VCO_2 exceeds that of peakVO_2 in the prognosis of cardiac hospitalization and mortality [21,29,30,33,34]. Despite a sensitivity of 66% for one-year cardiac mortality reported by Arena., *et al*. [33], this variable gained wide-spread acceptance among HF clinicians and, in many centers, supersedes peakVO_2 in the assessment of patients who might be candidates for advanced therapies, including heart transplant.

In a follow-up report [25], Arena and colleagues noted that the wide range of values for slope-Ve/VCO_2 found in HF patients pointed to a multi-level classification system. Their seminal research identified "cut points" in values for slope-Ve/VCO_2 that defined four ventilatory classes representing negligible risk, low risk, moderate risk, and high risk for adverse cardiac events in the ensuing two-year period. Not surprisingly, they found that a slope-Ve/VCO_2 of 29.0 or less was associated with a low risk of adverse events while a value of 45.0 or greater pointed to a high 2-year risk for adverse events. In these categories, a high value for slope-Ve/VCO_2 produced a sensitivity of 95% while a low value also produced a specificity of 95%. Two intervening classes represented low and moderate risk. A slope-Ve/VCO_2 of 36.0 yielded an optimal balance of sensitivity, at 74%, and specificity at 67%. Ferreira., *et al*. [35] found an optimal balance of sensitivity and specificity of 73% and 80%, respectively, at a much higher slope-Ve/VCO_2 of 43. Other researchers have reported optimal slope-Ve/VCO_2 ranging from 34 to 39 [34,36].

Following the observation of Arena., *et al*. [33] that CPX variables other than oxygen consumption may have utility in risk stratification and management of HF patients, we conducted a theoretical examination of ventilatory variables closely linked to changes in the metabolic character of graded exercise, other than slope-Ve/VCO_2, that may be affected by a disparity in oxygen delivery versus oxygen demand in active tissues. The purpose of this examination was to identify a paradigm composed of three variables that may have potential for tracking the status and prognosis of patients with HF through serial CPX.

Observations

In reviewing more than 200 CPX performed with HF patients in our lab, we observed significant variability in slope-Ve/VCO_2 among patients with similar peakVO_2, work capacity, NYHA class, and ejection fraction. We also noted that patients with more advanced clinical indicators of HF tended to reach high values for breath-by-breath measures of the ventilation equivalent for CO_2 (Ve/VCO_2) early in the performance of a graded exercise test, generally at less than 60% of the measured peakVO_2. In contrast, patients with less severe HF tended to have high values for Ve/VCO_2 only after exceeding 75% of the peakVO_2. This observation is illustrated in figure 1. Similarly, we noted that in graded exercise, end-tidal PCO_2 ($PetCO_2$) declined to 35 mm Hg at lower %peakVO_2 in patients with more advanced HF compared to those with milder HF (Figure 2).

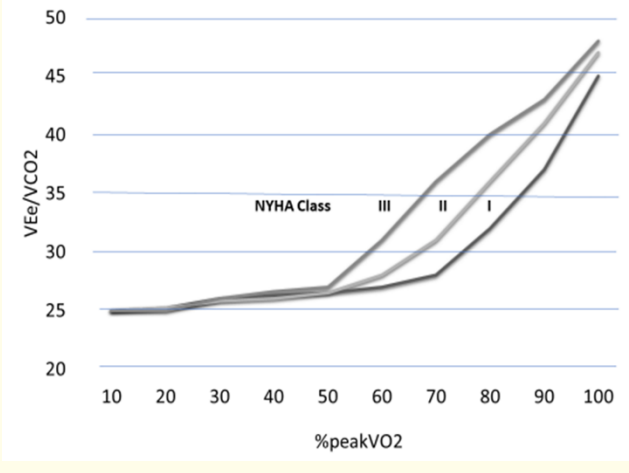

Figure 1: *Trend lines illustrating the ventilation equivalent for CO_2 (Ve/VCO_2) in graded cycle exercise from 10-100%peakVO_2 for HF patients with NYHA classification I-III.*

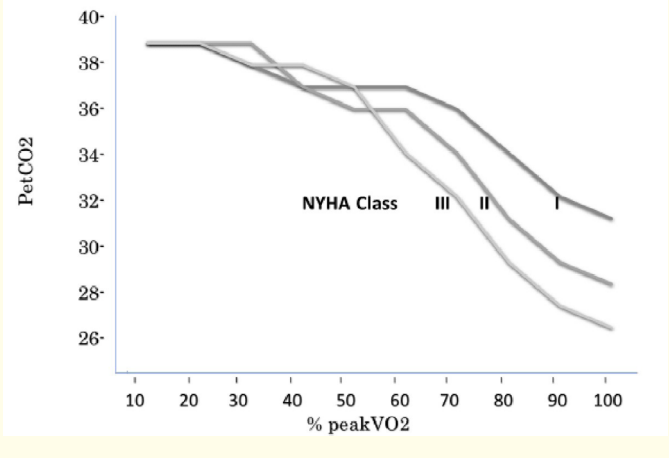

Figure 2: *Trend lines for end-tidal partial pressure of CO_2 ($PetCO_2$) in graded cycle exercise from 10-100% peakVO2 for HF patients with NYHA classifications I-III.*

In plotting the trend lines for both variables, $PetCO_2$ and Ve/VCO_2, most HF patients that we tested displayed a point where these lines intersected at a numerical value of about 35. The point of intersection occurred at high $\%peakVO_2$ for patients with mild HF whereas those with more advanced HF displayed an intersection at low $\%peakVO_2$. We hypothesized that the $\%peakVO_2$ at which these trend lines intersected (Figure 3) may have clinical significance in defining a patient's status since both variables have been found by others to be valid analogs of cardiovascular adaptations to the changing metabolic character of graded exercise [6,7,38]. Specifically, $PetCO_2$ declines while Ve/VCO_2 increases as exercise becomes more anaerobic and these changes occur at an earlier point in exercise when the cardiovascular system is compromised [6,9,31,38,39].

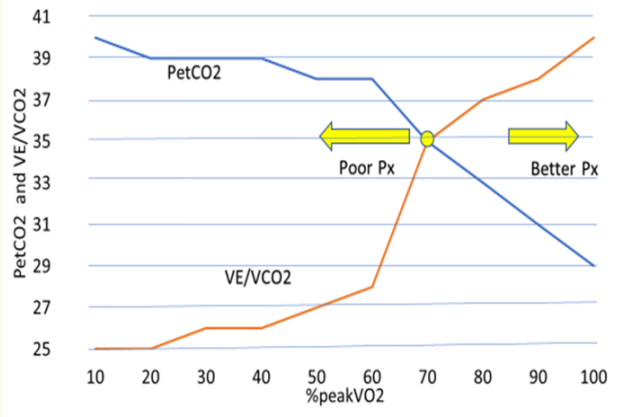

Figure 3: *Trend lines demonstrating the intersection of $PetCO_2$ and Ve/VCO_2 in exercise at a common numerical value of 35 (the 35-Crosspoint). Theoretically, prognosis, prognosis (Px), becomes less favorable as the intersection point moves to a lower $\%peakVO_2$.*

This brief communication describes our theoretical application of this phenomena to the evaluation of a patient with HF who eventually went on to L-VAD implantation and successful heart transplant.

Case History

At the age of 27, patient AB presented with malaise, dyspnea on exertion, lower extremity edema, and decreasing exercise tolerance. An echocardiogram revealed severely depressed left ventricular function with an ejection fraction of 20 - 25%. Months earlier, he was diagnosed with diabetes mellitus and started on metformin which controlled his fasting blood sugar between 110 - 120 mg/dl. His medical history also included gout, and substance abuse, primarily methamphetamines. An angiogram revealed normal coronary arteries and valve function with severely dilated left ventricle. AB was diagnosed with non-ischemic cardiomyopathy, NYHA class III, and started on Lasix, losartan, and carvedilol, in addition to diet and exercise counseling.

Over the next nine years AB's heart failure was stable and NYHA class improved to I, enabling him to resume work as a security guard. At age 37, he reported declining endurance and increasing dyspnea on exertion. He presented for evaluation by the Advanced HF/Transplant service and was found to be NYHA class II. CT angiogram revealed marked cardiomegaly, perihilar ground glass opacities interpreted as alveolar edema, and mediastinal and right hilar lymphadenopathy. At that time, an echocardiogram found an ejection fraction of 20 - 25% with severely dilated left atrium and mild-moderate mitral regurgitation. Medications were revised and, following improvement in his endurance and dyspnea, he was referred to a cardiac rehabilitation program to monitor blood pressures and heart rhythm in ECG-

monitored activity. The initial evaluation revealed blunted systolic blood pressures in low-intensity treadmill exercise with a threshold for dyspnea at 3.5 METs.

Over the next three years the patient was monitored by right-heart catheterizations which usually revealed low filling pressures, moderate-to-severe reductions in cardiac index, and normal right heart pressures. During this time, he diligently performed prescribed exercise at home and presented 2 - 4 times each month for assessments in the cardiac rehabilitation clinic. At age 40, the patient's NYHA class was designated II/III by his physicians and AB was admitted for ICD implantation. Prior to this surgery, an echocardiogram found an ejection fraction of 10 - 15%. Six months later, he required L-VAD implantation as a bridge to expectant heart transplant.

In the ensuing months, AB deteriorated rapidly and was admitted for successful heart and kidney transplantation. Eight weeks after transplant, AB resumed participation in cardiac rehabilitation and eventually achieved a high-level of fitness that enabled him to complete a 5-kilometer run without symptoms or undue fatigue.

During the four years prior to heart-kidney transplant, AB presented for several CPX to assess his peakVO_2, slope-Ve/VCO_2, and other indices of his cardiac status. Four CPX during the 16 months preceding L-VAD surgery were performed in the exercise non-invasive laboratory at Kaiser Permanente Medical Center in Vallejo, CA.

In each CPX, $PetCO_2$ and Ve/VCO_2 were plotted to identify the %peakVO_2 at which trend lines intersected at a numerical value of 35 (Figure 4). Figure 4 demonstrates that the "35-Crosspoint" occurred at progressively lower %peakVO_2 over the 16-month period prior to LVAD implantation. Furthermore, the peakVO_2 in the final three CPX were essentially identical (Table 1) during a period when the 35-crosspoint occurred at progressively lower %peakVO_2 as the patient's clinical status declined.

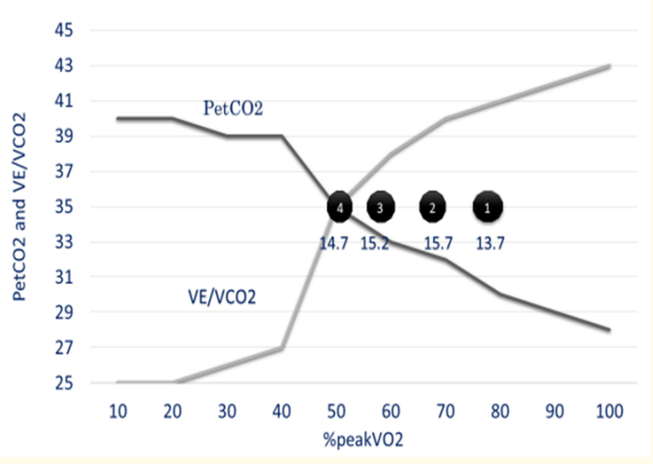

Figure 4: *Trend lines for patient AB's performance in CPX number 4 and position of 35-Crosspoint in three preceding CPX performed at 4-5 month intervals. Corresponding peakVO_2 are embedded.*

Test	peakVO_2 ml/kg/min	Work Rate Watts	Peak VE/VCO_2 $LVE/LVCO_2$	Slope VE/VCO_2	Oxygen-pulse ml VO_2/HR
1	13.7	70	39.0	34.0	10.4
2	15.8	93	35.0	31.0	12.1
3	15.2	74	42.9	36.0	9.3
4	14.7	70	41.8	36.0	9.9

Table 1: *Four CPX performed by patient AB, in descending order prior to heart-kidney transplant.*

Discussion

For many years, clinicians cited peakVO_2 as the foremost exercise variable prognostic for admission to hospital, cardiac events, and cardiac-related mortality. The dependence of VO_2 on cardiac output and, more specifically, adaptations in stroke volume and heart rate, provided a strong basis for interpreting poor values of peakVO_2 as the result of impaired cardiac performance. This strong association stands as the basis of the utility of the non-invasive CPX to assess the elements of oxygen transport and consumption. Without discounting the prognostic value of peakVO_2 measurement and the physiology it represents, Arena., *et al*. [25,33] suggested that other CPX variables, specifically ventilatory variables, may also reflect the impact of HF on cardiac performance. They reported compelling data that demonstrated the superior prognostic power of ventilatory variables derived from CPX performed by HF patients [25,31]. These researchers, and others [14,30,34] found that the steeper slope of Ve/VCO_2 that occurs with worsening heart failure reflects degrees of impairment of cardiovascular physiology.

Explanations for HF-induced changes in the slope-Ve/VCO_2 offered by early investigators [41-43] include increased pulmonary dead space, worsening pulmonary hemodynamics, decreased alveolar membrane conductance, exaggerated chemoreceptors and ergo-receptor sensitivity, decreased cardiac output, and heart rate variability. Some authors [44-47] reported ventilation-perfusion mismatch as an explanation for decreased VCO_2 that results in an increased value for slope-Ve/VCO_2. More recent investigations consider the pathophysiological basis of altered Ve/VCO_2 slope in heart failure [31,48-50] but, with few exceptions [50], many of the mechanisms studied by early researchers have not been subjected to rigorous laboratory investigation, leaving a number of operational concerns.

The high Ve/VCO_2 observed in the first minute of exercise, often above 40 $LVe/LVCO_2$, is well documented [9,12,51] and it has been suggested that this aberration should be excluded from the calculation of slope-Ve/VCO_2 [52]. In order to more accurately assess slope-Ve/VCO_2, Sun., *et al*. [53] deleted data above the "ventilatory compensation point," a method endorsed by Carriere., *et al*. [38] and others [31,55]. Furthermore, the role of oscillatory ventilation is often not appreciated as a source of error in calculating Ve/VCO_2 slope, yet its prevalence may be as high as 51% in the HF population [53,54]. Finally, a slope-Ve/VCO_2 derived by linear regression statistics does not recognize the difference metabolic domains (Figure 5) represented by various segments of the curvilinear Ve/VCO_2 demonstrated by several authors [9,39,52,55].

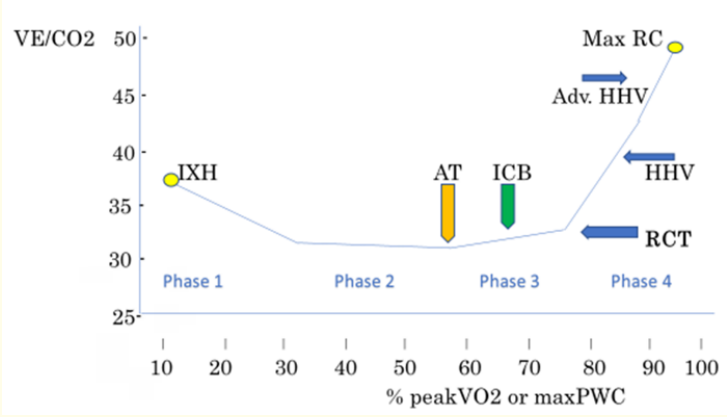

Figure 5: *The metabolic domains manifest in changes in the Ve/VCO_2 curve from initial exercise hyperventilation (IXH), to anaerobic threshold (L-AT), isocapnic buffering (ICB), threshold of respiratory compensation (RCT), through advanced hypocapnic hyperventilation (AHH) to maximal respiratory compensation (maxRC).*

Few authors emphasize the role that the changing metabolic character of exercise plays in determining the slope-VE/VCO_2 and its inherent variability. Decades of research have defined and established the physiologic relationships between certain ventilatory variables and lactate evolving from active tissues in graded exercise [1,8-10,39,37] and the impact of impaired hemodynamics on those relationships [5,16,38]. It is well-established that the ventilatory response to graded exercise demonstrates four phases that may be affected by the abnormal hemodynamics of HF [38]. Theses phases are illustrated in figure 5 and include, 1). initial exercise in which a high Ve/VCO_2 is common, 2). a relatively constant Ve/VCO_2 leading to the anaerobic threshold, 3). a period of isocapnic buffering (ICB) between AT ending at the respiratory compensation threshold (RCT), and 4). hypocapnic hyperventilation [9,38].

In an exercise test, after the initial minute in which a high Ve/VCO_2 from hyperventilation is common (Phase 1), pulmonary ventilation increases in proportion to VCO_2, maintaining Ve/VCO_2 and $PetCO_2$ at nearly constant values, comprising Phase 2 [9,38]. Phase 2 ends when Ve/VO_2 increases while Ve/VCO_2 remains unchanged, marking the V-AT. The increase in Ve/VO_2 occurs because ventilation matches VCO_2 which now exceeds the VO_2, raising the respiratory exchange ratio (RER) above unity. In phase 3, from V-AT to the end of isocapnic buffering (ICB), $PaCO_2$ and $PetCO_2$ are essentially unchanged from the initial exercise level as pulmonary ventilation increases in response to CO_2 evolving from lactate buffering and metabolism [9,38]. As work rate increases, demanding greater oxygen transport to muscles, reliance on anaerobic metabolism increases, generating greater amounts of lactic acid. The ICB period ends when the rate of Ve cannot maintain blood pH, triggering the onset of a respiratory compensation for a developing metabolic acidosis marked by a sharp increase in ventilation to eliminate CO_2 [38]. As exercise continues past the respiratory compensation threshold (RCT), $PetCO_2$ declines further as Ve/VCO_2 increases [31,38]. When these variables pass the numerical value of ~35, intense hypocapnic hyperventilation (HHV) is underway reflecting a significant lactate, probably above 4.0 mmol/L [9] and attendant buffering by bicarbonates. Advanced HHV is identified by a Ve/VCO_2 above 40 $LVe/LVCO_2$ and $PetCO_2$ of 30 mm Hg or less [9].

Several authors have linked ventilatory events, described as V-AT and RCT, to the impaired hemodynamics of HF [6,14,21,26,38,39]. Noting the consistent tendency of HF patients tested in our lab to display $PetCO_2$ of 35, and lower, while Ve/VCO_2 increased sharply above 35 $LVe/LVCO_2$, we devised the plot displayed in figure 3 and applied the paradigm to patient AB in serial CPX (Figure 4).

In patient AB, we noted that $peakVO_2$, work capacity, slope-Ve/VCO_2, and oxygen-pulse did not change significantly between the first CPX and the final test, a short time before L-VAD placement (Table 1). The stability of $peakVO_2$ measurements, during a period in which HF status declined (Figure 4), may be the result of a carefully-regulated and supervised exercise program that preserved Type I oxidative muscle fibers and enhanced the patient's comfort in exercise that demanded high volumes of pulmonary ventilation and evoked significant fatigue. During this same period, the $\%peakVO_2$ at which significant changes in $PetCO_2$ and Ve/VO_2 declined as the patient's clinical status deteriorated, leading to an earlier onset of anaerobic metabolism. This trend demonstrates the potential for the "35-Crosspoint" to serve as a sensitive indicator of a patient's HF changing status that may not be revealed by assessment of slope-Ve/VCO_2 or $peakVO_2$.

Research is currently underway in our lab to apply the 35-Crosspoint concept to a large cohort to assess its prognostic power and efficacy in tracking the clinical status of patients in chronic HF. We hypothesize that the position of 35-Crosspoint relative to $\%peakVO_2$ will correlate highly with NYHA class, as illustrated in figure 6, and provide a method of tracking patients as the risk of near-future adverse cardiac events changes. The potential for the 35-Crosspoint paradigm to enhance the prognostic power of other CPX variables is an integral part of this on-going investigation in our lab.

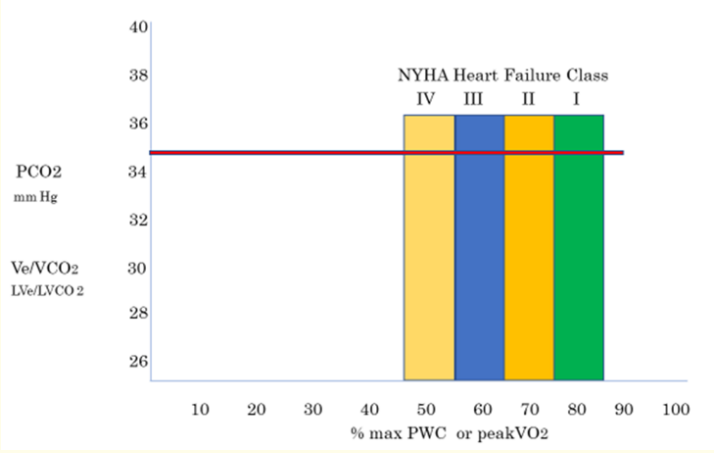

Figure 6: *Theoretical alignment of HF patient classes according to the range of %peakVO2 in which 35-Crosspoint occurs.*

Conclusion

Aside from the widely used prognostic indicators, peakVO_2 and slope-Ve/VCO_2, CPX generates many variables that may provide a better insight into a patient's capacity for circulatory adaptations to graded exercise. The 35-Crosspoint demonstrated in this communication may be a variable that, when assessed in serial CPX tests, reliably reveals trends in a patient's status that contribute to an accurate prognosis and improved patient care.

Bibliography

1. Katz SD., *et al*. "Anerobic threshold in patients with congestive heart failure". *The American Journal of Cardiology* 69.19 (1992): 1565-1569.

2. Metra M., *et al*. "Assessment of peak oxygen consumption, lactate and ventilatory thresholds and correlation with resting and exercise hemodynamic data in chronic congestive heart failure". *The American Journal of Cardiology* 65.16 (1990): 1127-1133.

3. Weber KT., *et al*. "Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure". *Cardiology* 65.6 (1982): 1213-1223.

4. McElroy PA., *et al*. "Cardiopulmonary exercise testing in congestive heart failure". *The American Journal of Cardiology* 62.2 (1988): 35A-40A.

5. Sullivan MJ and Cobb FR. "The anerobic threshold in chronic heart failure. Relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training". *Cardiology* 81 (1990): 1147-1158.

6. Wasserman K., *et al*. "Ventilation during exercise in chronic heart failure". *Basic Research in Cardiology* 91.1 (1996): 1-11.

7. Beaver WL., *et al*. "A new method for detecting the anaerobic threshold by gas exchange". *Journal of Applied Physiology* 60.6 (1986): 2020-2027.

8. Davis JA. "Anaerobic threshold: a review of the concept and directions for future research". *Medicine and Science in Sports and Exercise* 17.1 (1985): 6-18.

9. Wasserman K., *et al*. "Clinical exercise Testing". Principles of Exercise Testing and Interpretation Including Pathophysiology and Clinical Applications. Philadelphia: Lippincott Williams and Wilkins (2012).

10. Wasserman K and McElroy MB. "Detecting the threshold of anaerobic metabolism in cardiac patients during exercise". *The American Journal of Cardiology* 14 (1964): 844-852.

11. Weber KT., *et al*. "Exercise testing in the evaluation of the patient with chronic cardiac failure". *American Review of Respiratory Disease* 129.2 (1984): 560-562.

12. Romano M., *et al*. "Cardiopulmonary exercise response in patients with left ventricular dysfunction or heart failure: a non-invasive study of gas exchange and impedance cardiography monitoring". *Cardiology* 87.2 (1996): 147-152.

13. Baladay GJ., *et al*. "Clinician's Guide to Cardiopulmonary Exercise testing in adults: a scientific statement from the American heart Association". *Cardiology* 122.2 (2010): 191-225.

14. Gitt AK., *et al*. "Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients at high risk of early death". *Cardiology* 106.24 (2002): 3079-3084.

15. Cohen-Solal A., *et al*. "Can anaerobic threshold be used as an end point for therapeutic trials in heart failure?" *European Heart Journal* 15 (1994): 236-241.

16. Agostoni P., *et al*. "Prognostic value of indeterminable anaerobic threshold in heart failure". *Circulation: Heart Failure* 6 (2013): 997-978.

17. Brooks GA. "Anaerobic threshold: review of the concept and directions for future research". *Medicine and Science in Sports and Exercise* 17 (1885): 22-31.

18. Spurway NC. "Aerobic exercise, anaerobic exercise and the lactate threshold". *British Medical Bulletin* 48 (1992): 569-590.

19. Cohen-Solal A., *et al*. "Ventilatory threshold during exercise in patients with mild to moderate chromic heart failure: determination, relation with lactate threshold and reproducibility". *International Journal of Cardiology* 30.3 (1991): 321-327.

20. Corra U., *et al*. "Cardiopulmonary exercise testing and prognosis in heart failure. A prognosticating algorithm for the individual patient". *Chest* 126.9 (2004): 942-950.

21. Corra U., *et al*. "Cardiopulmonary exercise testing and prognosis in heart failure due to systolic left ventricular dysfunction: a validation study of the European Society of Cardiology Guidelines and Recommendations (2008) and further development". *European Journal of Preventive Cardiology* 19 (2012): 32-40.

22. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription". Philadelphia: Wolters Kluwer, Tenth edition (2017).

23. Astrand PO and Rodahl K. "Textbook of Work Physiology". New York: McGraw-Hill Book Co (1970).

24. Arena R and Humphrey R. "Comparison of ventilatory expired gas parameters used to predict hospitalization with heart failure". *American Heart Journal* 143 (2002): 427-432.

25. Arena R., *et al*. "Development of a ventilatory classification system in patients with heart failure". *Circul* 115 (2007): 2410-2417.

26. Agostini P., *et al*. "Prognostic value of indeterminable anaerobic threshold in heart failure". *Circulation: Heart Failure* 3.6 (2013): 977-987.

27. Mancini DM., *et al*. "Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure". *Circul* 83 (1991): 778-786.

28. Myers J., *et al*. "Cardiopulmonary exercise testing and prognosis in severe heart failure; 14 ml/kg/min revisited". *American Heart Journal* 139 (2000): 78-84.

29. Francis DP., *et al*. "Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value of VE/VCO2slope and peakVO2". *European Heart Journal* 21 (2000): 154-161.

30. Chua TP., *et al*. "Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure". *Journal of the American College of Cardiology* 29 (1997): 1585-1590.

31. Prado DML., *et al*. "Effect of exercise training on ventilatory efficiency in patients with heart disease: a review". *The Brazilian Journal of Medical and Biological Research* 49.7 (2016): e5180.

32. Myers, J., *et al*. "Cardiopulmonary Exercise testing in heart Failure". *Current Problems in Cardiology* 40.8 (2015): 322-372.

33. Arena R., *et al*. "PeakVO2 and VE/VCO2 slope in patients with heart failure: A prognostic comparison". *American Heart Journal* 147 (2004): 354-360.

34. Sue DY. "Excess ventilation during exercise and prognosis in heart failure". *American Journal of Respiratory and Critical Care Medicine* 183 (2011): 1302-1310.

35. Ferreira AM., *et al*. "Ventilatory efficiency and the selection of patients for heart transplantation". *Circulation: Heart Failure Journals* 3 (2010): 378-386.

36. Shen Y., *et al*. "VE-VCO2 slope and its prognostic value in patients with chronic heart failure". *Experimental and Therapeutic Medicine* 9 (2015): 1407-1412.

37. Simonton CA., *et al*. "The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and patients with congestive heart failure". *The American Journal of Cardiology* 61.1 (1988): 100-107.

38. Carriere C., *et al*. "Isocapnic buffering: from physiology to clinics". *European Journal of Preventive Cardiology* 26.1 (2019): 1107-1114.

39. Carriere C., *et al*. "Anaerobic threshold and respiratory compensation point identification during CPET in chronic heart failure". *Chest* 156.2 (2019): 338-347.

40. Tabet JY., *et al*. "A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure". *European Association for Cardiovascular Prevention and Rehabilitation* 10 (2003): 267-272.

41. Guazzi M. "Abnormalities in cardiopulmonary exercise testing ventilatory parameters in heart failure: pathophysiology and clinical usefulness". *Current Heart Failure Reports* 11 (2014): 80-87.

42. Narkiewicz K., *et al*. "Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure". *Circul* 100 (1999): 262-267.

43. Giannoni A., *et al*. "Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure". *Journal of the American College of Cardiology* 53 (2009): 1975-1980.

44. Wada O., *et al*. "Importance of abnormal lung perfusion in excessive ventilation in chronic heart failure". *The American Heart Journal* 125 (1993): 790-798.

45. Lewis NP., et al. "Impaired matching of perfusion and ventilation in heart failure detected by 133-xenon". Basic Research in Cardiology 91.1 (1996): 44-49.

46. Banning AP., *et al*. "Perfusion/ventilation mismatch during exercise in chronic heart failure: an investigation of circulatory determinants". *British Heart Journal* 74 (1995): 27-33.

47. Uren NG., *et al*. "Reduction of mismatch of global ventilation and perfusion on exercise is related to exercise capacity in heart failure". *British Heart Journal* 70 (1993): 241-246.

48. Tumminello G., *et al*. "Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance". *European Heart Journal* 28 (2007): 673-678.

49. Giannoni A., *et al*. "Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure". *Journal of the American College of Cardiology* 53.21 (2009): 1975-1980.

50. Olson TP., *et al*. "Influence of locomotor muscle afferent inhibition on the ventilatory response to execise in heart failure". *Experimental Physiology* 99.2 (2014): 414-426.

51. McArdle WD., *et al*. "Exercise Physiology: Nutrition, Energy, and Human Performance". Phil: Lippincott Williams Wilkins, 8th edition (2014).

52. Mezzani A. "Cardiopulmonary Exercise Testing: Basics of Methodology and Measurements". *Annals of the American Thoracic Society - ATS Journals* 14.1 (2017): S3-S11.

53. Sun XG., *et al*. "Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure". *Journal of the American College of Cardiology* 55.17 (2010): 1814-1823.

54. Murphy RM., *et al*. "Exercise oscillatory ventilation in systolic heart failure: An indicator of impaired hemodynamic response to exercise". *Circulation* 124 (20111): 1442-1451.

55. Chicharro JL., *et al*. "Effects of endurance training on the isocapnic buffering and hypocapnic hyperventilation phases in professional cyclists". *British Journal of Sports Medicine* 34 (2000): 450-455.

Volume 8 Issue 9 September 2021