Submaximal Cardiopulmonary Exercise Testing with Gas Exchange: An Objective Method for Serial Patient Assessment in Heart Failure

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Abstract

The robust predictive power of cardiopulmonary exercise (CPX) testing in heart failure assessment has allowed it to emerge as the gold standard for helping to identify the pathophysiology of exercise-induced dyspnea and for risk stratification. CPX imparts accurate, reproducible and objective baseline prognostic information and dynamic risk assessment of greater predictive value than other commonly used assessment methods. Traditionally, CPX testing has been used to measure oxygen uptake, either at maximal exercise (pVO_2) or at the ventilatory threshold, as a measure of patient functional capacity and for risk stratification. More recently, gas exchange measurements obtained during submaximal exercise, coupled with measures of autonomic balance, have been shown to provide prognostic and diagnostic information in the heart failure population that is equal to, or in some cases better than, pVO_2. Further, these alternative measures of breathing efficiency overcome limitations to pVO_2 testing that are evident in patients on β-blocker therapy and provide a basis for defining response to cardiac resynchronization therapy.

Overview of Patient Assessment in Chronic Heart Failure

Over the past 30 years cardiopulmonary exercise testing with gas exchange (CPX) has emerged as the gold standard for assessing heart failure patients being considered for transplantation and to help identify the pathophysiology of exercise-induced dyspnea. As a result of the robust predictive power of CPX testing, the AHA and ACC has identified this test as a class I indication for heart failure assessment.[1] In its recently released consensus statement,[2] the Heart Failure Society of America lists CPX as one of three assessment methods that have successfully undergone both extensive research and a history of successful application in clinical practice. In addition to CPX, listed assessment methods include the NYHA functional classification and the 6-minute walk test.

While the NYHA classification has been shown to correlate with likelihood and mode of death in heart failure patients with left ventricular systolic dysfunction,[3] assessment of NYHA functional class is inconsistent, with nearly 50% discordance between cardiologists.[4] The 6-minute walk test is a tool that is designed to reflect the patient's ability to carry out the activities of daily living.[5] It has been shown to be an independent predictor of mortality and hospitalization risk,[6] but correlates only moderately with peak oxygen uptake (indicating they may not be measuring the same thing).[7,8] Despite these benefits, the utility of the 6-minute walk test in risk stratification and assessing therapy response is not well defined, and lack of a standardized protocol presents a limitation to results interpretation, especially in patients unable or unwilling to complete the test.[2,9] Further, although the 6-minute walk test represents a submaximal exercise effort in patients with mild heart failure and no functional limitations, in more advanced disease the test elicits a maximal exercise response. For this reason, the degree of disease progression should be considered when using the 6-minute walk test to evaluate therapy outcome and clinical prognosis.[10]

By contrast to these methods, CPX testing provides a more sophisticated method for obtaining accurate, objective, and reproducible baseline prognostic information and dynamic risk assessment.[1] Clinical research has consistently demonstrated the robust prognostic value of CPX testing,[11,12] further noting that CPX techniques allow for accurate quantification of the effects of pharmacological, surgical, and lifestyle interventions.[13-15] Despite its proven clinical value, certain factors combine to limit the utility of CPX

testing in routine heart failure patient assessment. These include cost, a requirement that the healthcare professional responsible for data interpretation must have a specific understanding of the diagnostic and prognostic implications of the test variables, and that specific skills are required to assure proper calibration and maintenance of the test system and in the performance of the exercise test.[1] It is also noteworthy that the difficulty faced by patients in performing a peak CPX test limits the practical clinical utility of the test in routine patient assessment. Despite these limitations, the use of CPX testing in heart failure assessment is increasing in clinical practice and will likely play a more dominant role in guiding patient management in chronic heart failure.[1,16]

Historically, CPX testing has been used to measure peak oxygen uptake (pVO_2) or oxygen uptake at the anaerobic threshold during exercise. Over the past 10 years clinical evidence has emerged showing that other gas exchange testing variables, including the relationship between ventilation and carbon dioxide production (V_E/VCO_2 slope),[17-20] the partial pressure of end-tidal carbon dioxide,[21,22] and oxygen uptake kinetics[23,24] provide diagnostic and prognostic information in the heart failure population that equals, or in many cases exceeds, that of pVO_2 testing. Further, these alternative test parameters are shown to overcome limitations to pVO_2 testing that are evident in patients on β-blocker therapy[25] and to provide a basis for defining response to cardiac resynchronization therapy.[26,27]

Shape Medical Systems, Inc. (St. Paul, MN) has developed a simplified approach to cardiopulmonary gas exchange testing in the clinical setting. This miniaturized, self-calibrating system, along with clear and concise software and algorithms, allows a novel approach to quantifying disease status, defining the pathophysiology of patient dyspnea, and optimizing timing characteristics of bi-ventricular pacemakers. The device uses pre-programmed submaximal exercise protocols, of value in patients with chronic heart failure who tend to avoid strenuous effort and restrict themselves to submaximal exercise during daily activities.

The device, which has been clinically validated by the Mayo Clinic (Rochester, MN), overcomes the traditional limitations of CPX testing equipment. No manual calibration is required for patient testing, testing equipment is intuitive and easy-to-use, and measurements are interpreted by internal algorithms, overcoming the need for specific expertise in results interpretation. Importantly, the test is short and easy on the patient, presenting an opportunity for serial patient testing to track patient progress and response to therapy.

Scientific Basis for Routine Submaximal Cardiopulmonary Gas Exchange Testing in the Clinical Setting: The Link Between Breathing Pattern, Gas Exchange and Dynamic Cardiac Function

Chronic heart failure (CHF) is a holistic condition affecting every organ system involved with oxygen transport. In addition to the heart, CHF impacts the respiratory system, skeletal muscles, and the hormonal and neural feedback control mechanisms affecting breathing, cardiac output, blood pressure, and oxygen distribution via peripheral blood flow. These systems cannot be considered in isolation, but unite to describe the pathophysiology of CHF disease progression.

The lungs lie hemodynamically in series with the heart, share a common surface area, and are influenced by acute changes in left heart pressure and intrathoracic pressure. Cardiac stretch, intracardiac pressures (e.g., left atrial pressure) and dynamic changes in fluid balance within the lungs alter ventilatory control and influence ventilatory drive, ventilatory efficiency, as well as ventilation-perfusion matching and dead space ventilation.[28,29] As 98-99% of the cardiac output passes through the lungs, gas exchange reflects variability in cardiac status. In addition, breathing pattern is influenced by changes in ventilatory control and compliance characteristics of the lungs.[30] With light exercise the augmented venous return and increases in intrathoracic pressure in the setting of a large, dilated heart further influences cardiac pre- and afterload and may enhance ventricular interdependence.[31] Clinical studies suggest that breathing strategy is clearly linked to disease severity in heart failure.[16,32,33] Moreover, changes in ventilation and gas exchange are dynamic as they reflect changes in cardiac function. These important links between respiratory function and cardiac disease severity are becoming recognized, and combine with measures of heart rate response to exercise to provide a basis for the functional classification of patients with chronic heart failure and for the functional optimization of CRT devices.

Key Measures in Submaximal Cardiopulmonary Exercise Testing

Ventilatory Efficiency for Carbon Dioxide (V_E/VCO_2 slope)

Due to the insidious nature of chronic heart failure, the importance of accurately and objectively identifying heart failure patients at highest risk for morbidity and mortality cannot be over estimated. The rise in ventilation (V_E) relative to the rise in carbon dioxide

production (VCO_2, a measure of metabolic demand) is a hallmark manifestation of chronic heart failure. Three mechanisms have been identified that impact this relationship, all of which may occur early in the progression of CHF: (i) increased physiologic dead space ventilation resulting from ventilation-perfusion mismatching in the lung, which is primarily influenced by cardiac output and pulmonary artery pressure (ii) the early occurrence of lactic acidosis, explained by the imbalance between cardiac output and metabolic demand by working muscle and by the preponderance of Type IIb muscle fibers in CHF, and (iii) over activity of muscle ergoreceptors and peripheral chemoreceptors that contribute to autonomic imbalance, coupled with antagonism of baroreflex control.[34,35] The regulatory mechanisms involved in the tight control of ventilation, rather than lung function abnormalities, play a key role in the pathophysiology of ventilation inefficiency during exercise in heart failure patients, explaining why V_E/VCO_2 is considered a cardiovascular, not pulmonary, measurement parameter.

Augmented ventilatory response to exercise is common in heart failure. A rise in V_E/VCO_2 slope, is an indicator of worsening disease progression and is an independent marker of poor prognosis, regardless of severity as assessed by NYHA class[25] or LVEF[8,36]. Factors that influence ventilatory efficiency include pulmonary artery pressure,[34,37] increased pulmonary capillary wedge pressure,[38] cardiac output,[8] interstitial pulmonary edema,[38] reduced peripheral muscle quality,[16] and impaired reflex control.[8,25,34,39,40] The V_E/VCO_2 slope is prognostic over a wide range of clinical conditions, including in patients with systolic or diastolic heart failure,[36] pulmonary artery hypertension,[34,41] right heart failure,[34] heart transplant,[42,43] those treated with pharmaceutical agents (β-blockade or angiotensin-converting enzyme inhibition),[16,25,34,39,40,43] and in patients treated with pacemakers, including cardiac resynchronization therapy.[14,44,45] Importantly, the V_E/VCO_2 slope retains its prognostic power in the presence of a submaximal exercise effort.[22,25,36,43,46] The V_E/VCO_2 slope reflects the severity of derangement in almost all aspects of CHF, explaining its impressive power in predicting cardiac related events (Table 1), including hospitalization.[22,47]

Numerous studies have shown that the V_E/VCO_2 slope is prognostically superior to pVO_2, highlighting the clinical importance of assessing V_E/VCO_2 in chronic heart failure. Unlike pVO_2, which requires a maximal exercise effort and can be influenced by patient motivation or skeletal muscle health, the V_E/VCO_2 slope provides a consistent measurement that is not dependent on patient effort to provide prognostic power.[46,55] The threshold value for predicting increased risk in CHF has been defined as ≥34. To further discriminate various levels of risk for adverse events a 4-level classification system has been established, thus optimizing the clinical utility of the assessment.[43]

Table 1: Studies Providing a Prognostic Comparison Between V_E/VCO_2 Slope and Peak VO_2

Reference	Patients	V_E/VCO_2 Slope Cutoff for Increased Risk	V_E/VCO_2 Slope Superiority Versus Peak VO_2
Chua *et al.*[48]	104	34	Yes
Francis *et al.*[12]	203	Range, 30 to 55	Yes
Kleber *et al.*[49]	144	>130% of predicted	Yes
Ponikowski *et al.*[50]	344	34	Yes
Corra *et al.*[51]	600	35	Yes
Gitt *et al.*[52]	233	34	Yes
Guazzi *et al.*[53]	100	34	Yes
Arena *et al.*[17]	213	34	Yes
Guazzi *et al.*[36]	409	34	Yes in diastolic, similar in systolic
Nanas *et al.*[38]	98	34	Yes
Tsurugaya *et al.*[54]	215	34	Yes

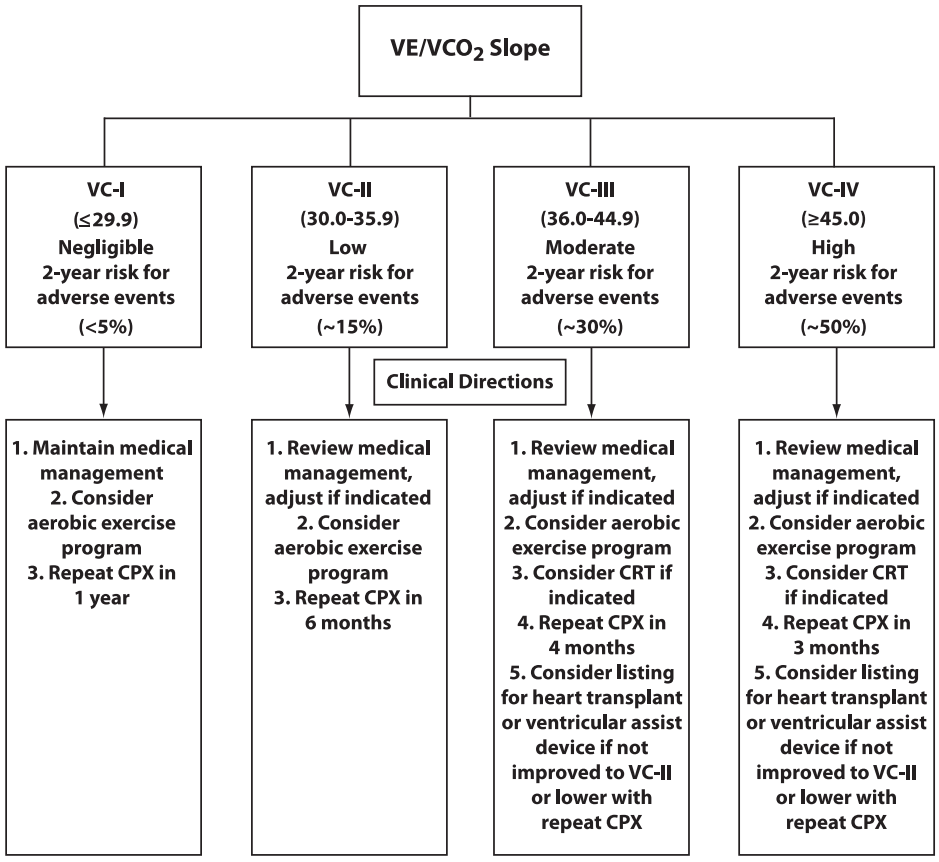
As presented in Arena, et al.[45]

The ventilatory class algorithm (Figure 1), as taken from Arena, et al.,[43] suggests that heart failure patients with V_E/VCO_2 slope ≤29.9 (VC-I) would be considered as having minimal 2-year risk for adverse events, and medical management could be maintained. As heart failure progresses through ventilatory classes II through IV, medical management should be reviewed and optimized when indicated. Cardiac resynchronization therapy, left ventricular assist device implantation, or heart transplant may be considered for patients in higher

ventilatory classes not showing improvement to a lower class following pharmacological intervention and exercise therapy. The ventilatory class algorithm can be used as a tool to steer minor adjustments in optimal medical therapy, or to provide objective guidance for making

co-morbid central or obstructive sleep apnea, also directly influences ventilatory efficiency.[34] For example, adding or adjusting the dosage of β-blockade may have the effect of improving V_E/VCO_2 slope such that a CHF patient may transform from a VC-II or VC-III to a lower

Figure 1: Ventilatory Classification Algorithm



From: Arena, et al.[43]

therapy decisions of major medical consequence. While the ventilatory class algorithm is based on assessment of patients with left ventricular dysfunction, values for V_E/VCO_2 correlating with severity of pulmonary hypertension in the absence of diagnosed left ventricular dysfunction have been reported.[56]

Treatment with β-blockade,[16,25,34,39,40] angiotensin-converting enzyme inhibition,[16,57] and modulation of the nitric oxide pathway by selective cyclic 3'-5' guanosine monophosphate phosphodiesterase inhibitors[34] have been shown to reduce V_E/VCO_2 slope in heart failure patients, which may allow them to perform normal activities of daily living at lower perceived difficulty, reduce symptoms, and improve quality of life. Nonpharmacological therapy, including exercise therapy and continuous positive airway pressure for patients with

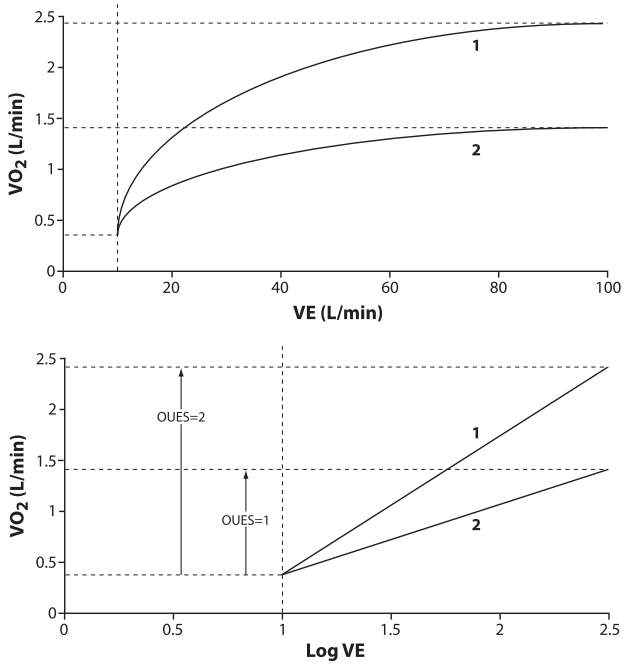
VC class, thus reducing the 2-year risk of adverse events by ≥ 10%. Similarly, a patient in VC-III considered for heart transplant candidacy may improve to a lower VC class through standard therapy structured to target improvement in V_E/VCO_2 slope. It is important to note that the prognostic strength of gas exchange variables, including V_E/VCO_2 slope, diminishes as time since prior testing increases,[43] emphasizing the importance of repeat testing regardless of previous testing results.

Oxygen Uptake Efficiency Slope

The oxygen uptake efficiency slope (OUES) is a curvilinear measure of ventilation response to exercise that integrates the functional capacities of several organ systems, including the cardiovascular, pulmonary, and skeletal muscle systems. It reflects the relationship

between oxygen uptake (VO_2) and ventilation during exercise and is often described by a single exponential function with VO_2 plotted on the Y-axis and V_E plotted on the x-axis using a logarithmic scale (Figure 2).[58] The transformed logarithmic regression is linear, and unlike the measurement of pVO_2, remains stable over the entire exercise duration.[8,58,59] Hollenberg, et al.[24] determined that the OUES measurement at 75% of peak exercise effort differed by 1.9% of that found with maximal exercise effort, while in a similar comparison between 50% and 100% of exercise effort Baba and coworkers[60] observed a 1.0% difference in OUES compared to a 25% variance in pVO_2. In evaluating 998 older patients

Figure 2: Physiological Meaning of Oxygen Uptake Efficiency Slope



From the definition of OUES, that is the value of 'a' in the regression relationship VO_2 = a log 10 VE + b, it is seen that 'a' is the slope of VO_2 upon log 10 VE (i.e., ventilation). Put simply, OUES is the absolute increase in VO_2 associated with a 10-fold rise in ventilation. *Adapted from Davies, et al.*[58]

free of clinically recognized cardiovascular disease, no difference was observed in the OUES measurement between men and women.[24] Oxygen uptake efficiency slope is highly reproducible and can provide an objective index of cardiopulmonary function that is less influenced by subjective, motivational factors than the pVO2.

Factors that influence OUES include (i) the arterial CO_2 set point ($PaCO_2$), (ii) metabolic CO_2 production (from muscle aerobic metabolism and the pH buffering function of bicarbonate), and (iii) the ratio of pulmonary dead space to tidal volume.[60] A large OUES and steep slope depend on a large mass of working muscle, a vigorous and unimpaired blood flow to the working muscles, efficient extraction and utilization of oxygen by the muscles, and the delayed appearance of lactic acid. Patients with heart failure show early metabolic acidosis and higher mixed venous lactic acid levels for the same absolute amount of exercise work. This excessive CO_2 production stimulates ventilation and leads to lower values of OUES. Similarly, high dead space ventilation from ventilation and perfusion inhomogeneities in the lungs along with a rapid-shallow breathing pattern will influence the ventilatory response to exercise and the OUES.[24,60] While similar to V_E/VCO_2 as a measure of breathing efficiency, OUES differs in that it considers changes in ventilation in terms of scale factor (i.e., multiples of baseline). In this way, OUES quantifies the pattern of ventilatory response to exercise alone having automatically controlled for abnormalities present at rest.[58]

Oxygen uptake efficiency is reduced in heart failure patients with systolic heart failure,[58,59] heart failure with preserved ejection fraction,[61] coronary artery disease,[62]

and has been suggested as a parameter for use in the selection of patients who may benefit from heart transplant.[58] While a risk classification system has not been reported for OUES, McRae, *et al.*[63] divided 1,661 patients with chronic heart failure into four quartiles based on average OUES values as follows: Quartile 1, 0.98 ± 0.15; Quartile 2, 1.31 ± 0.08; Quartile 3, 1.60 ± 0.10; and Quartile 4, 2.12 ± 0.33. Patients were followed for a median of two years (range 0 – 5 years) and those receiving cardiac transplant (n=190) were censored. The investigators found that compared to patients in the highest quartile, those in the lowest quartile had lower pVO_2 (10.5 vs. 23.7 ml/kg/min), were older (57 vs. 48 years), and were more likely to have coronary disease (54% vs. 27%). There was a strong correlation between OUES and mortality, with Quartiles 1 and 2 showing the highest risk based on Kaplan-Meier survivor plot analysis. Risk cut-off values have been defined in various studies as shown in Table 2.

Table 2: Summary of Studies in Which Cut-off Values or Values Reflecting Average OUES in Patients with Intermediate Exercise Tolerance Were Determined

Reference	Subjects/Diagnosis	Cut-off or Intermediate Exercise Capacity Value for Increased Risk
Davies, *et al.*[58]	243/HF	1.47
Van de Veire, *et al.*[62]	214/CAD	1.31
Van Laetham, *et al.*[59]	45/HF: 35/CAD	1.56
Myers, *et al.*[54]	710/HF	1.40
McRae, *et al.*[63]	1,661/HF	1.31
Arena, *et al.*[65]	341/HF	1.39

Weighted average cutoff value (based on cohort size) = 1.36±0.10.

Partial Pressure of End-Tidal CO_2

During exhalation, carbon dioxide (CO_2) concentration measured near the mouth or nose rises to an asymptote and reaches a peak value near the end of exhalation. This value reflects alveolar CO_2 and, since there is typically minimal arterial to alveolar CO_2 difference, the partial pressure of end-tidal CO_2 ($PetCO_2$ or $ETCO_2$) reflects the partial pressure of arterial CO_2 ($PaCO_2$). The partial pressure of end-tidal CO_2 decreases as pulmonary blood flow, and therefore cardiac output, is reduced, therefore making $PetCO_2$ a measure of changes in pulmonary circulation as opposed to abnormalities in the airways of the lung.[21,22,66]

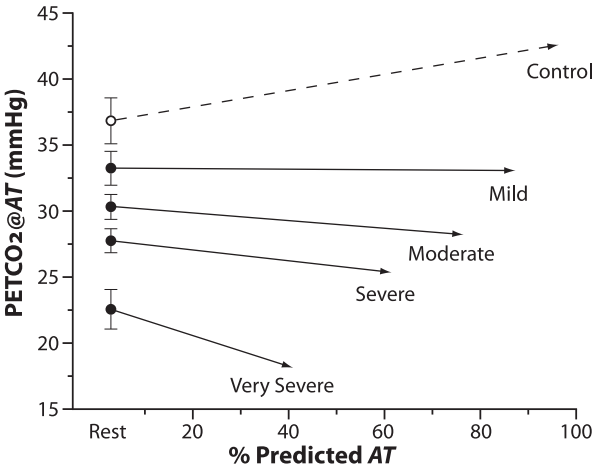
In normal subjects, $PetCO_2$ rises during exercise due to the increased delivery of CO_2 to the lungs. With cardiac disease, inadequate cardiac output during exercise hinders CO_2 delivery relative to increased work load during exercise. As such, an abnormal increase in $PetCO_2$ is related to cardiac output, rather than decreased CO_2 production, abnormal breathing patterns (such as rapid, shallow breathing), or hyperventilation.[21] In heart failure populations, numerous stimuli are present that increase ventilation contributing to a fall in $PetCO_2$. Fluid load, cardiac stretch, high cardiac filling pressures, lung congestion, along with other potential mediators increase the drive to breathe and cause a fall in $PetCO_2$. Greater ventilation and perfusion mismatching in the lungs may also increase the difference between $PetCO_2$ and arterial CO_2 values.[28]

Numerous studies have shown that abnormal $PetCO_2$ values in chronic heart failure, both at rest and during submaximal exercise, is associated with disease severity and prognosis,[20,21,47] the risk of major cardiac events,[11,22] can provide evidence of exercise-induced right-to-left shunting in patients with primary pulmonary hypertension,[67] and adds prognostic value to the measure of ventilatory efficiency.[22,47] In association with measures of ventilatory efficiency, $PetCO_2$ values may also effectively identify patients at high risk for hospitalization, improving the ability to provide appropriate interventions in the outpatient setting and helping to reduce healthcare costs.[22,47,66,68] As opposed to the confounding effect of β-blockade frequently seen in pVO_2 assessment, there is no reason to expect a similar attenuation in the prognostic value of $PetCO_2$.[47]

Recent studies have shown that abnormal $PetCO_2$ in the presence of dyspnea of unknown etiology may be reflective of pulmonary hypertension (PPH).[41,56,69] In a landmark study involving [52] patients and nine healthy controls, Yasunubo, *et al.*[56] determined that $PetCO_2$ measurements proportionately decreased as the percent age predicted pVO_2 decreased, and $PetCO_2$ values at rest and at the anaerobic threshold reduced as mean pulmonary artery pressure increased. It was further determined that $PetCO_2$ at rest and during exercise was reduced proportionate to the severity of PPH, and that directional changes in the $PetCO_2$ profile during exercise

and recovery are in the opposite direction of those expected in either normal subjects or in heart failure

Figure 3: $PetCO_2$ Directional Change Associated with PPH



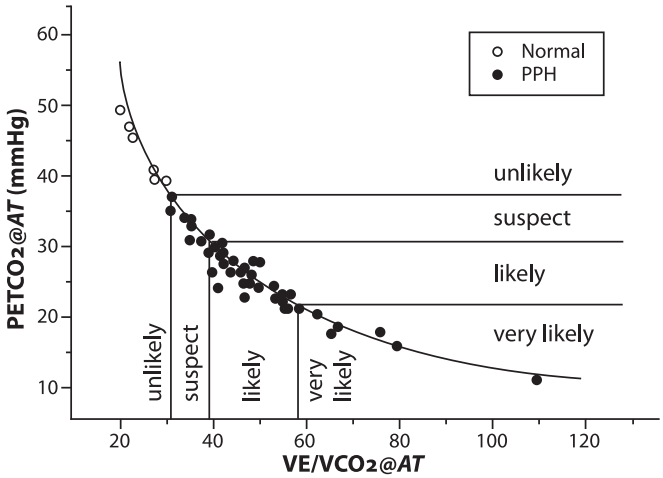
Change in $PetCO_2$ from rest to AT as a function of percentage of predicated AT for 52 PPH patients according to physiologic disease severity: mild, moderate, severe, and very severe. Included are the averages for nine normal subjects. Arrows go from mean resting values to the percentage of predicted AT. Data are presented as mean ± SE. *From: Yasunobu, et al.*[56]

patients. The authors concluded that primary pulmonary hypertension should be considered as a possible diagnosis to account for dyspneic symptoms considering the frequency with which abnormal $PetCO_2$ patterns or low resting $PetCO_2$ values occur in PPH in comparison to other disorders. As shown in Figures 3 and 4, Yasunubo and coworkers provide two examples comparing the directional change of $PetCO_2$ during exercise and the association between $PetCO_2$ and ventilatory efficiency in estimating disease severity.

Heart Rate Response to Exercise

The rise in heart rate in response to initiation of exercise (i.e., chronotropic response) and the heart rate recovery following exercise are parameters reflecting the interaction between the autonomic nervous system and the cardiovascular system and can provide significant prognostic information. Blunted heart rate response to exercise has been strongly associated with sudden cardiac death and an abnormal heart rate recovery from exercise has been shown to be predictive of mortality (see below). The autonomic nervous system, comprised of the parasympathetic and sympathetic divisions, innervates and controls heart rate and force of contraction,

Figure 4: Likelihood of Pulmonary Vasculopathy Accounting for Exertional Dyspnea of Unknown Cause



$PetCO_2$ at AT as related to the V_E/VCO_2 at AT, showing the likelihood of pulmonary vasculopathy accounting for exertional dyspnea of unknown cause. The curve through the points is hyperbolic. The grading of likelihood of PPH in patients with PPH is based on comparisons with normal subjects. *From: Yasunobu, et al.*[56]

constriction and dilation of blood vessels, contraction and relaxation of smooth muscles in various organs, and glandular secretions. Certain afferent autonomic fibers control the baroreceptors and chemoreceptors in the carotid sinus and aortic arch and are important in the control of heart rate, blood pressure, and respiratory activity.

Stimulated by acetylcholine, the vagus nerve provides primary parasympathetic system innervation and acts to conserve energy by reducing heart rate and blood pressure. Vagal tone declines with age and is positively influenced by regular dynamic exercise. By contrast, the chemical transmitter affecting the sympathetic nerve endings is noradrenalin emanating from hormonal secretion from the stimulated adrenal medulla in situations of physical or psychological stress. The sympathetic system provides a response to hemodynamic or respiratory challenge by increasing heart rate, blood pressure and cardiac output. Autonomic balance is required to maintain normal heart and vascular function, with chronic activation of the sympathetic system (hyperadrenergic state) and/or

limitation of parasympathetic (vagal) tone increasing the risk of cardiovascular events.

Interested readers are directed to Freeman, *et al.*[70] for a comprehensive review of the interaction between the autonomic nervous system and cardiovascular function.

Chronotropic Response Index

The change in heart rate with exercise is initially linked to vagal withdrawal but is subsequently coupled to sympathetic stimulation and the ability of the heart to respond to increasing metabolic demand (e.g., responsiveness of β-adrenergic receptors in the sinoatrial node to catecholamines). Vagal withdrawal at the initiation of exercise typically results in a heart rate increase of 30-50 bpm, with further increases due to sympathetic activation. Additional factors may contribute, such as baroreceptor reflexes and venous return. Numerous studies have demonstrated that a blunted heart rate response to exercise (i.e., chronotropic incompetence) is associated with poorer prognosis (Table 3) and that β-blockade has minimal impact on prognostic power.[71] Autonomic imbalance in asymptomatic subjects may precede the symptoms of cardiovascular disease, helping to identify patients at risk for sudden cardiac death (Figure 5).[72,73] Clinically, it is generally true that a higher heart rate achieved during exercise is associated with better prognosis. Thus, the initial slope of change in heart rate, even with submaximal exercise, provides an important index of disease severity.

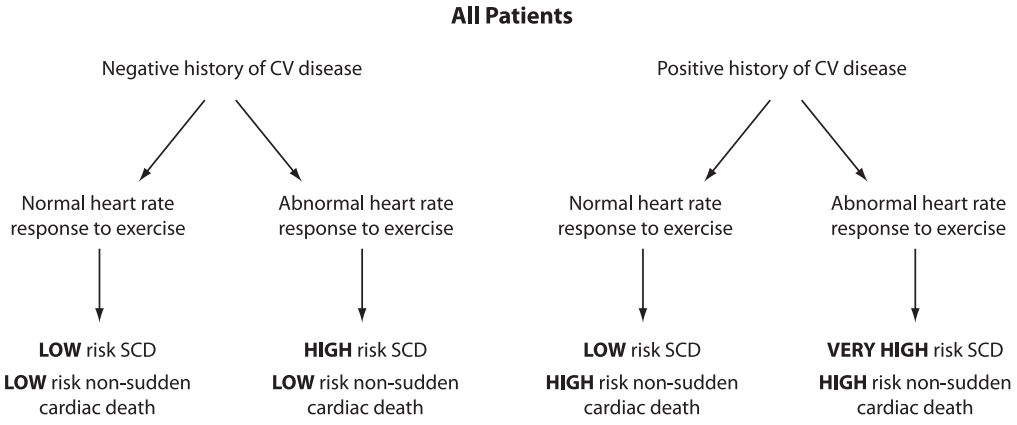
Heart Rate Recovery from Exercise

The decrease in heart rate occurring in the one to two minutes of recovery from dynamic exercise is associated with the reactivation of the parasympathetic system and deactivation of sympathetic stimulation. Initial recovery is dominated by vagal reactivation, with sympathetic withdrawal gaining importance later in recovery. The rate at which the heart rate recovers during the early post-exercise period is a powerful predictor of cardiovascular disease prognosis, with an abnormal rate of less than 12 bpm in 1 minute or 22 bpm in 2 minutes following exercise being associated with a significantly higher risk of death (Table 4) and hospitalization.[79] Rehabilitation

Table 3: Summary of Studies Relating Chronotropic Response to CV Disease Prognosis

Reference	Subjects/Diagnosis	Cut-off Value Defining Chronotropic Incompetence and Increased Risk
Lauer, *et al.*[74]	231/referred ECHO	<0.8
Lauer, *et al.*[75]	2,953/referred imaging	<0.8
Dresing, *et al.*[76]	384/referred angiography	<0.8
Robbins, *et al.*[77]	470/HF	≤0.51
Myers, *et al.*[71]	1,910/referred for stress test	<0.8
Elhendy, *et al.*[78]	3,221/referred for stress test	<0.8

Figure 5: Schematic Method for Stratifying CV Risk by Degree of Autonomic Imbalance and CV Status



Abbreviation: SCD, sudden cardiac death.
From: Freeman, et al.[70]

exercise training in a heart failure population has been shown to speed heart rate recovery,[80] and treatment with β-blocking agents to slow the response,[81] although prognostic value is maintained in patients treated with β-blockers[79,82,83] or Ca^{++}-channel blockers.[83]

Impaired endothelial function is associated with delayed heart rate recovery following exercise and may facilitate inflammatory processes that accelerate development of atherosclerotic plaque. In a study involving 12,712 middle-aged men, Jae and colleagues[81] determined the prevalence of carotid atherosclerosis was 1.5 times higher in the lowest quartile (<44 bpm in 2 minutes post-exercise) of heart rate recovery as compared to the highest (>61 bpm) quartile. When studying 547 healthy men, the same investigators further determined that heart rate recovery was inversely correlated with plasminogen activator inhibitor 1 (PAI-1) activity, tissue plasminogen activator (t-PA), and fibrinogen, factors shown to promote thrombus formation and increase risk of coronary heart disease and stroke events.[88] In this study population, men in the lowest quartile (≤14.7 bpm in 1 minute post-exercise) had significantly higher levels of PAI-1, t-PA and fibrinogen as compared to those in the highest quartile (≥37.4 bpm). Presence of other cardiovascular disease risk factors did not explain this association, although it has been determined that abnormal heart rate recovery is reflective of myocardial damage.[89]

Table 4: Summary of Studies Relating Heart Rate Recovery to CV Disease Prognosis

Reference	Subjects/Diagnosis	HRR (bpm) Cut-off Value of Increased Risk
Cole, *et al.*[84]	2,428/referred imaging	≤12
Nishime, *et al.*[85]	9,454/referred for stress test	≤12
Watanabe, *et al.*[86]	5,438/referred for ECHO	≤18
Shetler, *et al.*[82]	2,193 (all male)	<12- 1 min/≤22- 2 min
Vivenkananthan, *et al.*[83]	2,935/referred for CPX	≤12
Gera, *et al.*[87]	509 (male)/referred for MPI	≤12

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