THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardiopulmonary Exercise Testing
What Is its Value?

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ABSTRACT

Compared with traditional exercise tests, cardiopulmonary exercise testing (CPET) provides a thorough assessment of exercise integrative physiology involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems. Due to the prognostic ability of key variables, CPET applications in cardiology have grown impressively to include all forms of exercise intolerance, with a predominant focus on heart failure with reduced or with preserved ejection fraction. As impaired cardiac output and peripheral oxygen diffusion are the main determinants of the abnormal functional response in cardiac patients, invasive CPET has gained new popularity, especially for diagnosing early heart failure with preserved ejection fraction and exercise-induced pulmonary hypertension. The most impactful advance has recently come from the introduction of CPET combined with echocardiography or CPET imaging, which provides basic information regarding cardiac and valve morphology and function. This review highlights modern CPET use as a single or combined test that allows the pathophysiological bases of exercise limitation to be translated, quite easily, into clinical practice. (J Am Coll Cardiol 2017;70:1618–36) © 2017 by the American College of Cardiology Foundation.

In cardiopulmonary disorders, exercise intolerance is a major clinical feature from early stages, and becomes a source of symptoms and the reason for referral to a physician. Exercise limitation is one of the most disabling problems experienced by patients with heart failure (HF) (1). Its quantification may be approximated by several methods, but a thorough analysis of the organ systems and pathways involved in the impaired physiological response is obtained by exercise gas exchange analysis with cardiopulmonary exercise testing (CPET). This technique enables the clinician to scrutinize reasons for dyspnea and fatigue to precisely differentiate cardiac from pulmonary disorders, optimize the decision-making process and outcome prediction, and objectively determine targets for therapies (2). Furthermore, CPET has become a reproducible (3) and safe technique (4).

Despite this attractive evidence base and the clinical potential of CPET, the question put forth in the title of the present review (i.e., what is the value of CPET), is not trivial, and the definitive response requires mentioning a few historical notes and passages.

The idea of a CPET application in cardiology was introduced in the early 1980s by Weber et al. (5), whose work allowed the landmark classification of patients with HF with reduced ejection fraction (HFrEF) based on peak oxygen consumption (VO2), from A (peak VO2 > 20 ml ⋅ kg⁻¹ ⋅ min⁻¹) to D (peak VO2 < 10 ml ⋅ kg⁻¹ ⋅ min⁻¹) through B (peak VO2 < 15 ml ⋅ kg⁻¹ ⋅ min⁻¹) and C (peak VO2 < 15 and 10 ml ⋅ kg⁻¹ ⋅ min⁻¹).

A few years later, Mancini et al. (6), in their seminal 1991 paper, demonstrated that VO2 measured at peak exercise stratifies the risk of cardiovascular (CV) death at 1 year in ambulatory patients with advanced HF. These remarkable findings were subsequently
validated and reproduced by several laboratories (7,8). This solid evidence perhaps led to a quite paradoxical static vision of CPET applications for a long period (i.e., until the 2000s), with a single parametric approach focused just on advanced HF.

In the last 15 years, the utility of CPET has been increasingly recognized by both extending medical interest to the physiological bases of many variables that were previously under-recognized and by aligning evidence for a multivariable approach, including primarily abnormalities in ventilation and its control (1). In HF, the combined use of variables has led to the generation of algorithms (9) and risk scores (10–12) covering the entire set of HF stages. This process has been highly validated and supported by a significant number of official documents and statements definitively (1,2,13) entering exercise gas exchange variables as study endpoint in the assessment of the effects of emerging pharmacological therapies (14,15) and in interventional trials (16,17). Along with the main developments in HF, the role of routine CPET in cardiology has been extended to specific patient populations, including those with suspected ischemic heart disease (18), congenital heart defects (19), valve diseases (20), hypertrophic cardiomyopathy (21), suspected or confirmed pulmonary arterial hypertension (PAH) (22), and left-sided pulmonary hypertension (PH) (23).

In this paper, the modern key applications of CPET in CV diseases, with primary emphasis on HF, are discussed, starting from the principles that precipitate reduced exercise performance and impaired ventilation, and highlighting the most recent developments on combining exercise invasive hemodynamic and stress echocardiography with gas exchange evaluation. The large body of evidence on the established pathophysiological clinical and prognostic impact of CPET-derived variables will be emphasized, making a continuum of value from physiological bases to their translation into the practical applications. Accordingly, CPET is here proposed as a technique that may provide significant and synergistic advancements in the process of precision medicine and phenotyping.

GAS EXCHANGE ANALYSES AND THE PRINCIPAL BASES FOR EXERCISE LIMITATION IN HF

OXYGEN TRANSPORT AND USE. The body under physical stress behaves as a perfect machine that integrates and harmonizes the functional responses of multiple organs and pathways. In this process, the delivery of oxygen \( \text{O}_2 \) to mitochondria is essential to perform at aerobic capacity (24). Optimal \( \text{O}_2 \) delivery depends on a set of elegant biological interactions between the functional components of the \( \text{O}_2 \) transport chain, which requires oxygenation of the blood in the lung (alveolar diffusion), normal \( \text{O}_2 \)-carrying capacity of the blood by adequate cardiac output (CO), yielding to its redistribution to working muscles (delivery or convection) and adequate \( \text{O}_2 \) release, diffusion from capillaries to cells, and tissue extraction from the blood (Central Illustration).

HF represents the typical condition where most of these pathways exhibit a maladaptive response, impeding attainment of maximal \( \text{VO}_2 \) because of the reduction in muscle \( \text{O}_2 \) supply simultaneous with increasing demands for \( \text{O}_2 \). Maximal performance is therefore defined by \( \text{VO}_2 \) at peak exercise, conventionally measured as the \( \text{VO}_2 \) averaged over a 20- to 30-s period at maximal effort, pending attainment of a respiratory exchange ratio (RER) >1.15 (1).

Measuring peak \( \text{VO}_2 \) and, especially, the percentage predicted, normalized to age-, sex-, and weight-based normative values, is the gold standard to objectively assess functional limitations in cardiac patients (1).

What are the major pathophysiological reasons for a low peak \( \text{VO}_2 \) in cardiac patients? These can be described by analyzing the framework of the Fick principle (i.e., \( \text{VO}_2 = \text{CO} \times [\text{CaO}_2 - \text{CvO}_2] \), where \( \text{CO} \) is cardiac output \( \text{[stroke volume} \times \text{heart rate]} \), \( \text{CaO}_2 \) is arterial oxygen content, \( \text{CvO}_2 \) is venous oxygen content, and \( [\text{CaO}_2 - \text{CvO}_2] \) is the arteriovenous \([a-v]\) difference in \( \text{O}_2 \).

On the basis of this equation, delivery or convection and extraction are the 2 physiological processes that convey \( \text{O}_2 \) use through cellular pathways. \( \text{O}_2 \) delivery is not only described by \( \text{CO} \) distribution, but is also the \( \text{O}_2 \) content and the mechanisms involved in \( \text{O}_2 \) dissociation from hemoglobin (Hb). \( \text{O}_2 \) content is 1.34 (which corresponds to the ml of \( \text{O}_2 \) carried by each gram of Hb) \( \times \text{O}_2 \) saturation \( \times \text{Hb} \) concentration.

Extraction is the net result of the chain of \( \text{O}_2 \) transport and use, and depends on the ability of \( \text{O}_2 \) to diffuse from capillaries to cells and on mitochondria function.

Normal, healthy adults can increase \( \text{VO}_2 \) up to 6-fold during exercise. The relative contribution of Fick’s equation determinants to \( \text{VO}_2 \) changes is approximately 1.2-, 2.5-, and 2.5-fold for stroke volume, heart rate, and \( \text{CaO}_2 - \text{CvO}_2 \) respectively.

Landmark pioneering studies (5,25) performed in patients with HFrEF first demonstrated that low peak
VO2 is tightly related to a limited CO increase and quite reasonably preserved peripheral O2 use. When data were stratified according to functional impairment, even Weber class D patients, despite having no increase in CO, were still able to maintain their CaO2/CvO2 difference within the lower-normal range (12 to 16 ml/dl). The underlying pathophysiology needs, of course, to be complemented with the concept that along with reduced CO, several patients with HF may have anemia and a lower O2 concentration, thus further impairing O2 delivery and challenging the a-v O2 difference, irrespective of the ability to efficiently extract O2 (1).

Intriguingly, observations have suggested that iron deficiency in nonanemic patients with HF is responsible for worse exercise performance and exercise gas exchange phenotypes (26). These observations have been confirmed over time by several studies proving that in HFrEF, the capability to extract O2 remains preserved thanks to an “optimized” peripheral blood flow redistribution and high mitochondrial activity (27–29), and that the cause of an inadequate increase in CO is predominant, even though likely not exclusive. An additional set of remarkable works aimed at assessing how much an impaired O2 diffusion may be involved in the low aerobic performance (30), on the basis of Fick’s law of diffusion: VO2 = D × K × (PaO2 – PvO2), where D is equal to the O2 diffusive capacity (D), K is a constant, which is the ratio between arterial and venous O2 partial pressure (which is approximately 2), and (PaO2 – PvO2) is the capillary mitochondrial difference, assuming an intracellular partial pressure of O2 close to 0.

The relation of delivery or convection (Fick principle) and diffusion (Fick’s law) can be represented on a diagram relating VO2 and PvO2, which are common to both equations (Figure 1A).
As proposed by Wagner (30), the diagram relates VO₂ to the muscle-venous PO₂ from rest to peak exercise, with the lines of convection and diffusion crossing the axes and intercepts, and whose slope varies according to the muscle-venous PO₂, with an upper and leftward shift representing the best diffusion, whereas the point of intersection between the 2 lines represents the VO₂ max (i.e., the resultant of convection and diffusion).

In a set of elegant, controlled experiments performed in HFrEF (28), the relative impairment of convection versus diffusion was assessed by testing the same patients with 2 different exercise modalities, incremental test at maximum (A and B) versus local isolated knee extension (C and D) (28). (C) VO₂ and PVo₂ relationship in a group of patients with HFrEF, HFpEF, and controls, showing a limitation in either diffusion and convection (33). CaO₂ = arterial oxygen content; CvO₂ = venous oxygen content; D = the O₂ diffusive capacity; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; K = a constant (the ratio between arterial and venous O₂ partial pressure, which is approximately 2); O₂ = oxygen; Po₂ = oxygen pressure; PVo₂ = venous oxygen pressure; Q = cardiac output; VO₂ = peak oxygen consumption.

FIGURE 1 The Relationship Between O₂ Diffusion and Convection

(A) Scheme of the 2 relationships of delivery or convection (Fick principle) and diffusion (Fick’s law) in the diagram relating VO₂ and in venous O₂ pressure, which are common to both equations (30). (B) Relative impairment of convection versus diffusion by 2 different exercise modalities, incremental test at maximum (A and B) versus local isolated knee extension (C and D) (28). (C) VO₂ and PVo₂ relationship in a group of patients with HFrEF, HFpEF, and controls, showing a limitation in either diffusion and convection (33). CaO₂ = arterial oxygen content; CvO₂ = venous oxygen content; D = the O₂ diffusive capacity; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; K = a constant (the ratio between arterial and venous O₂ partial pressure, which is approximately 2); O₂ = oxygen; Po₂ = oxygen pressure; PVo₂ = venous oxygen pressure; Q = cardiac output; VO₂ = peak oxygen consumption.

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In a set of elegant, controlled experiments performed in HFrEF (28), the relative impairment of convection versus diffusion was assessed by testing the same patients with 2 different exercise modalities: an incremental test at maximal exercise (need for CO increase, central challenge) versus a local isolated knee extension (need for increase in O₂ extraction, peripheral challenge) (Figure 1B). These experiments were paralleled by the analysis of muscle fiber type, mitochondria volume, and the capillary-to-fiber ratio.

Interestingly, skeletal muscle and mitochondria contributed minimally to O₂ limitation, in agreement with the concept that mitochondrial oxidative capacity largely exceeds O₂ delivery at peak VO₂ (31). Rather, patients with HF, compared with controls, exhibited an attenuation of convective and diffusive components of O₂ transport, both during maximal exercise and knee extension.

How do these concepts adapt to HF with preserved ejection fraction (HFpEF) syndrome? Whereas some pathophysiology overlaps between the 2 HF phenotypes, there is more uncertainty and unequivocal definition on the O₂ transport/utilization-limiting steps involved in the functional response of patients with HFpEF. These patients are elderly and anemic in a high rate of cases, and exhibit a decreased total circulating red blood cell volume in 9 of 10 patients affected by Hb-based anemia, thus presenting with impaired blood O₂ carrying capacity (32). In addition, they may show a defect in O₂ diffusion and lower (a-v) O₂ (Figure 1C) (33).

COMPLEMENTARY CPET-DERIVED MEASURES OF AEROBIC EFFICIENCY. Although peak VO₂ describes the net limitation in exercise capacity, an even more comprehensive idea of aerobic efficiency is obtained by measuring the VO₂ at the first ventilatory threshold (VT). VO₂ at first VT reflects the metabolic condition above which blood lactate and pH start to increase and decrease, respectively, generating isocapnic compensatory acidic buffering by bicarbonate (HCO₃⁻). There are 3 CPET-derived methods for detecting VO₂ at the first VT: the V-slope (i.e., the point at which the incremental volume of carbon dioxide [CO₂] released [VCO₂] becomes higher, as compared with VO₂, due to the additional CO₂ produced by lactic acid buffering); the end-tidal CO₂ (PETCO₂) versus end-tidal O₂ (PETO₂) method (when a divergent kinetic point of these variables occurs with PETCO₂ progressively increasing and the PETO₂ slightly decreasing) and the minute ventilation (VE)/VO₂ versus VE/VCO₂ ratio change in
pattern of increase (identifying the point of continuous increase in VE/VO₂ and stable VE/VCO₂ kinetics). The lack of VO₂ at the first VT determination by any of these methods occurs in around 10% of patients with HF and carries a strong independent prognostic role (34). Measuring gas exchange during submaximal exercise response to constant workload is the gold standard for studying the early VO₂ kinetic time constant (tau) during exercise or recovery of exercise O₂ kinetics, which corresponds to 63% of the ΔVO₂ from rest to steady state (exercise) or vice versa (recovery) during a constant workload.

Tau provides additional objective information on the mechanisms that control the ability to adapt to and recover from exercise indicative of daily life activity (35). Along with an impaired tau, VO₂ may typically fail to linearly increase relative to energy demands as the work rate (WR) is increased (VO₂/WR), resulting in delayed post-exercise recovery from a maximal test. During a maximal test, VO₂/WR accurately reflects the extent of aerobically regenerated adenosine triphosphate. In physiological conditions and nonobese people, the VO₂/WR linearity corresponds to a 10 ml/min increase per watt, independently of the load imposed and slightly changing according to exercise duration (Figure 2A).

These assumptions, however, are not true in CV disorders, such as HF, and the pattern of VO₂ increase may change in a shallow downward shift (Figure 2B) or by VO₂ flattening at a given WR (Figure 2C). There is then an alarming, rare condition with VO₂ downsloping associated with an acute drop in cardiac output and blood pressure. VO₂ = peak oxygen consumption; WR = work rate.

The last 2 patterns of VO₂ generally match with a similar O₂ pulse, which is the ratio of VO₂ to heart rate and reflects the amount of O₂ extracted per heart beat. The O₂ pulse provides an estimate of left ventricular (LV) stroke-volume changes during exercise, assuming that C(a-v)O₂ is maximal and no anemia or hypoxia is present. As the relative contribution of stroke volume to CO is predominant during the initial and intermediate phases of exercise, the O₂ pulse has a typical hyperbolic profile, with a rapid rise during the initial stages of exercise and a slow approach to an asymptotic value at the end of exercise. Thus, once VO₂/WR changes in linearity, a flattening or even a downward displacement of O₂ pulse kinetics during progressive CPET would very likely reflect a
cardiogenic, rather than a peripheral vascular perfusion/extraction, limitation to exercise performance. Finally, the addition of systolic blood pressure to the peak VO2, as circulatory power, has been proposed as having the potential to better investigate the circulatory impairment (36).

VENTILATORY EFFICIENCY AND LUNG MECHANICS. Cardiac patients may exhibit a lung mechanical-related mechanism of exercise limitation, which is tightly related to restrictive physiology due to congestion and physical interaction between the heart and the lung (37). However, detection of lung mechanical dysfunction is often overlooked because patients with HF often display a normal breathing reserve, which is described by the relationship between exercise VE and maximal breathing capacity, as estimated by resting maximal voluntary ventilation. Values <15% suggest a ventilatory limitation, and may help to discriminate between patients with HF and those with comorbid chronic obstructive pulmonary disease (COPD) (38).

The impaired breathing reserve would, however, be insensitive to mechanical ventilatory constraints caused by differences in lung mechanics during exercise compared to the maximal voluntary ventilation maneuver. For this reason, the most recent consensus documents have introduced the use of flow-volume loops as standard for the assessment of mechanical VE limitation in cardiac versus lung disorders (2). Indeed, flow-volume loops supplement basic breathing mechanics information by identification of expiratory airflow limitation and changes in operational lung volumes during exercise.

Assessment of VE efficiency during CPET perhaps provides the most relevant clues for addressing the pathophysiological changes behind the impaired exercise performance in HFrEF and HFpEF, especially when associated with PH and right ventricular (RV) dysfunction (39,40). Similar reasoning may, in part, be applied to cases of post-embolic or idiopathic PAH.

An inefficient VE typically translates into an abnormal rate of increase in the slope of VE increase versus VCO2 production. This relationship shows a near-linear increasing pattern that is determined by 3 factors: the amount of CO2 produced; the physiological dead space/tidal volume ratio (VD/VT); and the arterial carbon dioxide partial pressure (Paco2). This relationship can be explained using the modified alveolar equation:

\[
    \text{VE} = 86.3 \times \frac{V_{\text{CO2}}}{(\text{Paco2} \times (1 - V_D/V_T))}
\]

For low and moderate intensities of work, the VE response is tightly regulated by the Paco2. At higher work intensities, VE is affected by the increased amount of VT over VD and the development of lactic acidosis and proton (H+) production from the prevailing anaerobic metabolism, which further increases CO2 release and the consequent amount of VE. In HF, 3 different orders of mechanisms mediate an impaired VE requirement for a given CO2 production: increased waste ventilation (41,42); early occurrence of decompensated acidosis (41,43); and abnormal chemoreflex and/or metaboreflex control (44). Recent findings obtained in HFpEF document a primary role of increased VD/VT in causing a steep VE/VCO2 slope (45). In cases of a comorbid condition with COPD or COPD in isolation, high VD/VT may prevail as a functional gas exchange abnormality sustaining dyspnea sensation and hyperpnea (46).

The oxygen-uptake efficiency slope (OUES) is an underused variable that reflects the global (pulmonary, CV, and skeletal muscle) functional impairment by combining VO2 and VE/VCO2 slope. OUES is calculated on the logarithmic transformation of VE data in liters/min (plotted on the x-axis), creating a linear relationship with VO2 (plotted on the y-axis, where VO2 = log10 [VE + b]). Given the tight linear relationship the OUES creates between VE and VO2 throughout a progressive exercise test (47), this calculation requires only submaximal effort.

Finally, an additional VE pattern at CPET evaluation, which is typically unmasked by gas exchange analysis, is an exercise oscillatory ventilatory (EOV) pattern (Figure 3) and consists of a cyclic fluctuation of VE and expired gas kinetics of variable amplitude, frequency, and duration detectable in up to 30% of symptomatic patients with HF (48). The source of this ventilatory abnormality is still controversial, but its ominous clinical and prognostic significance is clear (49,50). At variance with PAH, this pattern seems typical of HF and pulmonary interstitial congestion, and a delayed circulatory transit time may explain the observed differences (51).

APPLICATIONS OF CPET IN CLINICAL PRACTICE

EVIDENCE IN PREVENTIVE MEDICINE AND REHABILITATION PROGRAMS. Application of CPET to primary and secondary prevention is challenging. Interestingly, a role for CPET-derived data in detecting abnormal gas exchange pattern phenotypes has been just recently explored in the general population at CV risk. An example is the European Exercise (EURO-EX) population-based trial, whose preliminary data have highlighted some cases of EOV, typically occurring in the phenotype of elderly diabetic women (52).

Overall, despite a wealth of persuasive evidence and numerous statements supporting the utility of
CPET in prevention and in early HF stages, practitioners have not generally adopted a portfolio of variables that provides a 3-dimensional view of cardiorespiratory fitness with diagnostic and prognostic applicability, and an effective means to evaluate therapeutic benefits.

In the realm of patient care, exercise testing without the simultaneous collection of expired gases has seemingly taken on a static role, with the singular (but not exclusive) purpose of evaluating signs and symptoms of coronary insufficiency (53). However, despite observations pointing out the high sensitivity and specificity of gas exchange analysis in detecting suspected myocardial ischemia (53,54), few of them recognize a CPET role.

Implementation of rehabilitation and exercise training (ET) programs is a Class I (55) to IIa (56) guideline recommendation. In this context, implementation
of CPET is 3-fold: 1) to plan correct exercise intensity level or domain; 2) to assess benefits of exercise prescription by monitoring gas exchange variables and their related phenotypes; and 3) to identify subjects who, despite adherence to the program, are non- or poor responders to this multilevel intervention.

Although guidelines recommend the application of objective exercise prescriptions using CPET data (57), it is commonplace for programs without CPET capabilities or with limited resources to establish exercise intensity on the basis of resting heart rate (e.g., exercising heart rate threshold set 20 or 30 beats/min above the resting heart rate). This simple method has been criticized and demonstrated to be inadequate by many. For example, Reed et al. (58) reported that only 26% and 38% of participants were exercising at the recommended exercise intensity of 40% to 60% of heart rate reserve (confirmed by CPET) when using resting heart rate + 20 and 30 beats/min, respectively. Patients exercising at 30 beats/min or above their resting heart rates experienced significantly greater increases in 6-min walk distances compared with patients exercising at 20 to 29 beats/min above resting heart rate, suggesting that the implementation of CPET as a standard tool in cardiac rehabilitation programs can really help to optimize health-related outcomes.

Accordingly, the recent joint European Association for Cardiovascular Prevention & Rehabilitation (EACPR)/American Association of Cardiovascular and Pulmonary Rehabilitation Statement provided directions on the identification of ET intensity domains by using constant WR exercise tests, looking at the different kinetic responses to \( V_{O2} \) (57), which, although it may be impractical in most cases, remains the most accurate physiology-based approach. Briefly, \( V_{O2} \) kinetics during a constant WR exercise reflect 3 phases of adaptation of the organ systems and factors involved in the alveolar-to-cell \( O_2 \) coupling. The 3 phases are identified as: phase I, or cardiodynamic, during which the increase in \( V_{O2} \) is mediated by the immediate increase in \( CO \) and pulmonary blood flow at the start of exercise; phase II, or cell respiration, reflecting the decreased \( O_2 \) content (muscle extraction) and increased venous \( CO_2 \) content secondary to increased cell respiration, as well as a further increase in \( CO_2 \); and phase III, or the eventual steady-state phase, during which an equilibrium is reached between \( O_2 \) extraction and the \( CO_2 \) production rate. If the WR is above the subject’s first \( V_T \), the rate of increase during phase III is not steady and correlates tightly with the magnitude of lactate increase.

This background applies and allows for the precise identification of 4 exercise training domains whose intensity is based on the physiology of \( O_2 \) uptake kinetics: light to moderate; moderate to high; high to severe; and severe to extreme. The light-to-moderate- and moderate-to-high-intensity programs are performed by continuous exercise, a condition that is not sustainable for high-to-severe and severe-to-extreme protocols, requiring an interval exercise approach. Intensity domains of light to moderate encompass the corresponding WR that engenders a \( V_{O2} \) steady-state value below the corresponding first \( V_T \). During this constant workload range and in this domain, a \( V_{O2} \) steady state is attained relatively rapidly following the onset of exercise, and lactate is not produced. For this reason, exercise can be very well tolerated and is generally sustainable for long periods of time (30 to 40 min) with only a mild sense of fatigue and breathlessness. The moderate-to-high-intensity domain corresponds to workloads between the first and second \( V_T \)s.

An improvement in functional capacity is the most immediate and objective result of an effective ET program. Although functional capacity is governed by an integrated response of multiple organ systems that are wholly or partly involved in this response, benefits of ET interventions are generally quantified as changes in \( V_{O2} \). The physiological background behind exercise capacity response and the progressive familiarization of the cardiac rehabilitation personnel with the gas exchange analysis technique points, however, to a step forward that is a more in-depth analysis and comprehensive interpretation of exercise intervention trials. Indeed, attention to the determinants of exercise improvement that may add to peak \( V_{O2} \), and potentially result in even more remarkable demonstration of efficacy, seems quite timely.

One example of this reasoning is the unexplored, but perhaps intriguing, question of how much ET may improve \( V_{O2} \) kinetics (\( tau \) and \( V_{O2}/WR \) linearity), rather than peak \( V_{O2} \). Specifically, looking at favorable modifications that ET may induce in patterns of \( V_{O2}/WR \) (i.e., shallow, typical of deconditioned cardiac patients, flattening, or downsloping associated with acute drop in blood pressure and \( CO \)) (Figure 2). Thus, an analysis of the effects of different exercise training programs may be of value when considering the potential to modify these abnormal patterns, even when changes in peak \( V_{O2} \) per se are not remarkable.

**DIAGNOSTIC ROLE OF CPET IN HF.** As the severity of CV disease advances, the role of CPET in the diagnostic setting of HF is not completely recognized. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of HF highlight the subjective nature of the ACC Foundation/AHA stages of HF and the New York...
Heart Association functional classification system. These are primarily based on patient interviews pertaining to the “severity and triggers of dyspnea and fatigue, presence of chest pain, exercise capacity as well as physical and sexual activity” (59), and are then followed by objective procedures for characterization of LV structure/function and evaluation of diagnostic blood markers. Despite evidence of CPET as a strong predictor of future HF development, its consideration as a primary diagnostic tool is cautioned, mainly due to the manifestations common to other chronic conditions (e.g., PAH, congenital heart defects, and interstitial lung disease) (60). However, it seems more appropriate to use CPET variables to guide the diagnosis of secondary pathophysiological consequences of HF, irrespective of etiology. Assessment of exercise ventilatory patterns is particularly attractive in identifying left-sided PH due to its physiological link with ventilation-perfusion matching. Identification of left-sided PH is particularly important, given that it is prevalent in roughly 30% to 50% patients with overt HF and carries a poor prognosis (61). The VE/VCO₂ slope, the Pp,CO₂, and the presence of EOV hold a high level of prognostic utility (9). In a study of parallel evaluation of pulmonary pressure, a VE/VCO₂ slope of <36 was found to be the strongest predictor (odds ratio [OR]: 12.1; p < 0.001) of a pulmonary artery pressure (PAP) ≥40 mm Hg, followed by peak exercise Pp,CO₂ (<36 mm Hg; OR: 3.8; p < 0.001), and presence of EOV (OR: 3.2; p < 0.001) in patients with HFrEF. More compelling was the greater predictive utility when all measures were considered together (OR: 16.7; p < 0.001) (9). There have been significantly fewer studies evaluating the relationship between disease severity and CPET variables in patients with HFrEF, although most recent observations have shed new light on VE efficiency (45,62). Considering that the VE/VCO₂ relationship possesses prognostic value at submaximal levels of effort, this observation increases the feasibility of implementing CPET for prognostic purposes, particularly in an elderly population that is likely not accustomed to exercise or may be hesitant to provide maximal effort.

Collectively, the aforementioned CPET indexes should not be thought of as markers to identify specific pathophysiological conditions associated with HF, but rather for use of objective CPET data to help guide characterization of the HF disease state, which is staged, in part, by subjective determinants. Interpreting CPET outcomes in this manner helps confirming HF and identifying secondary issues and may provide a clear objective in deciding the best course of patient treatment.

**MONITORING THERAPEUTIC EFFICACY WITH CPET.** The ACC/AHA stages of HF provide a comprehensive outline of patient characteristics that define the stage of HF, as well as respective therapies and their associated goals. Many, if not all, therapeutic goals aim to mitigate HF-related symptoms (e.g., dyspnea at rest and/or upon exertion, fatigue), reduce hospital readmission rates, and improve survival. The acute efficacy of a number of therapeutic regimens are typically verified by standard follow-up visits that assess the patient’s resting blood pressure, weight, blood markers, and patient-reported changes in symptom severity/presence. This system of patient management is generally considered to be adequate in most clinical settings, and therefore leaves many practitioners with a lack of clarity as to the added value of CPET. However, an important consideration is that follow-up visit examinations are done at rest, thus providing no information on symptoms and on hemodynamic measures during physical exertion (when symptoms typically become evident). Furthermore, the main aim of any intervention is to improve prognosis, limit morbidity, and increase the quantity of years a patient is able to live a higher quality of life, all of which are markers associated with high peak VO₂ values and lower VE/VCO₂ slopes.

Furthermore, the current ACC/AHA guidelines recognize the therapeutic benefits of various pharmacological interventions to improve cardiorespiratory fitness. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) significantly improve peak VO₂ on their own and have led to greater enhancements when taken together (63). These improvements also translate to reductions in the VE/VCO₂ slope with ACE inhibitor therapy; however, there are conflicting outcomes with ARB therapy (64). The effects of β-blockers on exercise performance have been extensively studied, and CPET application has garnered relevant information, in terms of influence of different types of β-blockers on gas exchange (65). Moreover, decreases in PAP, with concomitant decreases in the VE/VCO₂ slope (66) and some reversal of EOV (67), have been demonstrated with sildenafil therapy in patients with HFrEF. By contrast, CPET outcomes in response to ACE inhibitor, ARB, or sildenafil therapy in patients with HFP EF have not been as favorable (68–70). The same seems to be true for ivabradine (71). Given the associated improvements in key prognostic CPET variables with the initiation of pharmacological therapy in certain patient populations, it may be interesting to explore the feasibility of titrating medications based on CPET “responders” or “nonresponders” in future clinical trials. Peak VO₂ is
an endpoint in trials of cardiac resynchronization therapy, LV assist device implantation, and valve surgical or percutaneous treatments, even though CPET-derived variables are not standardized criteria for these indications (2).

The frequency at which a patient should perform CPET evaluation to monitor the effectiveness of interventions is not well-defined. Certainly, in clinically stable patients, CPET should be considered at 2- to 4-year intervals, whereas in patients with signs and symptoms, the test should occur in a time frame that has been reported to cause significant improvements in the variable of interest (2).

**PROGNOSTIC UTILITY OF CPET.** Among the extensive list of criteria for determining candidates for transplantation, CPET variables are recognized to help refine the selection process. At time of Mancini et al.’s investigation (6), demonstrating a higher 1-year survival rate in HF patients with peak VO2 $>$14 ml · kg$^{-1}$ · min$^{-1}$ compared with patients with peak VO2 $<$14 ml · kg$^{-1}$ · min$^{-1}$, and a similar 1-year survival rate of transplanted patients compared with those above the 14 ml · kg$^{-1}$ · min$^{-1}$ threshold, β-blocker therapy was not part of routine clinical management of patients with HF, as it became in the early 2000s. Despite the marginal effects of β-blockers on peak VO2, survival rates were significantly improved, and therefore prompted reconsideration of Mancini et al.’s proposed cutoff for transplantation. Consequently, a threshold of 10 ml · kg$^{-1}$ · min$^{-1}$ was proposed to be the optimal prognostic threshold for transplantation consideration for β-blocked patients with HFrEF (72). In addition to these landmark studies, a continuing wealth of evidence has fortified the prognostic strength of peak VO2, so much so that the International Society for Heart Lung Transplantation provides a Class I, Level of Evidence: B recommendation for inclusion of maximal CPET (RER $>$ 1.05) to guide transplant listing, with peak VO2 $<$14 ml · kg$^{-1}$ · min$^{-1}$ (Class I, Level of Evidence: B) in the absence of a β-blocker and a peak VO2 $<$12 ml · kg$^{-1}$ · min$^{-1}$ (Class I, Level of Evidence: B) in its presence (73). However, an equally impressive and convincing body of published reports identifies ventilatory efficiency (e.g., the VE/VCO2 slope and EOV) as a more powerful prognostic index than peak VO2 (74). Despite the growing body of evidence highlighting the greater prognostic utility of the VE/VCO2 slope, current ACC/AHA guidelines recognize peak VO2 as the sole CPET outcome for transplant consideration. Similarly, the International Society for Heart Lung Transplantation recommended that the VE/VCO2 slope be reserved (slope $>$35; Class IIb, Level of Evidence: C) for CPET performances with a submaximal effort (RER $<$1.05). Both sets of recommendations are also similar in that they recommend the use of one of the CPET parameters, even though there is strong evidence for the increased discriminatory power of the VE/VCO2 slope and other variables considered together (2,10,75).

**Multiparametric CPET data table.** It is evident that across the years, there has been a surge of CPET variables, making it difficult for clinicians to identify and interpret measures of interest. To ameliorate this concern, early efforts by Wasserman (24) (Figure 3) provided 9 visually friendly panel plots incorporating the CPET variables of interest in a single-page report. A potential disadvantage of this method, however, was the lack of guidance or references to variable thresholds pertinent to CPET clinical application. Accordingly, Arena et al. (76) developed an early iteration of the figures by proposing color-coded interpretive tables applied to different diseases. An example is shown in Table 1 (for HF), where the list of CPET variables (the VE/VCO2 slope, peak VO2, EOV, resting P$a$CO2) was separated into primary (e.g., the VE/VCO2 slope and peak VO2) and secondary (e.g., EOV and resting P$a$CO2) CPET measures of interest, along with respective categories of risk. Furthermore, instructions were provided to help with guiding the interpretation of multivariable CPET results. This approach took valuable initial steps toward condensing a large amount of CPET-related information into a single table that could be used by clinicians in patient management. Many modifications were made and subsequently integrated and presented in the 2012 EACPR/AHA Scientific Statement (1). The color-coded tables now provide striking visual clues to facilitate the interpretation of CPET. Normal responses are identified in green, whereas intensifying abnormalities are highlighted in yellow, orange, and red. Expanded clinical recommendations for the overall severity of the patient’s condition are provided, based on the frequency of color occurrence in the table. Of note, the decision to include the respective CPET variables in the outcome tables was based on the available evidence, summarized in Table 2, for the predictive application of each measure independently, but more importantly, collectively across populations. Moreover, these tables were developed with the objective of being applicable and relevant to the qualifications for CPET (e.g., prognosis, therapeutic efficacy, and diagnosis) in order to promote their use. As such, the AHA, and EACPR have made an effort to increase the visibility of a multivariable paradigm that implements visual clues to trigger appropriate actions. Because no studies have yet tested the feasibility of this model’s
implementation in a clinical setting, as well as its effect on patient management, future studies are encouraged to do so.

**REAPPRAISAL OF INVASIVE CPET**

Invasive CPET (iCPET) allows better characterization of the hemodynamic reasons for exercise limitations, precisely dissecting central and peripheral mechanisms. As this approach has the potential to accurately phenotype cardiopulmonary disorders, it has been reappraised since its initial use in early 1980s as a routine approach in more laboratories (77). Measuring pulmonary hemodynamics, LV filling pressures, Fick CO, and a-v difference in O2, become essential in cases of unexplained exercise-induced dyspnea (78) and in the evaluation of exercise-induced PH of either idiopathic or secondary origin (79).

A recent analysis documented that iCPET allows to considerably shorten the time lag from manifestations of unexplained exercise-induced dyspnea to an organ-specific diagnosis. Conditions that can be ultimately diagnosed with iCPET are HFP EF, mitochondrial myopathy, and confirmation of deconditioning (78).

Pulmonary hemodynamic measurements during exercise, especially of PAP and pulmonary arterial wedge pressure (PAWP), have incremental prognostic value compared with evaluation at rest (79).

Borlaug et al. (80) first reported the potential to diagnose HFP EF in symptomatic euvolemic patients with normal levels of B-type natriuretic peptide and without clear signs and symptoms of HF at rest. In one-half of cases, looking at the PAWP and end-diastolic LV pressure increase, the observed increase in PAWP during exercise was diagnostic for HFP EF.

### TABLE 1  Clinical Stratification for Patients With HF

<table>
<thead>
<tr>
<th><strong>Primary CPET Variables</strong></th>
<th><strong>Standard ET Variables</strong></th>
<th><strong>Patient Reason for Test Termination</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary CPET Variables</strong></td>
<td><strong>Secondary CPET Variables</strong></td>
<td><strong>Reasons for Test Termination</strong></td>
</tr>
<tr>
<td>VE/VCO2 30</td>
<td>Peak VO2</td>
<td>EOV</td>
</tr>
<tr>
<td>Ventilatory Class I</td>
<td>Ventilatory Class A</td>
<td>Not Present</td>
</tr>
<tr>
<td>Ventilatory Class II</td>
<td>Ventilatory Class B</td>
<td>Present</td>
</tr>
<tr>
<td>Ventilatory Class III</td>
<td>Ventilatory Class C</td>
<td>Not Present</td>
</tr>
<tr>
<td>Ventilatory Class IV</td>
<td>Ventilatory Class D</td>
<td>Present</td>
</tr>
<tr>
<td>VE/VCO2 &gt;45</td>
<td>Peak VO2</td>
<td>EOV</td>
</tr>
<tr>
<td>Ventilatory Class V</td>
<td>Ventilatory Class E</td>
<td>Not Present</td>
</tr>
</tbody>
</table>

**Hemodynamics**

- Rise in systolic BP during ET
- Flat systolic BP response during ET
- Drop in systolic BP during ET

**ECG**

- No sustained arrhythmias, ectopic foci, and/or ST-segment changes during ET and/or in recovery
- Altered rhythm, ectopic foci, and/or ST-segment changes during ET and/or in recovery: did not lead to test termination
- Altered rhythm, ectopic foci, and/or ST-segment changes during ET and/or in recovery: led to test termination

**HRR**

- >12 beats at 1 min recovery
- <=12 beats at 1 min recovery

**Interpretation**

- All variables in green: excellent prognosis in the next 1–4 years (≥90% event-free)
- Maintain medical management and retest in 4 years
- All CPET variables in red: risk for major adverse event extremely high in next 1–4 years (>50%)
- Greater number of CPET and standard ET variables in red/yellow/orange indicative of progressively worse prognosis.
- All CPET variables in red: risk for major adverse event extremely high in next 1–4 years (>50%)
- Greater number of CPET and standard ET variables in red/yellow/orange indicative of increasing HF disease severity.
- All CPET variables in red: risk for major adverse event extremely high in next 1–4 years (>50%)
- Greater number of CPET and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options.

Example of a color-coded table for clinical stratification that applies to patients with either HFrEF or HFP EF. A list of evidence-based CPET variables (the VE/VCO2 slope, peak VO2, EOV, resting P50CO2) are separated into primary (e.g., the VE/VCO2 slope and peak VO2) and secondary (e.g., EOV and resting P50CO2) measures of interest, along with respective color-code categorizations of risk (78).

BP = blood pressure; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; EOV = exercise oscillatory ventilation; ET = exercise testing; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFP EF = heart failure with preserved ejection fraction; HRR = heart rate recovery; P50CO2 = partial pressure of end-tidal carbon dioxide; PH = pulmonary hypertension; VE/VCO2 = minute ventilation/carbon dioxide production; VO2 = oxygen consumption.
These data were reproduced by others, showing that in patients with normal biventricular function, an increased mean PCWP >20 mm Hg at peak exercise, in the absence of elevations in pulmonary vascular resistance, suggests exercise-induced HFP EF (81). Patients with early stages of PAH and still normal cardiopulmonary hemodynamics at rest demonstrate increased mean PAP >30 mm Hg and pulmonary vascular resistance >80 to 120 dyne s cm⁻² on functional CPET (82).

Exertional intolerance may be associated with pre-load–dependent limitations to stroke volume and CO (83). In this patient population, failure to augment right atrial pressure on exercise is observed despite abnormally decreased CO. Finally, impaired systemic vascular resistance indicates left-to-right shunting or a compromised CO/PC ratio (79). A mean PAP/CO provides robust indication of abnormalities in RV to PA coupling during exercise by plotting mean PAP versus CO (84). Accurate assessment of the pressure-flow relationship during exercise by plotting mean PAP versus CO provides robust indication of abnormalities in RV to PA coupling (79). The relationship between CO and ventricular pressure is robustly supported by the assumption that the left ventricle does not contribute to pulmonary pressure (39). These data were reproduced by others, showing that in patients with normal biventricular function, an increased mean PCWP >20 mm Hg at peak exercise, in the absence of elevations in pulmonary vascular resistance, suggests exercise-induced HFP EF (81). Patients with early stages of PAH and still normal cardiopulmonary hemodynamics at rest demonstrate increased mean PAP >30 mm Hg and pulmonary vascular resistance >80 to 120 dyne s cm⁻² on iCPET (82).

Accurate assessment of the pressure-flow relationship during exercise by plotting mean PAP versus CO provides robust indication of abnormalities in RV to PA coupling (79). A mean PAP/CO relationship >3 mm Hg/l/min is reflective of a PH response, which combines with an elevated VE/VCO₂ slope (39). Even more, occurrence of RV-to-pulmonary circulation (PC) uncoupling is responsible for a delayed V\textsubscript{O₂} on kinetics during early exercise (84).

The most relevant limitations to this approach are its invasive nature and technical inaccuracies in obtaining reliable pulmonary hemodynamic tracings during high respiratory frequencies, despite averaging of repeated measures.

**CPET IMAGING: A NEW FRONTIER**

CPET imaging is a quite recent and valuable testing modality, which is receiving attention for its potential to combine exercise physiological data with noninvasive recordings of cardiac function by measures of chamber volumes and geometry, valvular status, and systolic and diastolic function, including the evaluation of left atrium (LA) function (85). In addition, the assessment of cardiac “functional reserve” by CPET imaging is greatly improved by the study of the pathophysiologic response of the pulmonary circulation to exercise, whose clinical implications appear complementary to and synergistic with the information obtained with iCPET (86,87). A typical example of this concept is the identification of a basic role of RV to PA uncoupling in determining the flattening of the ΔV\textsubscript{O₂}/ΔWR relationship (88).

On a methodological basis, there is not yet standardization, but the semirecumbent position is suggested for a better Doppler evaluation of parameters that are strictly dependent on workload (i.e., systolic pulmonary pressure, transvalvular gradients, LV outflow gradients) and decline quickly during the first seconds of recovery. Feasibility is strictly dependent on the acoustic window and its variability.

### TABLE 2 Class Recommendation and Level of Evidence for CPET Applications in HF

<table>
<thead>
<tr>
<th>Class Recommendation and Level of Evidence for CPET Applications in HF</th>
<th>Classification</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognostic Recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPET should be performed in patients with HFrEF being considered for heart transplantation or mechanical device implantation. However, CPET provides robust prognostic information in all patients with HFrEF and therefore is also recommended in those not being considered for end-stage surgical management.</td>
<td>Class I</td>
<td>A</td>
</tr>
<tr>
<td>Primary CPET variables, including the VE/VCO₂ slope, peak V\textsubscript{O₂}, and EDV, are strong predictors of adverse events. The response of these 3 CPET variables is recommended to form the basis of the prognostic assessment in patients with HFrEF. A combination of a VE/VCO₂ slope &gt;45.0, peak V\textsubscript{O₂} ≤10 ml kg⁻¹ min⁻¹, and the presence of EDV carries a particularly poor prognosis.</td>
<td>Class IIa</td>
<td>B</td>
</tr>
<tr>
<td>Secondary CPET variables, including P\textsubscript{a}CO₂, O₂ pulse, systolic blood pressure, and the ECG response to exercise, are additional predictors of adverse events and can be useful during the prognostic assessment in patients with HFrEF. A resting P\textsubscript{a}CO₂ &lt;33 mm Hg, a rise in P\textsubscript{a}CO₂ ≤3 mm Hg during exercise, a drop in systolic blood pressure during exercise, and/or ECG abnormalities warranting termination of exercise indicate a worse prognosis.</td>
<td>Class IIa</td>
<td>B</td>
</tr>
<tr>
<td>Prognostic value in patients with HFrEF is showing initial promise, in particular, the VE/VCO₂ slope, peak V\textsubscript{O₂}, and EDV. These variables can be useful in providing prognostic information also in patients with HFrEF.</td>
<td>Class IIa</td>
<td>B</td>
</tr>
<tr>
<td>Use of a multivariate model composed of key CPET variables and thresholds, as illustrated in Figure 4, can be useful in improving prognostic resolution in patients with HFrEF in comparison with variables assessed independently.</td>
<td>Class IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>Recommendations for Gauging Therapeutic Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary CPET variables, including the VE/VCO₂ slope and peak V\textsubscript{O₂}, are responsive to numerous pharmacological, surgical, and exercise interventions in patients with HFrEF. As such, assessment of the change in the VE/VCO₂ slope and peak V\textsubscript{O₂} is recommended when gauging therapeutic efficacy in patients with HFrEF in both clinical and research settings.</td>
<td>Class I</td>
<td>A</td>
</tr>
<tr>
<td>Reversal of EDV also may occur with pharmacological and exercise interventions in patients with HFrEF. Therefore, assessing for reversal of EDV as a gauge of therapeutic efficacy can be useful in both clinical and research settings.</td>
<td>Class IIa</td>
<td>B</td>
</tr>
<tr>
<td>Primary CPET variables, including the VE/VCO₂ slope and peak V\textsubscript{O₂}, may be responsive to pharmacological, surgical, and exercise interventions in patients with HFP EF. As such, the VE/VCO₂ slope and peak V\textsubscript{O₂} can be useful as core variables when gauging therapeutic efficacy in patients with HFP EF in both clinical and research settings.</td>
<td>Class IIa</td>
<td>C</td>
</tr>
<tr>
<td><strong>Diagnostic Recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPET variables reflecting ventilatory efficiency, including the VE/VCO₂ slope, EDV, and P\textsubscript{a}CO₂ at rest and during exercise, may be considered in detecting left-sided PH in patients with HFrEF and HFP EF. If all 3 of these variables are in their respective red zones, as illustrated in Table 1, the suspicion that the patient has left-sided PH may be reasonable. A primary indication of CPET for diagnostic purposes cannot be recommended at this time. Diagnostic assessment may be considered in patients with HF and suspicion of PH.</td>
<td>Class IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
during exercise caused by breath, body motion, and heart movements.

Incremental ramps at low increasing workload (8 to 15 W/min) are preferable for fully acquiring images every 2 min. Loop storage of adequate duration (3 to 5 beats) is required in order to perform the averaging of measures, especially for Doppler parameters, accounting for physiological respiratory variations. Figure 4 summarizes the main parameters provided by CPET imaging, pointing out their applications to specific cardiac diseases, with some illustrative cases of HFrEF, HFpEF, mitral valve insufficiency, and hypertrophic cardiomyopathy.

**HF WITH REDUCED EJECTION FRACTION.** There are multiple applications of CPET imaging in HF. First, a good discrimination between circulatory rather deconditioning limitation is signaled by the inability to reach an exercise stroke volume >50 ml/m² (89). The importance of measuring CO reserve (90,91) in parallel with LV compliance and filling pressures is well-established (92). Furthermore, estimation of O₂ peripheral extraction by CPET imaging using the echocardiographic-derived Fick equation is an immediate method to explore the role of the periphery (90). Assessment of functional mitral regurgitation (MR) is of basic relevance as a marker of severity and adverse outcome (93), which, in early stages, may be detectable just during exercise (20). Exercise-induced MR determines the same extent of exercise limitation observed in patients with severe MR at rest. Dynamic PI is a further limiting mechanism, also induced by MR, and is associated with specific ventilatory phenotypes of gas exchange, such as EOV (20). In advanced HFrEF, assessment of exercise-induced RV contractile reserve may be investigated by CPET imaging. In a study of 97 patients with advanced HFrEF, RV exercise contractile reserve and RV-to-PC coupling response to maximal exercise were analyzed through the relationships of systolic pulmonary arterial pressure (sPAP) to tricuspid annular peak systolic excursion (TAPSE) and sPAP to CO using stress echocardiography and CPET. Categorization into 3 groups based on TAPSE at rest ≥16 mm (group A, n = 60) and patients with TAPSE at rest <16 mm, who were further divided into 2 subgroups (group B, n = 19; group C, TAPSE <15.5 mm, n = 18) according to whether their respective median TAPSE was higher or lower than 15.5 mm at peak exercise. Group B, at variance with group C, showed an upward shift of the TAPSE versus sPAP relationship and some degree of favorable coupling adaptation during exercise. Thus, severely impaired RV function at rest may still be associated with the capacity to improve RV-to-PC coupling during exertion in a proportion of the patients with HFrEF (87). Interestingly, the worst RV-to-PC coupling pattern was associated with the highest rate of exercise ventilation inefficiency. This analysis appears useful for unmasking different right heart phenotypes not detectable with rest evaluation.

Most recent findings suggest that impaired LA dynamics, estimated by LA strain response during maximal exercise and during the recovery phase, plays a central hemodynamic role in triggering RV to PC uncoupling and ventilatory inefficiency, especially when LV systolic function is reduced (85).

**HF WITH PRESERVED EJECTION FRACTION.** HFpEF is a syndrome whose diagnostic process and limited therapeutic options remain major challenges (94). The expanding body of published reports on CPET imaging in this syndrome is based on several points: to uncover unexplained dyspnea and suspected HFpEF; to confirm HFpEF diagnosis in subjects not meeting the criteria required at rest; and to stratify CV risk once a true diagnosis is established.

Recently, the American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations on diastolic function evaluation advocated the use of the exercise E/e’ ratio to detect diastolic dysfunction (95) and, for the past several years, changes in E/e’ were taken as a reference to interpret unexplained dyspnea and suspected HFpEF (96,97). In a study by Nedeljikovic et al. (98), performed in 87 patients with dyspnea unexplained by exercise and hypertension, gas exchange and Doppler analysis led to the ultimate diagnosis of HFpEF in the minority of patients presenting with a combination of E/e’ >15 at peak exercise, along with an elevated VE/VCO₂ slope.

A parallel number of observations have focused on how exercise E/e’ may add to the clinical follow-up of established HFpEF, especially looking at the associated changes in pulmonary pressure during effort (99,100). Interestingly, CPET imaging with immediately post-exercise echocardiographic assessment has documented that in about 1 of 3 patients with HFpEF, exercise elevation of LV filling pressure (E/e’_{EXE} >13) can be absent, but associated with reduced contractile reserve and ventriculoarterial coupling, as well as with a mild degree of functional impairment (101). However, a similar approach has shown that peak E/e’ >15 occurred in 9% of hypertensive patients with exertional dyspnea and normal resting LV function, being associated with lower peak V_{O2} and significantly impaired ventilator efficiency (higher VE/V_{CO2}), compared with patients with normal exercise E/e’ (98).

The intrinsic value of exercise echocardiography has been recently confirmed in an elegant
The figure shows the semirecumbent approach (center), allowing for simultaneous echocardiography and expired-gas analysis. The yellow table on the right lists the main parameters provided by exercise echocardiography; the disease-specific tables indicate prognostic parameters to collect during the test. The blue table on the left lists the main CPET parameters; the “red flags” table (left) points out CPET pathological patterns with prognostic impact. The 4 panels in blue depict cases of iCPET with the main CPET (left blue frame) and echocardiographic (right red frames) findings. (Upper left) A case of HFrEF due to post-ischemic LV dysfunction with a very abnormal functional phenotype; CPET frames show pronounced exercise oscillatory ventilation and severe impairment of ventilatory efficiency; echocardiographic frames show end-diastolic and systolic apical 4-chamber views with apical aneurysmatic evolution and severely reduced ejection fraction, transmitral pulsed wave Doppler, and annular TDI displaying grade III diastolic dysfunction and tricuspid continuous wave Doppler demonstrating severe pulmonary hypertension at rest and during exercise. (Upper right) A case of HCM with preserved functional phenotype, despite the evidence of severe left ventricular outflow obstruction; CPET frames show normal ventilatory response; echocardiographic frames show left ventricular outflow tract continuous wave Doppler demonstrating severe rest dynamic obstruction, enhanced by the Valsalva maneuver and by post-exercise period (when afterload is decreasing, but adrenergic inotropic drive is still present). (Bottom right) A case of HFpEF with typical abnormal functional phenotype characterized by chronotropic incompetence; CPET frames show the flattening of the ΔVO₂/ΔWR relationship, expression of blunted cardiac output during exercise, and the reduced chronotropic response related to VO₂ consumption; echocardiographic frames show transmirtal pulsed wave Doppler and annular TDI displaying grade II diastolic dysfunction with worsening during exercise, tricuspid continuous wave Doppler demonstrating a borderline rest gradient with a severe exercise-induced increase, and left ventricular outflow tract pulsed wave Doppler evidencing a slight increase of flow during exercise, consistent with abnormal stroke volume reserve. (Bottom left) A case of moderate left ventricular systolic dysfunction characterized by exercise-induced mitral regurgitation with mild exercise oscillatory ventilation. CPET frames show mild exercise oscillatory ventilation with preserved ventilatory efficiency; echocardiographic frames show rest and exercise mid-systolic color Doppler apical 4-chamber views with severe exercise-induced mitral regurgitation and tricuspid continuous wave Doppler demonstrating normal rest gradient with abnormal exercise-induced increase, reflecting dynamic pulmonary hypertension.

AT = anaerobic threshold; AVA = aortic valve area; CO₂ = carbon dioxide; EDA = end-diastolic area; EDV = end-diastolic volume; ESV = end-systolic volume; ERO = effective regurgitant orifice; ESA = end-systolic area; ESV = end-systolic volume; EXE = exercise; FAC = fractional area change; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; iCPET = invasive cardiopulmonary exercise testing; iEDV = indexed end-diastolic volume; iESV = indexed end-systolic volume; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; MG = mean gradient; MR = mitral regurgitation; PG = peak gradient; RegVol = mitral regurgitant volume; RER = respiratory exchange ratio; RV = right ventricular; SPAP = systolic pulmonary artery pressure; SV = systolic volume; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; WMSI = wall motion score index; other abbreviations as in Figures 1 to 3.
simultaneous invasive and echocardiographic study reporting increased sensitivity, but compromised specificity of guideline-recommended use of the exercise E/e’ ratio (77), proposing a screening role of exercise echocardiography aimed at ruling out the presence of HF.

**VALVULAR DISEASES.** Exercise echocardiography is extensively used for the evaluation of valvular diseases, as recently stated in the European Association of Cardiovascular Imaging/American Society of Echocardiography recommendations (95). Specific protocols and target parameters have been established according to the valve disease and the clinical question (102). The main goal of physical stress is to measure the “valve reserve” (i.e., the entity of exercise-induced worsening of valve disease) and the direct pathophysiological consequences (i.e., exercise-induced PH, LV transient systolic dysfunction, increase in transvalvular gradients). The main indication for testing patients with valvular disease is an unclear clinical presentation. Considering the advanced age of people with valvular disease and their high prevalence of dyspnea (103), it is quite common to experience some difficulties in understanding the origin of self-reported dyspnea. In the decision process for surgical treatment, what appears pivotal is the recognition of how much symptoms are related to the valve disease or reflective of other conditions, in order to optimize surgical timing. Of note, CPET imaging was recently used in patients with rheumatic mitral stenosis, providing evidence that functional limitation has a complex origin. Restrictive lung function, chronotropic incompetence, limited stroke volume reserve, and peripheral factors equally contributed to reduce ability to exercise (104). Interestingly, patients with attenuated functional responses showed the expected exercise-induced PH; however, this was not the main limiting factor. A similar combined approach has been used in functional MR to demonstrate that exercise-induced severe MR limits patients with HFpEF, mainly causing exercise PH. The rationale for using CPET imaging in valvular disease is strong; however, systematic data are still lacking and future investigations are desirable for defining surgical risk, especially in the assessment of complex conditions, such as paradoxic low-flow–low-gradient severe aortic stenosis (105).

**HYPERTROPHIC CARDIOMYOPATHY.** Hypertrophic cardiomyopathy (HCM) is commonly associated with exercise intolerance, and CPET analysis is helpful for improving prognostic stratification (106). Mechanisms underlying abnormal gas exchange during exercise can differ according to the predominant echocardiographic phenotype (107). CPET imaging allows the identification of LV outflow obstruction and diastolic dysfunction assessment during exercise, as well as objective measurement of functional limitations. In 156 patients with HCM evaluated with both CPET and noninvasive hemodynamic assessment, a high prevalence of exercise intolerance and ventilatory inefficiency has been reported (108). Impaired peak VO2 (<80% of predicted) was associated with peak cardiac index, age, male sex, and RV end-diastolic area, whereas ventilatory inefficiency (VE/VCO2 >34) was related to E/e’ and to indexed LA volume. Both functional parameters were predictive of increased risk of major events in the short-term follow-up.

The role of diastolic dysfunction as a limiting factor of functional response has been reinforced by a recent paper using iCPET imaging in 197 patients with HCM (109). Multivariate analysis showed that LV obstruction, LA dilation, and especially rest or latent diastolic dysfunction were the main determinants of exercise intolerance.

According to the European guidelines (110), CPET has a Class IIa indication in patients with HCM, irrespective of symptoms reported, and a Class Ia indication when consistent symptoms are present. Simultaneous exercise echocardiography has the advantage of evaluating LV outflow tract obstruction and weighing all potential causes of exercise intolerance, such as diastolic dysfunction, dynamic MR, and PH. An additive value of CPET imaging has been suggested for monitoring therapeutic response to septal reduction, looking at the linearity of the ΔVO2/ΔWR relationship, which can be flattened in case of severe obstruction and normalize after septal reduction (111).

**SUSPECTED OR CONFIRMED PH.** CPET imaging and exercise echocardiography have independent, specific roles in the diagnostic work-up, functional evaluation, and clinical management of patients with confirmed PH, irrespective of disease origin (95). Nonetheless, the combination of both tests in a single-step evaluation has the advantage of confirming suspected PH, making an early diagnosis, identifying secondary causes of PH, and improving overall patient characterization. Systolic pulmonary pressure during exercise is one of the most important variables to collect during exercise echocardiography in several clinical settings because it reflects the main mechanism of effort intolerance. Nonetheless, in the context of Group 1 or PAH, the role of exercise echocardiography in the diagnostic work-up is still debated and it is not recommended for diagnosis and clinical purposes (112).
The role of CPET imaging has been validated in several conditions for determining exercise-induced PH, however no prospective studies have tested the incremental value of this combined approach in the diagnostic work-up of PAH.

CONCLUSIONS

CPET now has a definitive place in the armamentarium of the practicing clinician for the evaluation of cardiopulmonary disorders, primarily HF. It provides a thorough assessment of the integrative multiorgan physiological response to exercise. A revival of invasive CPET and introduction of CPET imaging have now extended the amount of pathophysiologica and clinical information, providing new insights in systemic and pulmonary hemodynamics, along with direct knowledge of cardiac, valve, and functional data.

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