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Review
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The role of the cardiopulmonary exercise test in the hypertensive population

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Abstract

The cardiopulmonary exercise test is a noninvasive method that provides an integrative assessment of exercise response and allows the evaluation of functional capacity and exercise limitation. It can be used in a wide spectrum of clinical applications, such as the evaluation of patients with unexplained exertional dyspnea or heart failure, for identifying myocardial ischemia and assessing valvular heart disease. In the hypertensive population, the cardiopulmonary exercise test allows the identification of patients with masked hypertension or with masked heart failure with preserved ejection fraction. Also, it can provide information about the efficiency of antihypertensive treatment.

Keywords: cardiopulmonary exercise test, masked hypertension, hypertensive response to exercise.

Introduction

The cardiopulmonary exercise test (CPET) allows for an integrative assessment of exercise physiology, including the pulmonary, cardiovascular, muscular and cellular oxidative systems [1, 2]. Traditionally, the main indication for CPET in cardiology has been the selection of candidates for cardiac transplantation; however, current CPET applications have grown remarkably and include all forms of exercise intolerance [3]. It can be used for risk stratification and selection of management options in patients with heart failure, for evaluation of patients with unexplained exertional dyspnea, for identification of myocardial ischemia, assessment of valvular disease/dysfunction and chronotropic competence [3–7]. CPET plays an increasing role in the evaluation of the hypertensive population, allowing the assessment of antihypertensive treatment efficacity [8, 9] and the identification of patients with masked hypertension (MH) [10] or with masked heart failure with preserved ejection fraction (HFpEF) in this population [11].

CPET allows the analysis of a broader range of variables derived from the measurement of pulmonary gas exchange at rest, during exercise and recovery (oxygen uptake- VO_2, carbon dioxide output – VCO_2, ventilation- VE), along with standard variables measured during exercise testing, including blood pressure (BP), heart rate (HR), work rate, electrocardiography (ECG) and symptoms [1, 12].

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CPET is typically performed using a cycle ergometer or a motorized treadmill [13–15]. The cycle ergometer is considered to be safer, allows better monitoring of ECG and blood pressure and has the ability to quantify the external work rate throughout the test precisely [16]. Cycle ergometry can be used for a wide range of patients: with gait or balance instability, obesity, deconditioning, and orthopedic limitation [1, 16].

Several studies have shown that exercise on a cycle ergometer tends to produce a lower peak VO2, on average 10–20% below the treadmill peak VO2 [17, 18]. CPET is usually performed as a symptom-limited exercise test, and the selection of the test protocol should be tailored to the individual to yield a fatigue-limited exercise duration of 8–12 minutes. For lengthened exercise tests, longer than 12 minutes, muscular fatigue or orthopedic factors, rather than cardiopulmonary endpoints, can cause the termination of exercise [1]. Exercise test protocols can continuously increase the work rate –ramp protocol (increase in work rate every 2–15 seconds) or stepwise increase in work rate (for cycle ergometer-increments of 5–30 W/min). The contraindications and the major complications of CPET are similar to those of exercise ECG. The variables derived from CPET and their interrelationships were systematically summarized in the Wasserman nine-panel display [19]. To facilitate the analysis and interpretation of CPET data, the large numbers of CPET variables (around 150) were reduced to a few clinically relevant key variables, which are collected through a standardized method in a universal reporting sheet [6, 20]. Some variables are applicable to all patients undergoing CPET, while other CPET variables are relevant and collected only for certain pathologies.

CPET evaluation in hypertensive patients

One of the benefits of the CPET evaluation in the hypertensive population consists in identifying patients with MH [10]. MH can be found in approximately 15% of patients with a normal office BP [21] and is more likely to be found in people with a BP in the high-normal range. It is defined by normal clinic BP but elevated BP outside the office environment [22]. The methods used to identify MH involve 24-h ambulatory BP monitoring (ABPM) and home BP monitoring [23]. Patients detected with masked hypertension have an increased risk for further developing sustained hypertension and a higher risk for cardiovascular events [24, 25–28] and mortality [29]. Schultz *et al.* showed in their study that MH could be unmasked by the systolic BP response to low-intensity exercise, so CPET could become an alternative, rapid screening test to identify these patients. In their study, MH patients had a significantly higher systolic BP, with a greater change from baseline. Systolic BP at low-intensity exercise was independently associated with masked hypertension [30].

Also, CPET could be a useful tool in the hypertensive population to evaluate and monitor the effectiveness of antihypertensive medication. The systolic BP response to low-intensity exercise correlates well with BP during daily activities and may reflect the degree of control of BP values. Studies are showing that some antihypertensive drugs, such as angiotensin receptor antagonists [31, 32], thiazide diuretics [32] and aldosterone antagonists [33], have a modulating effect on the systolic BP response to exercise.

HFpEF is commonly associated with hypertension – at least 74% of patients with HF also present hypertension [34, 35]. As symptoms may only appear during exercise, the diagnosis of HFpEF could be delayed. Another clinical application of the CPET performed alone or in combination with exercise stress echocardiography could be the early identification of masked HFpEF in patients with hypertension. The study of Nedelikovic *et al.* evaluated this hypothesis and showed that a combined exercise stress echocardiography with CPET could improve the identification of masked HFpEF in patients with hypertension, exertion dyspnea and normal echo parameter at rest. From the 87 patients studied, 8 patients (9.2%) had an increase in E/e' > during the test, considered a marker of masked HFpEF. These patients also had lower values for peak VO_2 and peak $PetCO_2$ and the higher VE/VCO_2 slope. The VE/VCO_2 slope was an independent predictor of HFpEF, with a cut-off value of 32.95 [11]. The finding that inadequate ventilation (VE/VCO_2 slope) rather than peak VO_2 is the main indicator of significantly impaired diastolic function is consistent with previous findings, which showed that a steep VE/VCO_2 slope was a more powerful prognostic marker than peak VO_2 in patients with HFpEF [36].

Also, CPET proved to be useful in unmasking a hypertensive response to exercise (HRE). HRE is generally defined as a peak systolic blood pressure ≥210 mmHg in men and ≥190 mmHg in women during exercise [37–39] and is associated with a greater risk of cardiovascular events (CV) [40, 41] and mortality [42] for both hypertensive and normotensive subjects.

During exercise, the hemodynamic response is directly proportional to cardiac output and peripheral resistance. The systolic BP increases in a stepwise manner due to an increase in cardiac output, while diastolic BP remains constant or drops slightly [43].

Schultz *et al.* completed a systematic review and meta-analysis of published literature to determine

the predictive value of exercise BP for subsequent CV events and mortality. They reviewed data from 46,314 individuals without significant coronary artery disease, followed up for a mean of 15 years. This meta-analysis demonstrated that an HRE at moderate exercise intensity predicted a 36% greater risk of CV events and mortality, independently of age, office BP and CV risk factors. Moreover, for every 10mm Hg increase in systolic BP during moderate intensity, there was an increase of 4% in CV events and mortality, independent of office BP, age, or CV risk factors. However, they found no significant association between the value of BP at maximal workload and an increased rate of CV [44].

Normotensive individuals who develop an HRE have a higher risk of developing essential hypertension [45–48] and left ventricular hypertrophy [49], as well as a higher risk for cardiovascular events [40, 41] and mortality [42]. There are several mechanisms that are incriminated for HRE: decreased aortic distensibility [50, 51], an exaggerated sympathetic tone during exercise, increased left ventricular mass [52], endothelial [53] and diastolic dysfunction [52]

The reduction in aortic distensibility occurs inevitably and irreversibly with age and leads to a decrease in the blood pressure buffer capacity that can cause an exaggerated response of BP to exercise [50, 51, 54]. It can also increase with the severity of hypertension [55]. Dernellis *et al.* showed that in non-hypertensive subjects, elevations in aortic stiffness predict progression toward hypertension over a four-year period [56].

Kraft *et al.* evaluated the impact of aerobic capacity on aortic stiffness between normotensive and hypertensive. They showed that neither a higher peak aerobic capacity nor antihypertensive medication was associated with lower aortic stiffness for the hypertensive subjects. However, for the normotensive group, the aortic stiffness was significantly lower in the fit (defined as the percentage of predicted VO_2max achieved ≥100%) *versus* unfit (defined as the percentage of predicted VO_2max achieved <100%) subgroups. The hypertensive subjects had elevated aortic stiffness compared to normotensive, even after matching for age, sex, and aerobic fitness [57].

Conclusion

CPET provides useful exercise-related parameters which allow for a better characterization of the hypertensive population by evaluating the cardiovascular risk and the efficacy of the antihypertensive treatment. Also, CPET might be useful in the early identification of patients with masked HFpEF in the hypertensive population or those with masked hypertension.

Conflict of interest

The authors declare no conflict of interest.

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