Review Article

The Importance of Cardiopulmonary Exercise Testing in the Diagnosis, Prognosis and Monitoring of Patients with Pulmonary Arterial Hypertension

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Cardiopulmonary exercise testing (CPET) is a non-invasive, dynamic method that allows the simultaneous and complete evaluation of parameters related to the cardiovascular, respiratory, haemopoietic, neural and skeletal muscle systems that play a part during the performance of physical exercise. As a result, CPET provides an integrated evaluation of both the patient's functional capacity and the severity of the disease, as well as the course of its development.[1-4]

A person's physical condition and any limitations thereof with regard to physical exercise are evaluated during CPET via the parameter peak oxygen consumption (VO_2max), in terms of both absolute values (Weber classification stages A-E) and as a percentage of the predicted maximum value for the individual examined (a normal result requires the achievement of VO_2max >84% of the predicted maximum value). Along with the remaining metabolic, cardiac and respiratory parameters, it is possible to check the degree of contribution of the cardiovascular and respiratory systems to a person's decreased capacity for physical exercise.[3-4] The main parameters determined during CPET are given in Table 1.[3-5]

Pulmonary arterial hypertension is defined as a situation in which the mean pulmonary artery pressure during cardiac catheterisation is ≥25 mmHg at rest. These findings are accompanied by normal values for pulmonary capillary wedge pressure (<15 mmHg), increased levels of pulmonary vascular resistance (>3 Wood units), and normal or reduced cardiac output.[6-7]

Exercise physiology

During physical exercise, normal pulmonary capillaries receive an increased volume of blood. As a result, the alveoli have to increase their ventilation in order to expel the increased CO_2 produced, and to maintain the partial CO_2 pressure and the pH at acceptable levels. Pulmonary arterial hypertension is characterised by reduced perfusion and normal ventilation of the alveoli. The over-ventilation of alveoli with insufficient perfusion is known as "dead space" ventilation, an increase in which leads to an increase in the ratio of normal dead space to total respiratory volume (V_D/V_T), and to permanently positive end-expiratory CO_2 pressure. The consequent hypoxaemia stimulates the carotid bodies and causes an increase in ventilation.[5,8,9]

Table 1. Main parameters evaluated during a cardiopulmonary exercise test.

Metabolic:	
VO_2max (ml/min)	The peak oxygen consumption as an absolute value and in relation to body weight (VO_2/kg)
VO_2AT (ml/min/kg)	Oxygen consumption at the anaerobic threshold, which also marks the start of anaerobic production of adenosine triphosphate, resulting in the concentration of lactic acid in the muscles and blood.
RER (respiratory exchange ratio)	The gas exchange ratio, which expresses the relation between CO_2 elimination and O_2 uptake per unit time.
Workload (W-METS)	The maximum load to which the examinee is subjected, in relation to the predicted value, in order to produce work.
Cardiac:	
BP (mmHg)	Blood pressure before, during, and after exercise.
HR, HRR (beats/min)	Maximum heart rate in relation to the predicted value (220 - age) and the heart rate reserve (predicted maximum - maximum achieved)
O_2 pulse (ml/beats)	Oxygen pulse, which represents the cardiac output.
Respiratory:	
VE (L/min)	Minute ventilation at peak exercise in relation to the predicted value.
BR	Breathing reserve at peak exercise.
VE/VCO_2 slope	The prognostic index of the slope of the respiratory equivalent with regard to CO_2.
O_2 recovery slope	The slope of the oxygen consumption curve in relation to time during recovery.

During physical exercise, a patient with pulmonary arterial hypertension exhibits dyspnoea and/or fatigue. These symptoms are due to increased pulmonary vascular resistances, resulting in both reduced gas exchange and the consequent inability of the right ventricle to increase cardiac output proportionately via the pulmonary artery.[9]

In more detail, the mechanisms that lead to the occurrence of dyspnoea during physical exercise in a patient with pulmonary arterial hypertension are: a) a disturbance of the ventilation-perfusion relation, resulting in an increase of the V_D/V_T ratio because of the under-perfusion of the alveoli; b) an increase in hydrogen cations because of the early production of lactic acid (faster achievement of anaerobic threshold: reduction of bicarbonates, increase in VCO_2), resulting in an increase in minute ventilation; and c) hypoxaemia, which is due to a pathological pulmonary arterial bed with a clearly reduced circulation of red cells, either within it or via a right-to-left shunt through a patent *foramen ovale*. The fatigue is due to the reduced production of adenosine triphosphate (ATP) under aerobic conditions. The ATP production process under anaerobic conditions triggers anaerobic glycolysis, resulting in the early appearance of lactic acidosis.[9]

Exercise tests

Nowadays, we are in a position to evaluate the severity of pulmonary arterial hypertension and to follow its course over time using various non-invasive methods (echocardiographic examination, CPET, 6-minute walk test).[10]

The reduction of exercise capacity is significantly correlated with the haemodynamic parameters of cardiac catheterisation, the time course of patients' clinical worsening, as well as survival. Thus, exercise tolerance has proven to be a significant prognostic factor for the evaluation of patients with pulmonary arterial hypertension.[11]

CPET is able to assess quantitatively the patient's physical exercise capacity in a more integrated way than can more simple tests, such as the 6-minute walk. CPET can evaluate separately the contributions of various pathophysiological mechanisms that are implicated in pulmonary arterial hypertension.[12]

The 6-minute walk test is a sub-maximal form of exercise, usually used for patients who are unable to undergo maximal stress testing. It is a simple test, which requires no special equipment, can be easily repeated, and is considered safe, since the patient determines the limits for its termination.[13-14]

Peak oxygen consumption (VO_2max) and the VE/VCO_2 slope seem to be correlated with mortality in patients with heart failure. Reduced peak oxygen consumption (VO_2max <14 ml/kg/min) and a VE/VCO_2 slope ≥ 34 are negative prognostic factors for survival

in heart failure patients.[15-17] Since the results of the 6-minute walk test in patients with heart failure are significantly correlated with both VO_2max and the VE/VCO_2 slope, parameters that are evaluated during CPET, the 6-minute walk test is also used as a prognostic index of survival.[18-19]

Patients with idiopathic pulmonary arterial hypertension who during the 6-minute walk test cover a distance <332 m have significantly lower survival compared to those who cover longer distances. This distance is a powerful and independent prognostic parameter for mortality in patients with idiopathic pulmonary arterial hypertension.[20] Another prognostic parameter evaluated during the test is the decrease in haemoglobin saturation (O_2 saturation), where a decrease by 1% corresponds to a 27% increase in mortality.[21]

The question of the substitution of CPET by the 6-minute walk test in patients with pulmonary arterial hypertension has been raised, based on the ease of performance of the latter. It appears that, for such a substitution to be scientifically correct, it should satisfy certain criteria: a) the laboratories that carry out CPET must have experience in interpreting its results; and b) during the performance of the 6-minute walk test the patient's body type must be taken into consideration, multiplying the distance achieved in metres by the patient's body weight in kilograms.[22-23] In the multi-centre STRIDE trial, in which patients with pulmonary arterial hypertension were under treatment with the selective endothelium antagonist sitaxestan, it was found that if these criteria are not met, there is no correlation between the results of the 6-minute walk test and the peak oxygen consumption during CPET.[24-26]

The quantity and completeness of the data obtained during CPET make it the examination of choice during the diagnostic evaluation and monitoring of patients with pulmonary arterial hypertension, who from the first stages of the disease show severe limitation of their capacity for physical exercise, with right heart failure coming later, and the final endpoint being death. D'Alonzo et al found that patients with idiopathic pulmonary arterial hypertension show a reduction in peak oxygen consumption and an increase in the VE/VCO_2 ratio during CPET, while Rhodes et al showed the superiority of CPET over other non-invasive methods as regards the diagnosis of patients with idiopathic pulmonary arterial hypertension who were ineligible for catheterisation because of a high risk.[27-28]

CPET in patients with pulmonary arterial hypertension

During the evaluation of the results of CPET in patients with pulmonary arterial hypertension the following changes are seen regarding the main parameters:[9]

- A reduction in VO_2max to <84% of the predicted value, which expresses the patient's reduced capacity for maximal exercise.
- A reduction in the anaerobic threshold (VO_2AT) to <40% of the predicted value, which shows the early appearance of anaerobic metabolism and seems to be an independent prognostic factor in the course of pulmonary arterial hypertension.
- A reduction in the O_2 pulse to <80% of the predicted value, which expresses indirectly the reduction in stroke volume and cardiac output.
- An increase in the respiratory equivalent slope as regards CO_2 consumption (VE/VCO_2 ≥34), suggesting failure of the respiratory system in terms of the gas exchange during exercise.
- Desaturation of haemoglobin (Δsat >4-5%).
- An increase in alveolar-arterial oxygen difference, with a simultaneous drop in partial arterial oxygen pressure.

CPET provides information about the prognosis of patients with primary pulmonary arterial hypertension. Patients who achieve a VO_2max ≤10.4 ml/kg/min are at risk of early death during the first (50%) or second (85%) year after the examination. In contrast, patients who achieve a VO_2max >10.4 ml/kg/min have corresponding risks of 10% and 30%, respectively. Patients who achieve a VO_2max ≤10.4 ml/kg/min and a peak arterial pressure during the test of <120 mmHg show 23% survival in the next 12 months, whereas those who have one or none of the preceding risk factors have better 1-year survival: 79% and 97%, respectively.[29]

As regards the diagnostic value, it has been found that patients who undergo CPET as part of an investigation of symptoms of dyspnoea and fatigue and show a reduction in breathing reserve, with a simultaneous increase in the VE/VCO_2 slope, dead space (V_D/V_T) and alveolar-arterial oxygen difference, have an 88% possibility of exhibiting increased pulmonary vascular resistances (>120 dyn/s/cm) during cardiac catheterisation; however, the examination is not considered front line for the diagnosis of pulmonary hypertension.[30]

Groepenhoff et al compared the prognostic value of CPET and the 6-minute walk test in patients with

pulmonary arterial hypertension. They found that the patients with the best prognosis ($p<0.05$) were those who achieved a VO_2max >13.2 ml/kg/min, a VE/VCO_2 slope <48, and ΔO_2pulse >3.3 ml/beat during CPET, or covered a distance >399 m in the 6-minute walk test. In addition, the prognostic value of the latter test reached a statistically significant level ($p<0.05$) when the parameter ΔO_2pulse was included in the statistical model.[31]

Conclusions

CPET is considered the examination of choice for the evaluation of reduced exercise tolerance in patients with cardiovascular or respiratory diseases, based on the principle that the dysfunction of a system (cardiovascular, respiratory, and musculoskeletal) becomes apparent when that system is assessed under maximum loading conditions. CPET is the only non-invasive method that provides such a large quantity of information regarding the physical condition of the examinee within a short space of time. The use of CPET in a diagnostic algorithm, in monitoring, and in assessing the prognosis should be considered an essential prerequisite in patients with pulmonary arterial hypertension,[32] although the contribution of the 6-minute walk test should not be underestimated as an alternative form of exercise for patients who are unable to undergo maximal exercise.

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