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Prognostic value of cardiopulmonary exercise testing in Idiopathic Dilated Cardiomyopathy

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ABSTRACT

Background: Although cardiopulmonary exercise testing (CPET) is considered as an important tool in risk stratification of patients with heart failure (HF), prognostic data in the specific setting of Idiopathic Dilated Cardiomyopathy (iDCM) are still undetermined. The aim of the study was to test the prognostic value of CPET in a large cohort of iDCM patients.

Methods and results: We analyzed 381 iDCM patients who consecutively performed CPET. The study end-point was a composite of cardiovascular death/urgent heart transplantation (CVD/HTx). In the overall population the average values of peak oxygen consumption (peak VO_2/kg) and percent-predicted peak VO_2 (peak VO_2%) were 17.1 ± 5.1 ml/kg/min and 59 ± 15%, respectively. Mean VE/VCO_2 slope was 29.8 ± 6.1. During a median follow-up of 47 months (interquartile range 23–84), 83 patients experienced CVD/HTx. Peak VO_2% (Area Under the Curve [AUC] 0.74; 95% CI 0.71–0.85, $p < 0.001$) and VE/VCO_2 slope (AUC 0.78; 95% CI 0.74–0.84, $p < 0.001$) were more accurate in predicting CVD/HTx compared to peak VO_2/kg (AUC 0.60; 95% CI 0.54–0.68, $p = 0.003$) ($p < 0.001$ for both comparisons). The most accurate threshold values for outcome prediction in our iDCM cohort were <60% for peak VO_2% and >29 for VE/VCO_2 slope. At multivariable analysis peak VO_2% and VE/VCO_2 slope were the strongest predictors of CVD/HTx, either as continuous and categorical variables, whereas peak VO_2/kg was not independently related with prognosis.

Conclusion: In a large population of iDCM patients peak VO_2% and VE/VCO_2 slope emerged as the strongest prognostic CPET variables. Prospective studies will be necessary to confirm these data.

1. Introduction

Idiopathic Dilated Cardiomyopathy (iDCM) is a primary heart muscle disease characterized by a progressive dilation and dysfunction of the left ventricle (LV) in the absence of abnormal loading conditions or coronary artery disease (CAD), sufficient for justifying systolic impairment [1]. In the last decades, advances in pharmacological and non-pharmacological therapies, along with the extensive application of familial screening, the systematic revaluation of patients during follow-up and improved prognostic stratification have significantly changed the long-term survival expectancy of iDCM patients [2,3]. Therefore, iDCM currently represents a

Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; CVD/HTx, cardiovascular death/heart transplant; HF, heart failure; ICD, implanted cardioverter defibrillator; iDCM, Idiopathic Dilated Cardiomyopathy; NYHA, New York Heart Association; peak VO_2%, percent of predicted peak VO_2; peak VO_2/kg, oxygen consumption at peak of exercise/kg; VE, ventilation; VCO_2, carbon dioxide production.

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peculiar HF model affecting a specific subset of patients with respect to other HF etiologies [3].

The management of this disease still remains challenging for clinicians, due to the absence of large studies specifically targeting this population [3,4].

Cardiopulmonary exercise testing (CPET) provides an objective evaluation of the functional capacity and represents a cornerstone in defining clinical severity and predicting outcomes in HF patients.

Peak of oxygen consumption (peak VO2/kg) is a main prognostic parameter for selecting candidates to HTx [5]. Due to the advancements in knowledge of exercise impairment in HF, new promising indexes have been proposed, including the percentage of predicted peak VO2 (peak VO2%) [6,7], peak systolic blood pressure [8] and ventilatory efficiency, expressed as VE/VCO2 slope [9,10]. However, in iDCM patients the abovementioned markers need further validations considering the different clinical, etiological and pathophysiological characteristics of iDCM compared to the other, more frequent, HF etiologies (i.e. ischemic, hypertensive or valvular disease) [5–10].

The aim of the present study was to assess the prognostic value of CPET among a large cohort of well-selected patients with iDCM on optimal evidence-based therapy.

2. Methods

2.1. Study population

This retrospective observational study evaluated patients with iDCM who consecutively underwent CPET from the 1st of May 1998 to the 1st of October 2012 in two Italian tertiary referral Centers for Cardiomyopathies as part of their regular clinical follow-up. iDCM was defined as LV systolic dysfunction (LV ejection fraction [LVEF] < 50%) at baseline evaluation without any known causative condition.[1,3] Patients with a history of significant hypertension (systolic blood pressure > 160/100 mm Hg), CAD (obstruction > 50% of a major epicardial coronary artery), congenital heart disease, persistent high-rate supraventricular arrhythmias, documented skeletal muscle myopathy or other acquired heart diseases, such as alcohol abuse, were excluded. Endomyocardial biopsy was performed only in patients with recent-onset of severe HF (≤6 months) with severe LV dysfunction refractory to standard therapy and/or life threatening ventricular arrhythmias without known causes [11]. Patients with active myocarditis were excluded. All patients underwent a physical examination, blood sampling for laboratory tests, 12-lead electrocardiography, complete transthoracic echocardiography and CPET for prognostic evaluation. Complete transthoracic echocardiography was performed in all patients according to international guidelines. [12] LVEF was assessed using Simpson's biplane method. Measurements were normalized for body surface area. The glomerular filtration rate was calculated using the MDRD formula.[13] All patients had been receiving optimal medical treatment (OMT) for at least six months prior to CPET performance. Only patients with no modifications in drugs, dosages or other significant medical interventions in the three months prior to CPET were included in the study analysis. Cardiac resynchronization therapy and implanted cardioverter–defibrillator (ICD) for primary or secondary prevention were considered according to the most recent international guidelines [14]. Informed consent was obtained from all participants according to the policy of the institutional review board of the two enrolling centers' administration. The investigation complies with the Declaration of Helsinki [15].

2.2. Cardiopulmonary exercise testing

CPET was performed using a cycle-ergometer ramping protocol, as previously reported [5,16]. Prior to each test, the equipment used was calibrated in a standard manner using reference gases. The exercise protocol was set to achieve peak exercise in ~10 min [17]. In the absence of clinical events, CPET was interrupted whenever patients reached their maximal effort capacity, regardless of peak respiratory exchange ratio (RER) reached, and exercise parameters were calculated as previously described [7]. Breath-by-breath analyses of expiratory gases and ventilation were performed. A 12-lead electrocardiogram and transcutaneous oxygen saturation was also continuously monitored throughout the study and blood pressure was determined manually every 2 min.

The VO2 max was defined as the highest VO2 rate observed during exercise over the last 20 s of exercise, before the subject stopped. Anaerobic threshold (AT) was measured by V-slope analysis of VO2 and VCO2, and was confirmed analyzing the ventilatory equivalents and the end-tidal pressures of CO2 and O2. If no agreement was obtained, AT was considered unidentifiable. We defined ventilatory efficiency as the amount of ventilation required to eliminate a given amount of CO2; therefore, VE/VCO2 slope was calculated as the slope of the linear relationship between VE and VCO2 from one minute after the beginning of the loaded exercise to the end of the isocapnic buffering period, as previously described [18]. RER was calculated using the last breath method. Peak exercise oxygen pulse was calculated as peak VO2/peak heart rate. Predicted heart rate values were calculated as: peak heart rate predicted = (220 − Age) if male, =(210 − Age) if female [19]. The Wassermann equation, adjusted for age and sex, was used [19]. Previously suggested cut-points of 14–12 ml/kg/min, according to the presence or absence of beta-blocker therapy, were used to validate our results.

2.3. Follow-up data and end-point

The date of enrolment was considered as the date of CPET performance. All patients systematically underwent subsequent follow-up that ended at the date of the primary end-point or at the time of the last available medical contact. The primary study end-point was considered to be the combination of cardiovascular death and urgent HTx (CVD/HTx). Information regarding the end-point was obtained from primary care physicians, civil registries of death or by telephone interview with patients or their relatives. Indication to HTx was considered in patients with refractory HF requiring inotropic treatment and/or mechanical support. Causes of CVD (i.e., pump failure death or sudden cardiac death [20] or thromboembolic death) were also determined. Patients who died because of non-cardiovascular causes were censored at the date of the event.

2.4. Statistical analysis

Comparisons between baseline characteristics of survivors and non-survivors were made by ANOVA test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold. The Chi-square test was calculated for discrete variables.

The area under receiver operating characteristic curve (ROC AUC) methodology was used to evaluate the prognostic accuracy of single CPET parameters and all their possible combinations. Differences between AUCs were tested using the De Long test. 'Optimal' cut offs for CPET parameters were found to maximize the sum of sensitivity and specificity values of the corresponding ROC curves. Kaplan–Meier survival curves were estimated and compared between groups by means of the log-rank test. Univariable logistic regression models were estimated for all parameters measured and multivariable logistic regression models were fitted using a backward-conditional stepwise algorithm in order to find the most powerful subset of independent predictors. Considering the limited number of events observed, we started from different lists of parameters, each one containing a maximum of 8 candidate predictors chosen on the bases of clinical a priori evaluation, from the list of the significant ones at univariable screening, trying to minimize for each list the known biological collinearity between parameters. As a final list, we maintained the subgroup of variables each time selected by the backward-conditional stepwise algorithm. The only exception