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Clinical and prognostic impact of chronotropic incompetence in patients with hypertrophic cardiomyopathy☆

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ABSTRACT

Background: A blunted heart rate (HR) response is associated with an impaired peak oxygen uptake (pVO_2), a powerful outcome predictor in hypertrophic cardiomyopathy (HCM). The present multicenter study sought to determine the prognostic role for exercise-induced HR response in HCM.
Methods: A total of 681 consecutive HCM outpatients on optimized treatment were recruited. The heart failure (HF) end-point was death due to HF, cardiac transplantation, NYHA III-IV class progression, HF worsening leading to hospitalization and severe functional deterioration leading to septal reduction. The sudden cardiac death (SCD) end-point included SCD, aborted SCD and appropriate implantable cardioverter defibrillator discharges.
Results: During a median follow-up of 4.2 years (25–75th centile: 3.9–5.2), 81 patients reached the HF and 23 the SCD end-point. Covariates with independent effects on the HF end-point were left atrial diameter, left ventricular ejection fraction, maximal left ventricular outflow tract gradient and exercise cardiac power (ECP = pVO_2*systolic blood pressure) (C-Index = 0.807) whereas the HCM Risk-SCD score and the ECP remained associated with the SCD end-point (C-Index = 0.674). When the VO_2-derived variables were not pursued, peak HR (pHR) re-entered in the multivariate HF model (C-Index = 0.777) and, marginally, in the SCD model (C-index = 0.656). A pHR = 70% of the maximum predicted resulted as the best cut-off value in predicting the HF-related events.
Conclusions: The cardiopulmonary exercise test is pivotal in the HCM management, however the pHR remains a meaningful alternative parameter. A pHR < 70% identified a HCM population at high risk of HF-related events, thus calling for a reappraisal of the chronotropic incompetence threshold in HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by markedly heterogeneous clinical spectra [1]. Nowadays, although the sudden cardiac death (SCD) remains the most devastating clinical manifestation, the emerging challenge is to identify those HCM patients at high risk of overall relevant cardiovascular events [2–4]. Recently, few large studies indicated the reduced peak oxygen uptake (pVO_2) during a maximal cardiopulmonary exercise test (CPET) as a strong outcome predictor in HCM [5–9]. However, notwithstanding the heart rate (HR) contributes physiologically to the pVO_2 value [10,11], the so-called chronotropic incompetence (CI) in HCM has been poorly investigated. Indeed, the different CI definitions, the lack of a uniform methodology and the concomitant negative chronotropic therapies acted all as possible confounders [12].

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Nonetheless, the exercise-induced HR response analysis could be an easy available tool in daily clinical practice and, up to now, no study yet clarifies its possible clinical and prognostic role in a large consecutive HCM population.

The present multicenter study sought to investigate the impact of the exercise-induced HR variables as regards the cardiovascular events prediction in HCM and, possibly, to define a clinically meaningful cut-off value to be adopted. Accordingly, we analysed separately a heart failure (HF) and a SCD end-point, using two methods selected from the most often used, the maximum age-predicted pHR (pHR%) and the maximum pHR reserve (pHRR%).

2. Methods

2.1. Study sample

The initial study cohort consisted of 767 consecutive outpatients with HCM, recruited and followed in 6 HCM Italian centers between September 2007 and August 2017: Azienda Ospedaliera Sant'Andrea, Sapienza University, Rome ($n = 423$); Azienda Ospedaliera San Camillo Forlanini, Rome ($n = 221$); Ospedale Monaldi–Second University of Naples, Naples ($n = 52$); Centro Cardiologico Monzino, University of Milan, Milan ($n = 20$); Ospedali Riuniti, University of Foggia, Foggia ($n = 18$); Ospedali Riuniti Trieste, University of Trieste ($n = 33$). Diagnosis of HCM was based on the presence maximal wall thickness ≥ 15 mm unexplained by abnormal loading conditions or in accordance with published criteria for the diagnosis of disease in relatives of patients with unequivocal disease [2,3].

Primary study inclusion criteria were stable clinical conditions with unchanged medications for at least 6 months and capability to perform a maximal, symptom-limited CPET. Exclusion criteria were: previous septal reduction therapy, pacemaker-dependent atrial rhythm and atrial fibrillation. Patients with known metabolic diseases or syndromic causes of HCM were also excluded from the analysis; specifically we excluded two patients affected by Fabry Disease, 1 with Noonan and 1 with Leopard syndrome. Data were independently collected at each participating centre using a uniform methodology. A computerized collection data form was created and approved, and clear rules to fill in were established. Regular feedback to investigators was organized by the data director center (Azienda Ospedaliera Sant'Andrea – Sapienza University-Rome). Checking data quality included range and consistency checks and checking for missing data. The study complied with the ethical standards of the Declaration of Helsinki and was reviewed and approved by the institutional ethics committee. Written informed consent was given by all participants. The authors from each participating center guarantee the integrity of the data from their institution and have agreed to the article as written.

2.2. Patients' clinical assessment

Each HCM patient who fulfilled the initial inclusion criteria underwent a full clinical assessment, including clinical history with pedigree analysis and New York Heart Association (NYHA) classification, 24-h ECG Holter monitoring, transthoracic Doppler echocardiography and CPET. The usual five SCD risk factors were also collected: (a) familiar history of SCD (history of HCM-related SCD in at least 1 first-degree or other relatives <50 years old); (b) massive LV hypertrophy (maximal wall thickness ≥30 mm); (c) at least 1 run of non-sustained ventricular tachycardia (≥3 consecutive ventricular beats at ≥120 beats/min and < 30 s in duration on 24-h ECG Holter monitoring); (d) unexplained syncope judged inconsistent with neurocardiogenic origin; (e) abnormal blood pressure response to exercise (failure to increase systolic blood pressure by at least 20 mm Hg from rest to peak exercise or a fall of ≥20 mm Hg). The HCM Risk-SCD score was also obtained by using the calculator provided with the 2014 ESC guidelines [3]. The following echocardiographic measurements, obtained according to international guidelines [13], were considered: LV end-diastolic diameter (parasternal long axis), the greatest LV thickness (maximal wall thickness measured at any LV site), left atrial diameter (LAd, parasternal long axis), the highest maximal LV outflow tract gradient among those measured at rest, in the orthostatic position and after the Valsalva maneuver ($LVOTG_{max}$, apical 4-chamber view) [14], and LV ejection fraction (LVEF) with Simpson's biplane methods (LVEF, apical 4-chamber view). A maximal, symptom-limited CPET was performed on an electronically braked cycloergometer and a personalized ramp exercise protocol was chosen, aiming at a test duration of 10 ± 2 min [15]. The exercise was preceded by a few minutes of resting breath-by-breath gas exchange monitoring and by a 3 min unloaded warm-up. CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort but it was considered truly maximal or nearly maximal if the respiratory exchange ratio was ≥1.05.

A 12 lead ECG, diastolic and systolic blood pressure were recorded during CPET. Baseline HR, peak HR, and ΔHR (pHR – baseline HR) were also collected during CPETs, baseline HR being measured after at least 2 min of rest in a seated position on the cycloergometer. Peak HR and ΔHR were also analysed as a percentage of the maximum predicted values according to the standard formulas [12,16]:

$$\%\text{pHR} = \{[\text{pHR}/(220-\text{age})] * 100\};$$

$$\%\text{pHRR} = \{\Delta\text{HR}/[(220-\text{age})-\text{baseline HR}] * 100\}.$$

The presence of CI was classified according to the abovementioned methods and its prevalence described using different cut-off values varying between 65% and 80% of the maximum predicted values.

A breath-by-breath analysis of expiratory gases and ventilation was performed, and peak values were the highest observed (20 s average). The predicted peak VO_2 was determined by using the sex, age, and weight-adjusted Hansen/Wasserman equations [10,11]. The exercise cardiac power (ECP = pVO_2 * peak systolic blood pressure), also known as "circulatory power", was obtained considering pVO_2 value as percentage of predicted (ECP%) [17].

2.3. Clinical outcomes

All patients had planned clinical reviews every 6–12 months or earlier according to their clinical status. Follow-up duration was defined as the time interval between the CPET examination and either the first event or the last visit/telephone interview in the case of no events.

Two distinct end-point were tested. The HF endpoint included the following events: death from HF, cardiac transplantation, progression to NYHA class III–IV caused by end-stage phase with or without LVEF <50% (hypokinetic dilated phase or restrictive phenotype evolution), hospitalization because of HF symptoms or signs development, and septal reduction procedure for significant HF signs/symptoms development. The SCD end point included only SCD, aborted SCD and appropriate implantable cardiac defibrillator (ICD) shock on ventricular fibrillation or sustained ventricular tachycardia. Death from other causes or other cardiovascular events were not considered in the present survival analysis. The causes of death, as well as the other events, were ascertained by experienced cardiologists at each center using hospital and primary healthcare records, death certificates, postmortem reports, and interviews with relatives and/or physicians.

2.4. Statistical analysis

Unless otherwise indicated, all data are expressed as mean ± SD. Categorical variables were compared with a difference between proportion tests; a two-sample *t*-test was used to compare the continuous data between groups. Preliminarily, an extension of the Shapiro-Wilk test of normality was performed. We therefore focused on the distribution of the survival times by adopting the Cox proportional hazards regression model. We performed a step-wise selection of the predictors to be included in the model. A 5% significance level was used to select covariates for the final HF multivariate model whereas, as respect to the SCD end-point analysis, a 15% significance level was adopted due to the relatively small number of events [18]. Both the univariate and the multivariate survival analysis were performed by adopting the stratified Cox regression model, allowing for separate baseline functions for each strata according to the beta-blocker use. Due to multicollinearity, in the multivariate Cox analysis all the chronotropic variables (r values for Pearson correlation between pHR, pHR%, pHRR% always higher than 0.8), as well as the VO_2-derived parameter were added to the prognostic model one at a time to prevent possibly misleading inference on the parameter estimates (maximum number of covariates tested for the HF and SCD endpoint equal to 7 and 3 respectively). Furthermore, we fit a multivariate Cox proportional hazards regression model including all clinical variables except from those VO_2-derived. Discrimination of variables to be included in the final multivariate model specification was performed by the well-known C-index. We retained the models with the best trade-off between model complexity and model fit judged by the log-likelihood (using the Akaike Iinformation Criterion). To determine whether a fitted Cox regression model adequately describes the data, we considered three kinds of diagnostics: (i) for violation of the assumption of proportional hazards; (ii) for influential data; and (iii) for non-linearity in the relationship between the log hazard and the predictors. A test of the proportional hazards assumption was performed for each covariate by correlating the corresponding set of scaled Schoenfeld residuals with a transformation of time based on the Kaplan–Meier estimate of the survival function. Moreover, to check for non-linearity - that is, an incorrectly specified functional form in the parametric part of the model - the martingale residuals were considered (against covariates). Last, a receiver operating characteristic (ROC) analysis has been used to determine the predictive capability of the pHR% and pHRR% in identifying the pre-specified end-points. The behaviour of a cut-off dependent performance measure, such as accuracy, was considered across the range of all cut-offs. Cut-off values were identified maximizing the accuracy [(true positive + true negative)/total sample]. The optimal cut-off was the threshold that maximized the distance to the identity (diagonal) line according to Youden's J statistic. The cut-off values were accordingly tested in the univariate survival analysis.

We therefore validated all the models via an internal validation of a model via a bootstrap procedures, which enable to estimate the degree of optimism of a fitted model and the extent to which the model will be able to generalize outside the training dataset [19]. Statistical analysis was performed using R (R Development Core Team, 2014). A *p* value lower than or equal to 0.05 was generally considered as statistically significant.

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