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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

What about chronotropic incompetence in heart failure with mildly reduced ejection fraction? Clinical and prognostic implications from the Metabolic Exercise combined with Cardiac and Kidney Indexes score dataset

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Aims

Chronotropic incompetence (CI) is a strong predictor of outcome in heart failure with reduced ejection fraction, however no data on its clinical and prognostic impacts in heart failure with mildly reduced ejection fraction (HFmrEF) are available. Therefore, the study aims to investigate, in a large multicentre HFmrEF cohort, the prevalence of CI as well as its relationship with exercise capacity and its prognostic role over the cardiopulmonary exercise testing (CPET) parameters.

Methods and results

Within the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) database, we analysed data of 864 HFmrEF out of 1164 stable outpatients who performed a maximal CPET at the cycle ergometer and who had no significant rhythm disorders or comorbidities. The primary study endpoint was cardiovascular (CV) death. All-cause death was also explored. Chronotropic incompetence prevalence differed depending on the method (peak heart rate, pHR% vs. pHR reserve, pHRR%) and the cut-off adopted (pHR% from ≤75% to ≤60% and pHRR% ≤ 65% to ≤50%), ranging from 11% to

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62%. A total of 84 (9.7%) CV deaths were collected, with 39 (4.5%) occurring within 5 years. At multivariate analysis, both pHR% [hazard ratio 0.97 (0.95–0.99), $P < 0.05$] and pHRR% [hazard ratio 0.977 (0.961–0.993), $P < 0.01$] were associated with the primary endpoint. A pHR% ≤ 75% and a pHRR% ≤ 50% represented the most accurate cut-off values in predicting the outcome.

Conclusion The study suggests an association between blunted exercise-HR response, functional capacity, and CV death risk among patients with HFmrEF. Whether the CI presence might be adopted in daily HFmrEF management needs to be addressed in larger prospective studies.

Lay summary

- Chronotropic incompetence is an easy-to-obtain additive parameter for cardiovascular death risk stratification in heart failure with mildly reduced ejection fraction (HFmrEF).
- Peak heart rate and peak heart rate reserve are associated with exercise capacity in HFmrEF.
- Peak heart rate and peak heart rate reserve are associated with cardiovascular death in HFmrEF.

Keywords Heart failure • Heart rate • Chronotropic incompetence • Cardiopulmonary exercise test • Prognosis • MECKI score

Introduction

The concept of heart failure with mildly reduced ejection fraction (HFmrEF) has been introduced almost 10 years ago,[1] but its clinical trajectories and correlating factors are still unclear, most likely due to an under-representation of these kind of patients in randomized controlled trials and in clinical registries.[2,3] Recently, increasing evidence has supported the use of cardiopulmonary exercise testing (CPET) to obtain a comprehensive functional and a prognostic assessment in this setting.[4–9] Indeed, we correctly identified, in a large multicentre HFmrEF cohort, a subgroup with the highest cardiovascular (CV) risk, solely by using a combination of ventilatory efficiency and peak oxygen uptake (pVO_2) values.[10] Conversely, the clinical implications of a blunted exercise-induced HR response in this context have not yet been explored, as there are no available data regarding the prevalence of chronotropic incompetence (CI) and its possible prognostic significance. As in the other two HF categories (i.e. reduced ejection fraction, HFrEF, and preserved ejection fraction, HFpEF),[11–15] a relationship between CI and functional capacity appears likely, which implies a possible prognostic role in this population. Thus, this aspect is undoubtedly of pathophysiological and clinical interest as it might be helpful in refining HFmrEF risk stratification, particularly in centres where CPET cannot be executed.

Therefore, we used the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) dataset,[16–19] likely the world largest repository of clinical data, that includes CPET information obtained from stable HF outpatients on optimized treatment, to address the following items in a sizeable HFmrEF cohort: (i) prevalence of CI, estimated by using the age-predicted peak HR (pHR%) and the peak HR reserve (pHRR%); (ii) relationships between exercise-induced HR response and functional capacity, assessed objectively in terms of pVO_2; and (iii) prognostic value of HR-derived variables in terms of CV and overall mortality risk.

Methods

Study sample

We retrospectively analysed data of 1168 consecutive stable HFmrEF outpatients from the MECKI Score database followed by the MECKI Score Research Group in 27 Italian HF centres.[16,17] All patients included in the MECKI Score database had HF signs and/or symptoms (NYHA functional classes I to IV, stage C of American College of Cardiology/American Heart Association (ACC/AHA) classification) and were on stable clinical conditions with unchanged medications for at least three months. For the present analysis, primary inclusion criteria were no major cardiovascular treatment or intervention scheduled, availability of a maximal symptom-limited CPET performed on a cycle ergometer, and a left ventricular ejection fraction (LVEF) ranging from 40% to 49% at the time of CPET execution. The exclusion criteria were history of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive/restrictive lung disease, primary pulmonary hypertension, moderate-to-severe anaemia (haemoglobin < 10 g/dL), significant peripheral vascular disease, and exercise-induced angina and/or ST changes. Furthermore, to avoid confounding variables, HF patients with atrial fibrillation at the study run-in,[20–22] those with second or higher degree atrioventricular block as well as with a pacemaker-dependent HR were also excluded. The study and the access to personal health data were approved by local internal review boards, and all patients gave written informed consent to participate in the study.

Cardiopulmonary exercise testing

A maximal, symptom-limited CPET was performed on an electronically braked cycle ergometer connected to a metabolic chart. A personalized ramp exercise protocol was chosen, aiming at a test duration of 10 ± 2 min.[23] The exercise was preceded by a 2 min resting phase with breath-by-breath gas exchange monitoring followed by a 3 min unloaded warm-up. CPET was self-terminated by the patient when referring maximal effort and as confirmed by a peak respiratory exchange ratio ≥ 1.05. A breath-by-breath analysis of O_2, carbon dioxide (CO_2), and ventilation (VE) was performed, and peak values were computed as the highest observed measurements (20 s average). The predicted pVO_2 was determined by using the sex, age, and weight-adjusted Hansen/Wasserman equations.[24] The anaerobic threshold (AT) was identified through a V-slope analysis of VO_2 and CO_2 production (VCO_2), and was confirmed through the specific behaviour of the ventilatory equivalents of O_2 (VE/VO_2) and CO_2 (VE/VCO_2), as well as through the end-tidal pressure of O_2 and CO_2. The relation between VE and VCO_2 (i.e. the ventilatory efficiency) was analysed as the slope (VE/VCO_2 slope) of the linear relationship between VE and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period.[24,25]

A 12-lead electrocardiogram, blood pressure, and HR were recorded. Specifically, pHR was collected during CPETs whereas rest HR was measured after at least 2 min of rest in a seated position on the cycle ergometer. Peak HR and ΔHR (pHR – rest HR) were also analysed as a percentage of maximum predicted values according to the standard formulas.[14,20] The possible clinical impact of the exercise-induced HR-derived variables was explored using continuous values as well as defining CI according to different cut-off values with 5% of the predicted values incremental steps.

Patients' follow-up and study endpoints

Patients' prospective follow-up was carried out according to the local HF programme. All HF centres participated in the MECKI Score Research Group, whose protocol was preliminarily established and reported.[16,17] Briefly, follow-up started when clinical evaluation and CPET were performed, and it ended with either the last clinical evaluation in the respective enrolling centre or with the patient's death or cardiac transplantation/left

ventricular assistance device (LVAD) implantation. Notably, in the present analysis, the primary study endpoint was exclusively CV death, but a composite endpoint of all-cause mortality was also explored. Patients who underwent urgent cardiac transplantation or LVAD implantation were considered as censored at the time of the event.

Statistical analysis

Unless otherwise indicated, all data are expressed as mean ± standard deviation. Data with skewed distribution are given as median and interquartile range (75th percentile–25th percentile). Categorical variables were compared with a difference between proportion test; a two-sample *t*-test was used to compare the general characteristics and other continuous linear data between the study groups; and Wilcoxon test was used to compare non-normally distributed variables. Possible linear correlations between exercise-induced HR variables and main CPET parameters have been explored by Pearson correlation coefficient (*r*).

We began our analysis by initially examining the distribution of survival times within the entire study group. This exploration involved the application of the univariate Cox proportional-hazards regression model. A gamma-distributed frailty is included in the model at the centre level to allow for intra-centre correlation in patients' survival. Subsequently, we conducted a stepwise selection process to determine which predictors should be incorporated into the multivariate model. This selection process combined elements of both forward and backward selection methodologies. The identification of variables to include in the final multivariate model was guided by the C-index, allowing us to prioritize those variables with superior discriminatory power. We retained models that struck an optimal balance between complexity and goodness of fit, a judgment guided by the log-likelihood and the Akaike Information Criterion (AIC).

Recognizing the need to mitigate multicollinearity issues, we introduced parameters one at a time into the prognostic model (cut-off used to define multicollinearity equal to 0.75). Specifically, we added pVO_2 and VO_2AT separately and then pHR% and pHRR% to ensure the integrity of the multivariate Cox procedure. To address multicollinearity, however, other techniques with different pros and cons can be employed, such as variable selection, combining correlated variables, or utilizing dimensionality reduction methods like principal component analysis before conducting Cox regression analysis. 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 nonlinearity 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. Focusing on residuals, a graphical diagnostic can be provided to check for influential observations. A matrix of estimated changes in the regression coefficients was obtained upon deleting each observation in turn. Then, the magnitudes of the largest obtained values were compared to the regression coefficients. Given that an incorrectly specified functional form in the parametric part of the model (e.g. nonlinearity) might be a potential problem in Cox regression, the Martingale residuals were plotted against predictors to detect nonlinearity. Nonlinearity was obviously not an issue for dichotomous predictors.

Eventually, receiver operating characteristic (ROC) curves were also estimated to display the capacity of pHR% and pHRR% to discriminate between survivors and non-survivors with respect only to the 5-year CV endpoint. According to this approach, we reported the thresholds corresponding to the best sum of sensitivity and specificity. Furthermore, we also tested the accuracy of a number of possible alternative pHR% and pHRR% cut-off values, usually adopted in clinical settings. Statistical analysis was performed using R (R Development Core Team, 2009) packages. All tests were two-sided. A $P \leq 0.05$ was considered as statistically significant.

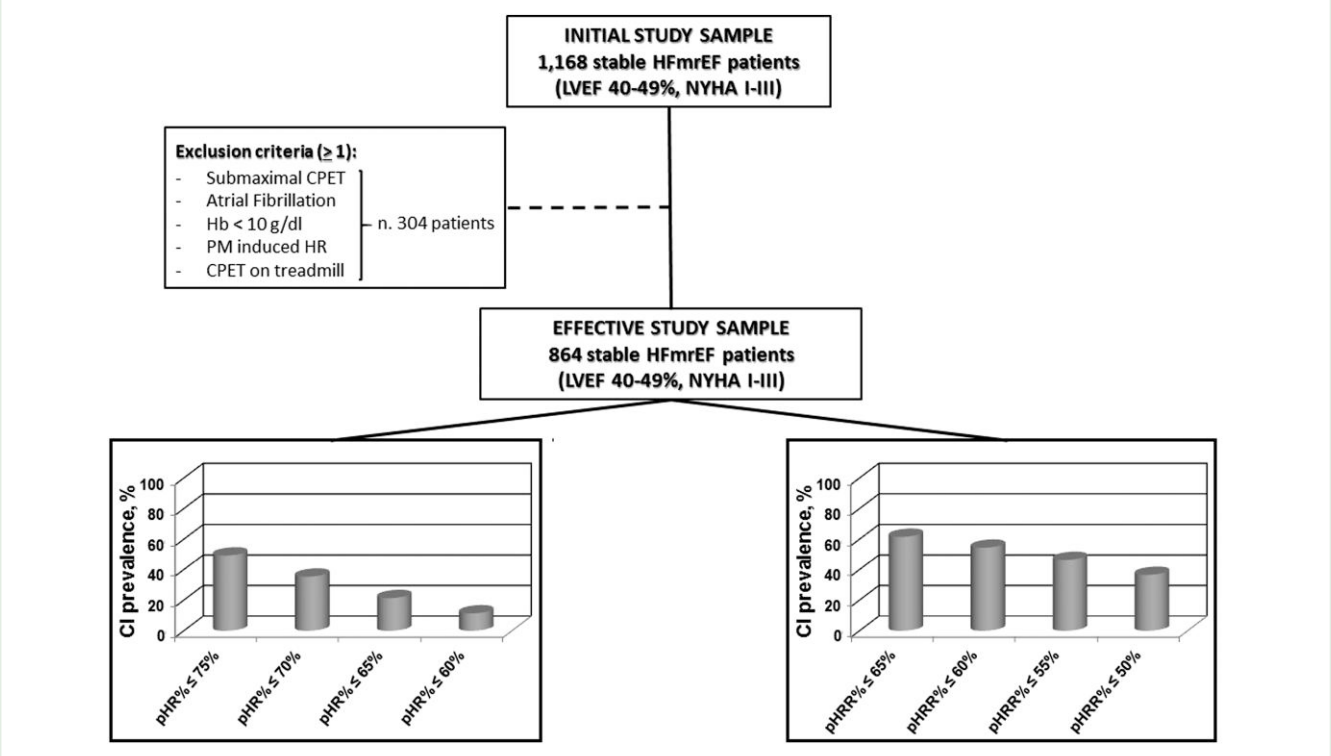

Figure 1 Study screening procedures and CI prevalence in the effective HFmrEF sample. Diagram showing the step-by-step screening procedures and data about the CI prevalence according to different methods and cut-off values. HFmrEF, heart failure with mildly reduced ejection fraction; CI, chronotropic incompetence; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; R.E.R., respiratory exchange ratio; CPET, cardiopulmonary exercise test; Hb, haemoglobin levels; PM, pacemaker; CI, chronotropic incompetence; HR, heart rate; pHR%, peak HR expressed as percentage of the maximum predicted; pHRR%, peak HR reserve expressed as percentage of the maximum predicted.

Table 1 Main clinical variables of the overall heart failure with mildly reduced ejection fraction study sample (n. 864 patients)

General data	
Age, years	60 ± 13
Male, *n* %	688 (79)
Body mass index, kg/m^2	26.9 ± 4.4
NYHA I–II, *n* (%)	735 (85)
Ischaemic aetiology, *n* (%)	416 (48)
LVEF, %	43.3 ± 2.8
ICD, *n* (%)	130 (15)
Exercise testing variables	
Rest HR, b.p.m.	66 ± 10
pHR, b.p.m.	122 ± 23
ΔHR, b.p.m.	55 ± 22
pHR%, % of predicted	77 ± 13
pHRR%, % of predicted	59 ± 22
AT identified, *n* (%)	772 (89)
VO_2 at AT, mL/kg/min	11.8 ± 3.8
pVO_2, mL/kg/min	17.5 ± 5.4
pVO_2, % of predicted	66 ± 17
VE/VCO_2 slope	30.2 ± 6.1
RER	1.17 ± 0.11
Treatment	
ACEi/ARBs, *n* (%)	766 (89)
Beta-blockers, *n* (%)	730 (85)
Beta-blockers dosage[a], mg	25 ± 19
MRA, *n* (%)	314 (36)
Loop diuretics, *n* (%)	512 (59)

Data are expressed as mean ± SD, as absolute number of patients (% on total sample), or as median [25th–75th percentile].
ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AT, anaerobic threshold; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; pHR, peak HR; ΔHR, (pHR – rest HR); pHRR, peak HR reserve; pVO_2, peak oxygen consumption; RER, respiratory exchange ratio; VE/VCO_2, ventilatory equivalents of carbon dioxide.
[a]Carvedilol dose equivalent.

Results

General characteristics of the study population

Starting from 1168 HFmrEF consecutive outpatients, a total of 864 met the inclusion/exclusion criteria and were considered for the present study. Indeed, data from 304 patients were ruled out due to one or more of the previous mentioned exclusion criteria (*Figure 1*). *Table 1* reports in detail the main clinical and exercise test data as well as concomitant therapeutic strategies collected at the study run-in in the overall sample. The study population consisted of middle-aged male patients, mostly in NYHA functional classes I–II, with a moderate exercise limitation (pVO_2 averagely 65% of the maximum predicted). Notably, there was a substantial percentage of patients in whom the AT could not be identified (nearly 10% of the total sample). Heart failure treatment was in accordance with the guidelines applied at the time of the CPET, with β-blocker treatment being considered optimized by the patients' HF cardiologist.[26] To avoid possible confounding with respect to the different β-blocker agents, the doses were converted to equivalent doses of carvedilol. The daily dosage in patients taking atenolol, metoprolol, or metoprolol XL was divided by two whereas the dose for bisoprolol or nebivolol was multiplied by five.[1,14,27,28] Within the 730 patients on β-blockers (85%), the carvedilol-equivalent daily dose was 25 ± 19 mg, with 323 patients (44%) having a carvedilol-equivalent dose ≥ 25 mg/day (high dose group). Lastly, a small percentage of subjects received digoxin (n. 53 patients, 6.1%) and amiodarone (n. 57 patients, 6.6%), which were not considered to be sufficient to interfere with the results that were obtained.

Chronotropic incompetence prevalence and association with functional capacity

The prevalence of CI was remarkable, but it differed significantly depending on the method and the cut-off value, ranging from 11%, with a pHR% cut-off value ≤ 60%, to 62%, with a pHRR% cut-off value ≤ 65% (*Figure 1*). A significant relationship was found between pVO_2 and the exercise-induced HR response, either in terms of pHR or ΔHR (*Figure 2*, upper panels). Accordingly, the lower the pHR% and pHRR% cut-off values, the worse was the functional capacity characterizing the subgroup (*Figure 2*, lower panels). *Table 2* supplies a detailed overview of the baseline relationship between each of the exercise-induced HR indexes and the main CPET parameters. In completion, Supplementary material online, *Table S1* of the supplementary file details the main clinical and exercise test data in the overall sample, grouped according to the different methods and cut-off criteria, while Supplementary material online, *Figure S1* shows the pHR%, pHRR%, and deltaHR average values according to β-blocker therapy.

Survival analysis according to cardiopulmonary exercise testing-derived variables

The median follow-up was 4.97 years (25th–75th interquartile range, 2.25–8.1 years). During the entire follow-up, a total of 143 (16.5%) deaths were collected (n. 84 cardiovascular deaths), with 39 cardiovascular deaths (4.5%) on a total of 62 deaths (7.2%) registered at the 5th year of follow-up. Notably, an additional eight patients underwent urgent heart transplantation or LVAD implantation and, as previously stated, were censored at the time of the event.

Supplementary material online, *Table S2* reports the univariate analysis of the main CPET-derived variables with respect to the prespecified endpoints at 5 years. Despite some marginal difference in magnitudes, most of the CPET-derived data confirmed their well-known association to the risk of both overall and CV death. Of note, all the exercise-induced HR-derived parameters were able to predict the two endpoints, pHR and ΔHR absolute values, and therefore represent the most powerful predictive variables.

Thereafter, by pursuing a multivariate approach at 5 years, pHR% remained independently associated to the primary CV endpoint, together with pVO_2 and VE/VCO_2 (C-index for the entire model 0.817) (*Figure 3*). Conversely, the addition of pHRR% undermined the pVO_2 from to the multivariate model (C-index for the entire model 0.821) (*Figure 3*). Possible interactions between β-blocker treatment (none, high dose, low dose) and independent variables have been explored, the AIC not speaking in favour of the inclusion of any interactions. Similar results have been found by pursuing a multivariate approach at 10 years (see Supplementary material online, *Table S3*) as well as considering the entire follow-up (see Supplementary material online, *Table S4*) whereas the low number of events precluded survival analysis at 1 year (n. 8 events) and at 2 years (n. 12 events).

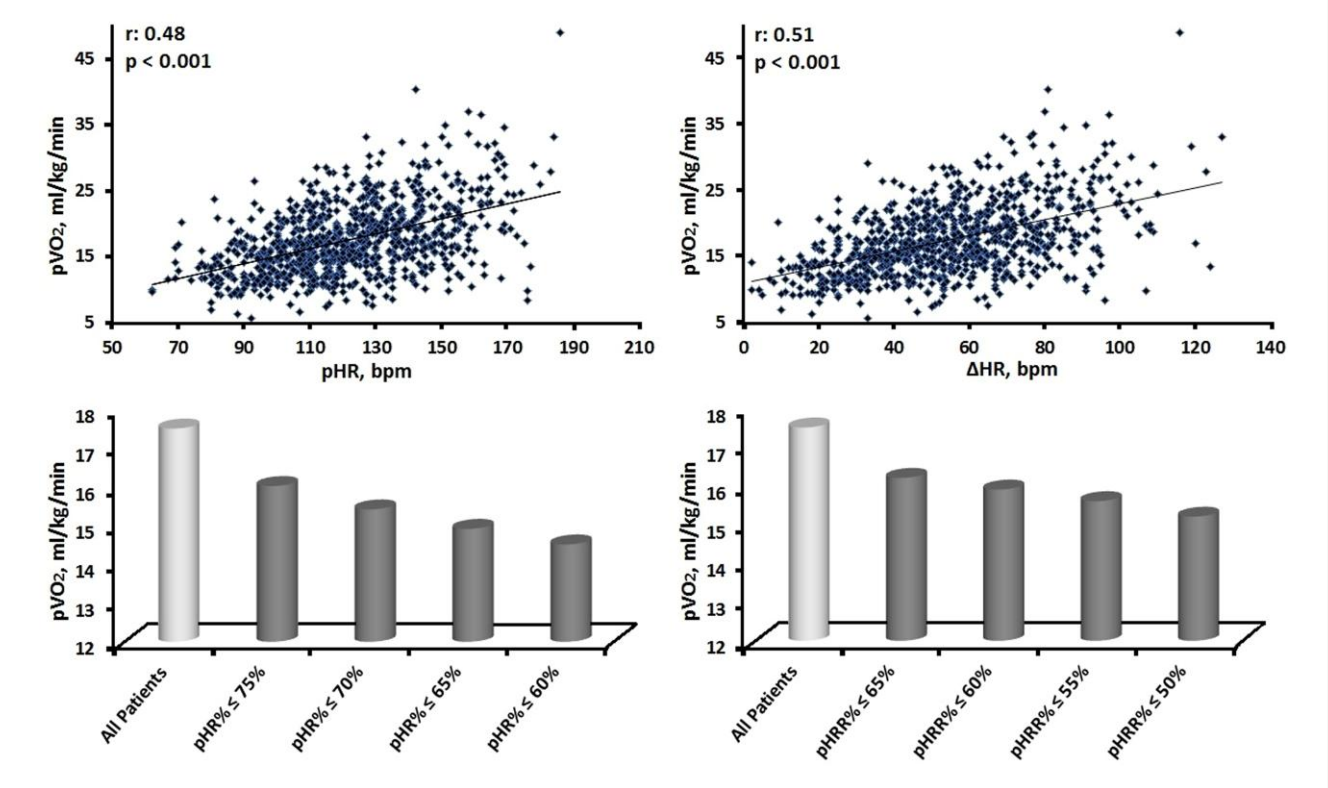

Figure 2 Relationships between exercise-induced HR response and pVO_2 in the HFmrEF sample (n. 864). Upper panels: Pearsons' relationship between pVO_2 and pHR (left) and between pVO_2 and ΔHR (right). Lower panels: average pVO_2 values distribution in CI groups categorized according pHR% (left) and pHRR% (right) different cut-off values. HFmrEF, heart failure with mildly reduced ejection fraction; pVO_2, peak oxygen uptake; pHR, peak heart rate; ΔHR, difference between peak HR and rest HR; pHR%, peak HR expressed as percentage of the maximum predicted; pHRR%, peak HR reserve expressed as percentage of the maximum predicted.

Chronotropic incompetence accuracy analysis (receiver operating characteristic analysis)

Finally, focusing on the discrimination power of CI in detecting the risk of cardiovascular death, the ROC analysis showed that the best pHR% threshold was equal to 75.6% [sensitivity 77%; specificity 52%; area under the curve (AUC) 66%] whereas the best pHRR% cut-off value was 49% (sensitivity 65%; specificity 69%; AUC 69%) (*Figure 4*). For clinical purposes, *Table 3* supplies the accuracy data of several routinely used pHR% and pHRR% cut-off values, the most accurate ones being pHR% ≤ 75% and pHRR% ≤ 50%, as their performance resembles the best cut-off values obtained at the ROC analysis.

Discussion

The present multicentre retrospective analysis, conducted on a large cohort of stable HFmrEF outpatients, showed that a significant proportion of these patients suffered from a blunted exercise-induced HR response, with the effective CI prevalence varying greatly based on the different methods and cut-off values adopted. Overall, the presence of CI has been found as strongly correlated to a poor functional capacity, but, most importantly, both pHR% and pHRR% remained independently associated to the HFmrEF CV death risk over the historical CPET parameters (i.e. pVO_2 and VE/VCO_2 slope). Lastly, our data suggest a pHR% ≤ 75% and a pHRR% ≤ 50% as the most accurate CI cut-off values in terms of HFmrEF cardiovascular risk stratification, particularly in those HF centres where CPET cannot be executed.

Table 2 Baseline relationship between exercise-derived heart rate variables and main cardiopulmonary exercise testing variables within the overall heart failure with mildly reduced ejection fraction study sample (n. 864 patients)

	VO_2 at AT, mL/kg/min	pVO_2, mL/kg/min	pVO_2, % of predicted	VE/VCO_2 slope
pHR, b.p.m.	*r*: 0.38	*r*: 0.48	*r*: 0.31	*r*: −0.19
	P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001
ΔHR, b.p.m.	*r*: 0.37	*r*: 0.51	*r*: 0.33	*r*: −0.20
	P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001
pHR%, % of predicted	*r* 0.28	*r*: 0.34	*r*: 0.31	*r*: −0.10
	P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.05
pHRR%, % of predicted	*r*: 0.32	*r*: 0.40	*r*:0.33	*r*: −0.12
	P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.01

For abbreviations, see *Table 1*.

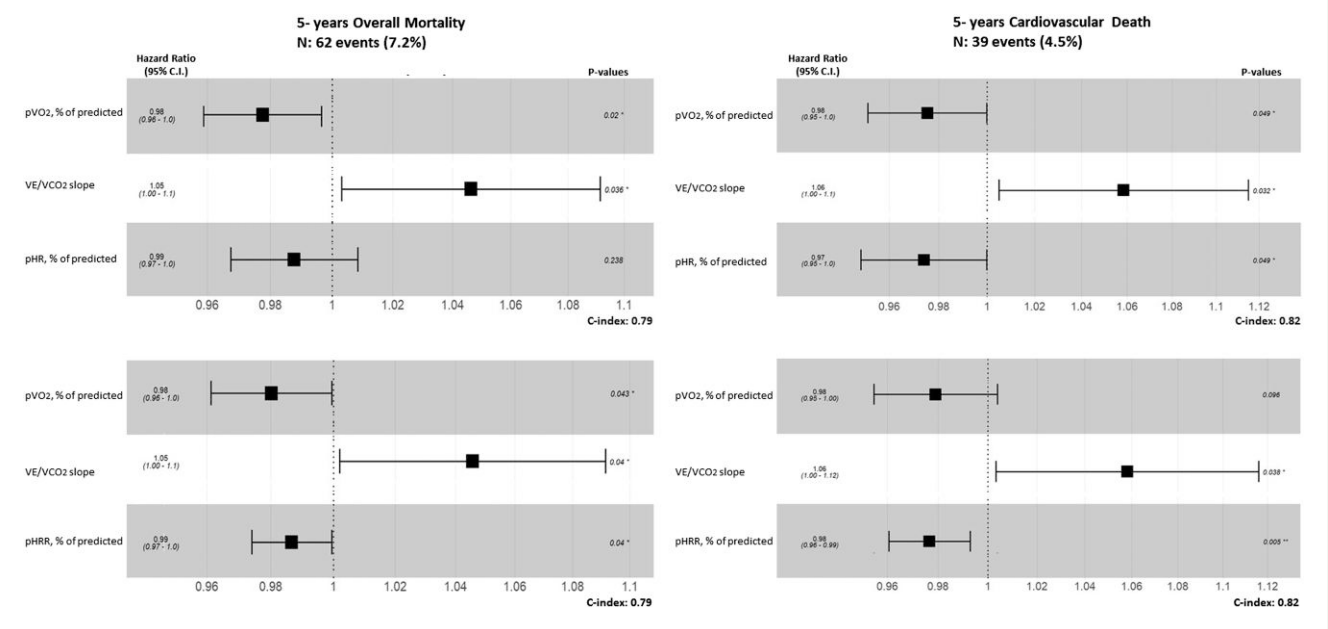

Figure 3 Multivariate Cox proportional survival analysis within the HFmrEF population (n. 864 patients). Forest plots based on the results of multivariate analysis at 5 years of the variables associated with overall (left panels) and cardiovascular mortality (right panels). Note that pHR% (upper panels) and pHRR% (lower panels) have been pursued one at time into the multivariate model (see text for the statistical methods).

A reduced HR response to maximal exercise has been extensively shown to be related to an impaired functional capacity as well as to a poor outcome in HFrEF[11–14] and, recently, in HFpEF patients as well.[15,29,30] A reduced myocardial sensitivity to sympathetic modulation, together with a β-receptor down-regulation as well as the anatomical and functional changes in the sinus node properties, represents the most common hypothesized underlying mechanisms.[31–35] Supporting a connection between pHR and HF progression, we recently highlighted how complex predicting the maximal HR may be in the single HFrEF patient, depending on several factors (i.e. ageing, LVEF, Hb levels, body mass index, and modification of diet in renal disease) involved in determining true HF severity.[36] In the context of HFpEF, some recent experimental studies explored the possible functional and clinical outcomes that may be obtained through CI-targeted interventions, such as β-blocker withdrawal,[37] moderately accelerated personalized pacing rate,[38] or, even *ad hoc* implantation of a pacemaker.[39] Despite some promising results obtained even in the HFpEF setting, numerous issues ought to address (i.e. long-term effects, adverse events, and prognostic impact). However, although studies have supported the use of exercise-induced HR-derived variables in both HFrEF and HFpEF, literature regarding its use in HFmrEF is lacking. Growing evidence suggests that the CPET and specifically the pVO_2 assessment represent a useful tool in the HFmrEF management and risk stratification.[6–10] Of note, as per the Fick law, the pVO_2 and the HR response are closely dependent variables, with an average four-fold VO_2 increase observed in a healthy subject during maximal exercise being associated with a 2.2-fold HR increase.[11,40,41] Thus, it seems reasonable that in a HFmrEF setting, a careful chronotropic response evaluation might help the physician in daily clinical practice, especially considering that the CPET is not always available in all HF centres whereas the HR-derived variables are easily obtainable from a simple exercise test. This is supported by the fact that this clinical feature affects a considerable proportion of these patients, as shown in the present study. As expected, the estimated CI prevalence varied significantly according to the method (pHR% or pHRR%) and the cut-off values adopted, ranging from 11% up to 62% of the study population. Moreover, as in the HFrEF population,[14,36,42] the prevalence of CI was, on average, three- to four-fold higher for each cut-off value when adopting the pHRR% with respect to the pHR% method. A novel finding from the analysis carried out in the HFmrEF cohort was the significant relationship between exercise-induced HR response and functional capacity, as assessed objectively in terms of pVO_2. Notably, the resulting coefficients were slightly lower than those we previously reported in a study conducted in HFrEF population.[27] This may be accounted by a greater role of increased HR in determining pVO_2 in patients with a blunted increase in stroke volume (i.e. HFrEF) as well as in a wider contribution of the O_2 artero-venous difference to pVO_2 values (i.e. HFmrEF).

Besides the historical variables (i.e. pVO_2 and VE/VCO_2 slope), most of the other gas-exchange variables obtained at CPET confirmed their significant association with the pre-specified endpoints, including the VO_2 measured at the AT.[22,27] These findings reinforce the emerging role of a full CPET assessment even in HFmrEF category.[7,9] The present study provides data regarding the significance achieved by the HR-derived variables. Indeed, not only at univariate but also at a multivariate analysis, both pHR% and pHRR% were constantly associated to overall and cardiovascular mortality. The addition of pHRR% to the prediction model for cardiovascular mortality resulted in a loss of significance of pVO_2, most likely because of a certain collinearity between these two parameters. Our findings seem to confirm that an accurate analysis of the exercise-induced chronotropic response, possibly together with other most easily available variables (age, NYHA class, LVEF, Hb, etc.), might represent an appropriate alternative in case of CPET unavailability. Although chronotropic variables may be considered as continuous from a pathophysiological viewpoint, the present study provides data regarding the accuracy of various possible pHR% and pHRR% cut-off values, with the 75% and the 50% thresholds being the most accurate in predicting cardiovascular outcome, respectively. Albeit merely speculative, the highly prevalent β-blocker treatment in a setting of 'mildly' impaired myocardial sensitivity to sympathetic modulation might have exerted a more pronounced effect on pHRR

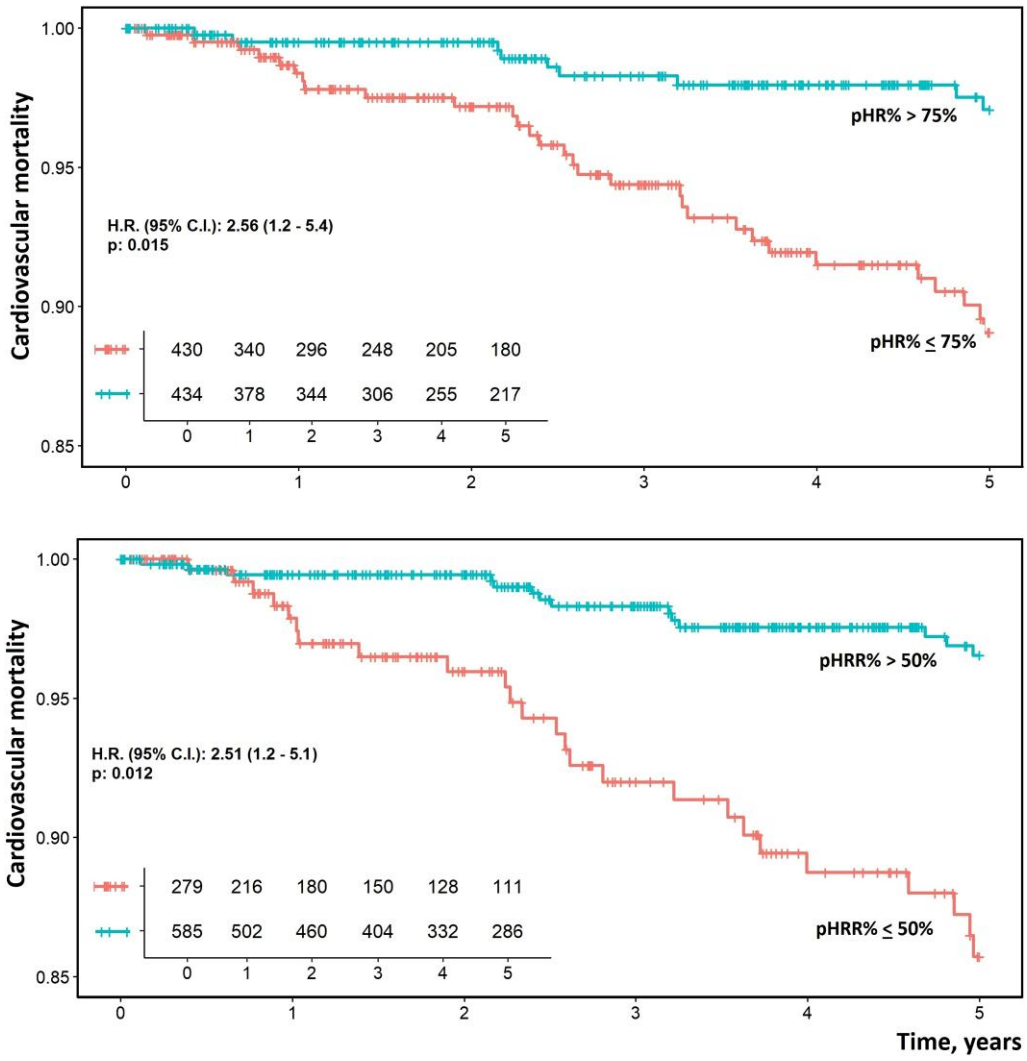

Figure 4 Cardiovascular mortality in the HFmrEF sample (n. 864) according to CI categories. Kaplan–Meier estimator of CV mortality at 5 years conditional on significant independent variables (multivariate analysis) in the HFmrEF sample for pHR% ≤ 75% (upper panel) and for pHRR% ≤ 50% (lower panel). HFmrEF, heart failure with mildly reduced ejection fraction; CI, chronotropic incompetence; CV, cardiovascular.

Table 3 Accuracy of the heart rate-derived variables according to different clinical cut-off with respect to the 5-year cardiovascular death endpoint

HR variables	R.R. (95% C.I.)	*P* value	Sensitivity,%	Specificity,%	PPV, %	NPV, %
pHR% ≤ 75% of predicted	2.806 (1.596–6.555)	0.003	75	52	7	98
pHR% ≤ 70% of predicted	2.801 (1.568–5.257)	0.001	59	67	8	97
pHR% ≤ 65% of predicted	2.759 (1.416–5.118)	0.001	41	81	9	96
pHRR% ≤ 60% of predicted	2.968 (1.592–7.393)	0.003	77	47	6	97
pHRR% ≤ 55% of predicted	3.411 (1.817–9.184)	0.001	74	55	7	98
pHRR% ≤ 50% of predicted	3.272 (1.871–6.853)	0.001	64	68	9	98

C.I., confidence interval; NPV, negative predictive value; PPV, positive predictive value; R.R., relative risk; HR, heart rate; pHR, peak HR; pHRR, peak HR reserve.

% index than on pHR%. Regardless of these findings and although defining CI by cut-off values is desirable in the clinical setting, this categorization shows several limits to its clinical application. Accordingly, considering their negative predictive values, the proposed cut-off values might exert their best clinical utility as screening tool to identify HFmrEF patients at low CV risk.

Limitations

The retrospective nature of the study, together with the low number of cardiovascular events, implies that the data collected may represent merely an approximation of the true importance in evaluating the chronotropic for CV mortality stratification. Furthermore, our analysis involved only recovered HFmrEF patients, which represents a distinct HFmrEF entity[41] whose clinical characteristics, in the context of the MECKI score dataset (patients all in stable clinical condition and on optimized treatment), resembled more those of HFrEF than those of HFpEF. Another possible limitation may be that we examined the prognostic impact of exercise test variables at a single time point, without considering that some clinical strategies may have altered our survival analysis[43] and may have affected patients' transition to another HF category.[44] Similarly, due to the design of the dataset, the pre-specified study endpoints were just overall mortality and pure cardiovascular mortality, which precluded any discussion regarding the use of the explored variables in identifying the mode of death and the use of a composite endpoint that included hospitalization due to HF worsening. Lastly, due to the well-known differences in HR kinetics during effort and peak exercise value as well as in pharmacological strategies,[21,22,45] we excluded patients with atrial fibrillation from the present analysis. Similarly, to avoid further confounding, we also excluded tests executed on a treadmill (i.e. <5% of the usable HR data, all of them deriving from a single centre).

Conclusions

Our retrospective analysis of the clinical and exercise testing data collected in a large multicentre HFmrEF cohort confirms the independent role of pVO_2 and VE/VCO_2 slope in stratifying the HFmrEF risk as well as identifies a poor exercise-induced HR response as detrimental on the functional capacity and, especially, as an easy-to-obtain additive independent parameter for both overall mortality and CV death risk. Cut-off values of 75% and 50% for pHR% and pHRR%, respectively, translate our results well into clinical practice, as they might be useful in centres without CPET availability. Larger prospective studies are necessary to confirm our findings and to evaluate the possible advantages of a CI-targeted treatment in this HF subset.

Authors' contributions

D.M., G.G., and P.A. contributed to the conception of the work. D.M., A.M., P.A.D.L. contributed to data analysis and interpretation. D.M., G.G., E.F., M.L.M. drafted the manuscript. M.P., E.S., and P.A. critically revised the manuscript. All the authors contributed to data collection and finally approved the version to be published.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix

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