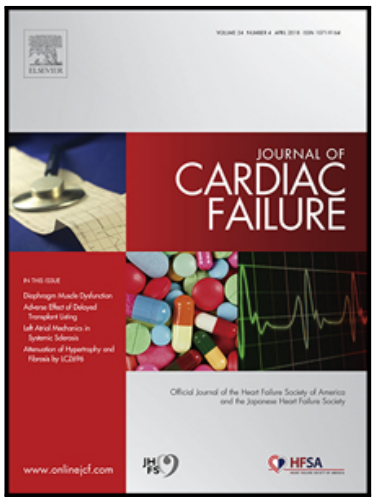

CARDIOVASCULAR DEATH RISK IN RECOVERED MID-RANGE EJECTION FRACTION HEART FAILURE: INSIGHTS FROM CARDIOPULMONARY EXERCISE TEST

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HIGHLIGHTS

- CPET is a useful tool to stratify cardiovascular death risk in rec-HFmrEF population
- Peak VO_2 is the strongest independent predictor of cardiovascular death in rec-HFmrEF
- Most of the CPET variables are associated to the cardiovascular risk in rec-HFmrEF
- $VO_2 \leq 55\%$ and $VE/VCO_2 \geq 31$ identify the rec-HFmrEF subgroup at the highest risk

CARDIOVASCULAR DEATH RISK IN RECOVERED MID-RANGE EJECTION FRACTION HEART FAILURE: INSIGHTS FROM CARDIOPULMONARY EXERCISE TEST.

Running Title: Cardiopulmonary exercise test in rec-HFmrEF

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ABSTRACT

Background–Heart failure with midrange ejection fraction (HFmrEF) represents a heterogeneous category where phenotype, as well as prognostic assessment, remains still debated. The present study explores a specific HFmrEF subset, namely those who recovered from a reduced EF (rec-HFmrEF) and, particularly, it focuses on the possible additive prognostic role of cardiopulmonary exercise testing (CPET).

Methods and Results–We analyzed data of 4,535 HF with reduced EF (HFrEF) and 1,176 rec-HFmrEF outpatients from the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) database. The end-point was cardiovascular death at 5 years. The median follow-up was 1,343 days (25th–75th range, 627-2,403 days). Cardiovascular death occurred in 552 HFrEF and 61 rec-HFmrEF patients. The multivariate analysis confirmed an independent role of the MECKI score's variables in HFrEF (C-index=0.744) whereas, in the rec-HFmrEF group, only age and peak oxygen uptake (pVO_2) remained associated to the end-point (C-index=0.745). A pVO_2 ≤55% of predicted and a ventilatory efficiency ≥31 resulted as the most accurate cut-off values in the outcome prediction.

Conclusions–Present data support the CPET and, particularly, the pVO_2, as a useful tool in the rec-HFmrEF prognostic assessment. Peak VO_2≤55% predicted and ventilatory efficiency ≥31 might help to identify a high risk rec-HFmrEF subgroup.

Key-words: Heart failure; cardiopulmonary exercise test; prognosis; MECKI score.

INTRODUCTION

The heart failure with midrange ejection fraction (HFmrEF) has been introduced originally in the 2016 European Society of Cardiology (ESC) HF Guidelines and defined as a specific setting of HF characterized by an EF ranging between 40% and 49% (1). Differently from the well-known HF with reduced EF (HFrEF), conclusive data about the HFmrEF clinical profile are still lacking due to its relatively recent introduction and, most likely, its heterogeneous composition. Accordingly, again underlining the inherent difficulties in the HFmrEF univocal assessment, significant differences in prognosis between those HFmrEF patients who did not ever experienced a EF lower than 40% and those who recovered from a previous evidence of reduced systolic function (rec-HFmrEF) have been reported (2).

The cardiopulmonary exercise test (CPET) pivotal role in the HFrEF clinical management either as a single CPET parameter (i.e. peak oxygen uptake, pVO_2) (3), as a combination of CPET parameters (i.e. VO_2 at the anaerobic threshold and ventilatory efficiency) (4), or as a part of more comprehensive scores (i.e. MECKI score, Metabolic Exercise combined with Cardiac and Kidney Indexes; HFSS, Heart Failure Survival Score) (5,6), is well established. Particularly, the MECKI score, including pVO_2 and ventilatory efficiency together with four non-CPET prognostic variables (EF, haemoglobin, sodium, renal function), has been created (5), recently validated (7-9) and found, at present, as the most powerful outcome predictor at 1-2 and 4 years of patients with HFrEF (9,10). Accordingly, it might reasonable that also in a multifaceted group, such as the HFmrEF population, the CPET might be extremely useful both to obtain a comprehensive functional and a prognostic assessment. Notwithstanding, up to now, just two studies, on relatively small and inhomogeneous populations, deal with a possible CPET role in the HFmrEF risk stratification (11-12).

Therefore, aim of the present large Italian multicenter study was to characterize and to compare a large cohort of stable HFrEF and rec-HFmrEF patients on an optimized drug regimen both in terms of exercise capacity as well as of instrumental and laboratory variables. Thereafter a possible independent and incremental prognostic value of CPET parameters in identifying those rec-HFmrEF patients at high cardiovascular death risk has been explored.

METHODS

- Study sample

We retrospectively analyzed data of patients with HFrEF and rec-HFmrEF from the MECKI Score database which consists of 6,224 consecutive stable HF patients recruited and followed by MECKI Score Research Group in 27 Italian HF centres (5,10).

All patients included into the MECKI Score database had HF signs and/or symptoms (NYHA functional class 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. All patients had a former evidence of LVEF < 40% but all of them underwent an echocardiographic re-evaluation before the CPET execution, thus allowing a re-categorization in HFrEF and rec-HFmrEF. Other primary inclusion criteria were no major cardiovascular treatment or intervention scheduled, and capability to perform a maximal, symptom-limited CPET. Conversely, 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 anemia (haemoglobin < 10 g/dl), significant peripheral vascular disease, and exercise-induced angina and/or ST changes. HF patients with second or higher degree atrio-ventricular block and those with a pacemaker-dependent heart rate 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 in 95% of the cases on an electronically braked cycloergometer connected to a metabolic chart. A personalized ramp exercise protocol was chosen, aiming at a test duration of 10±2 min (13). The exercise was preceded by a 2 minutes of resting breath-by-breath gas exchange monitoring and by a three-minute unloaded warm-up. A 12-lead electrocardiogram (ECG), blood pressure, and heart rate (HR) were also recorded. Specifically, baseline HR and peak HR were collected during CPETs, baseline HR being measured after at least 2 min of rest in a seated position on the

cycloergometer. In around 5% of the cases, CPETs were performed applying a modified Bruce protocol on a treadmill and in such a cases, peak VO_2 values were reduced by 10% in order to compare functional data obtained from these two different exercise protocols. Peak HR was also analyzed as a % of maximum predicted value according to the standard formula (14). CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort and as confirmed by a peak respiratory exchange ratio (RER) ≥ 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 peak VO_2 was determined by using the sex, age, and weight-adjusted Hansen/Wasserman equations (15).

AT was identified through a V-slope analysis of VO_2 and CO_2 production (VCO_2), and it was confirmed through the specific behaviour of the ventilatory equivalents of O2 (VE/VO_2) and CO2 (VE/VCO_2), as well as through the end-tidal pressure of O_2 and CO_2 (16) The relation between VE and VCO_2 was analysed as the slope (VE/VCO_2 slope) of the linear relationship between VE and VCO_2 from one minute after the beginning of loaded exercise to the end of the isocapnic buffering period. Notably, all tests were re-evaluated by experts blinded to patients' clinical features, and at least one of the local CPET experts underwent a training program at Centro Cardiologico Monzino.

- **Patients' follow up and study end-point**

Patients' prospective follow-up was carried out according to the local HF program. All HF centres participated in the MECKI Score research group, whose protocol was preliminarily established and reported (5). Briefly, follow-up started when clinical evaluation and CPET were performed, and it ended with the last clinical evaluation in the respective enrolling centre, or with the patient's death or cardiac transplantation/left ventricular assistance device (LVAD) implantation. In the present analysis the selected study end-point was pure cardiovascular death, whereas patients who died from non-cardiac causes as well as those who underwent 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 (SD). Data with skewed distribution are given as median and interquartile range (75^{th} percentile - 25^{th} 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; Wilcoxon test was used to compare non-normally distributed variables.

We focused firstly on possible difference with respect the distribution of survival times at 5 years in the two study groups (HFrEF and rec-HFmrEF) by adopting the Cox proportional-hazards regression model. We performed a stepwise selection of the predictors to be included in the model as a mix between forward and backward selection. Given that we cannot include parameters with multicollinearity in the multivariate Cox analysis, pVO_2 and VO_2AT were added to the prognostic model one at a time. In order to determine whether a fitted Cox regression model adequately describes the data, we considered three kinds of diagnostics: (a) for violation of the assumption of proportional hazards; (b) for influential data; (c) 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.

As a confirmation of the first survival analysis, to exclude a possible interference of a number of general parameters known to impact *per se* on HF prognosis, we performed 1:1 statistical matching between the two study groups according to the main clinical variables possibly acting ad confounders (nearest neighbor matching). Kaplan–Meier survival analysis was then repeated on a total of 1069 patients

per group matched for the following variables: age, gender, BMI, MDRD, NYHA class, Hb, Na and pVO_2 (% of predicted), VE/VCO_2 slope and disease modifier drugs (angiotensin converting enzyme inhibitors/angiotensin receptor antagonists, β-blockers and mineralocorticoid receptor antagonists).

Finally, within the rec-HFmrEF group only, receiver-operating curves (ROC) were also estimated to display the capacity of pVO_2 (% of predicted) and ventilatory efficiency (VE/VCO_2 slope) to discriminate between survivors and non-survivors. According to this approach, we reported the thresholds corresponding to the best sum of sensitivity and specificity. Moreover, we tested the additive role of age on top of the pVO2 and VE/VCO2 slope to predict cardiovascular risk. To validate the CPET-derived parameters accuracy data, we introduce confidence intervals (CI) for all the considered quantities and all the CI of the sensitivity at the given specificity points (and *viceversa*) were computed based on 2,000 bootstrap replicates. A similar approach was adopted for the positive and negative predictive values.

Statistical analysis was performed using R (R Development Core Team, 2009) packages. All tests were two-sided. A p value lower than or equal to 0.05 was considered as statistically significant.

RESULTS

Starting from 6,224 patients, a total of 5,711 met the inclusion/exclusion criteria and were considered for the present study. At the run-in, which included clinical, laboratory, instrumental assessment with echocardiographic and CPET execution, 4,535 patients had still a LVEF < 40% (HFrEF group) whereas the remaining 1,176 patients showed a LVEF between 40% and 49% (rec-HFmrEF group).

- General characteristic of the study groups

Table 1 reports a detailed comparison between the main clinical, echocardiographic, laboratory, CPET data as well as concomitant therapeutic strategies collected at the study run-in in the two study groups, namely the rec-HFmrEF and HFrEF. Echocardiographic and laboratory data (LVEF, pulmonary artery systolic pressure, Na+, BNP/NT-proBNP) were significantly better in the rec-HFmrEF group. Particularly, the rec-HFmrEF group was older with a higher prevalence of female gender, atrial fibrillation as well as a lower percentage of ischemic etiology (Figure 1, panel A). With respect the therapeutic strategy, angiotensin

converting enzyme inhibitors (ACEi)/angiotensin receptor antagonists (ARBs), β-blockers and mineralocorticoid receptor antagonists (MRA) were less represented in the rec-HFmrEF group than in the counterpart (Figure 1, panel B). Finally, as expected, the rec-HFmrEF group showed a less severe functional impairment in terms of all available CPET parameters (Figure 1, panel C).

TABLE 1. Main clinical variables of the overall HF study sample according to LVEF category.

	rec-HFmrEF (n: 1,176)	**HFrEF (n: 4,535)**	**P value**
General data			
Age, years	63±13	61±12	<0.001
Male,n %	916 (78)	3848 (85)	<0.001
Body mass index, kg/m^2	27±4	27±4	NS
NYHA III, n (%)			<0.001
1	250 (21)	600 (13)	
2	731 (62)	2433 (53)	
3	195 (17)	1502 (34)	
Ischemic etiology, n (%)	412 (35)	1936 (43)	<0.001
AF, n (%)	217 (19)	678 (15)	0.004
Hemoglobin, g/dL	13.4±1.6	13.5±1.6	NS
Sodium, mmol/L	139±3	138±3	0.015
MDRD, ml/min/	72 ±24	71±24	NS
Rest HR, bpm	68±11	71±13	<0.001
SBP, mm Hg	121±17	116±17	<0.001
DBP, mm Hg	75±10	72±10	<0.001
LVEF, %	44 ±3	28 ±7	<0.001
PASP, mmHg	33 ±11	38 ±13	<0.001
NT-proBNP, pg/ml	443 [800]	1002 [1842]	<0.001
BNP pg/ml	110 [210]	377 [764]	<0.001

ICD, n (%)	167 (14)	1736 (38)	<0.001
CRT-D, n (%)	71 (6)	686 (15)	<0.001
Exercise test variables			
AT identified, n (%)	939 (80)	3691 (81)	NS
VO_2 at AT, ml/min	891±318	783±284	<0.001
VO_2 at AT, ml/kg/min	11.4±3.8	10.1±3.2	<0.001
pVO_2, ml/min	1252±473	1111±401	<0.001
pVO_2, ml/kg/min	16.1±5.5	14.4±4.5	<0.001
pVO_2, % of predicted	63±18	53±16	<0.001
VE/VCO_2 slope	30.8±6.5	33.4±8.1	<0.001
Peak HR, bpm	121±26	118±24	0.001
pHR%, % of predicted	79±17	75±15	<0.001
Peak workload, Watts	92±38	79±32	<0.001
RER	1.13±0.6	1.11±0.07	NS
Treatment			
ACEi or ARBs, n (%)	1081 (86)	4261 (93.2)	0.011
Beta-blockers, n (%)	981 (83)	4048 (89.3)	<0.001
Beta-blockers dosage, mg	18.75 [12.50]	18.75 [12.5]	0.819
MRA, n (%)	478 (40)	2624 (58)	<0.001
Loop diuretics, n (%)	822 (70)	3832 (84)	<0.001
Digoxyn, n (%)	161 (14)	1027 (23)	<0.001
Amiodaron, n (%)	255 (22)	1241 (27)	<0.001

Data are expressed as mean ± SD, as absolute number of patients (% on total sample) or as median [25^{th}-75^{th} percentile]. ACEi: angiotensin converting enzyme inhibitors; AF: atrial fibrillation; ARBs: angiotensin receptor blockers; AT: anaerobic threshold; BNP: b-type natriuretic peptide; CRT-D: cardiac resynchronization therapy implantable cardioverter defibrillator; DBP: diastolic blood pressure; HR: heart rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MDRD: Modification of Diet in Renal Disease; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; pHR: peak heart rate; RER: respiratory exchange ratio; SBP: systolic blood pressure; VE/VCO2: ventilatory equivalents of CO2; pVO_2: peak oxygen consumption.

The median follow-up was 1343 days (25th–75th interquartile range,627 - 2403 days). Survival analysis showed a significantly better survival of the rec-HFmrEF group with respect the counterpart ($p < 0.0001$) (Figure 2, panel A) being cardiovascular death occurred in 93 rec-HFmrEF patients (7.5%) and 754 (16.6%) HFrEF patients with most of the cardiovascular death registered within the fifth years of follow up [61 patients (5.2% event rate) in the rec-HFmrEF group and 552 patients (12.2% event rate) in the HFrEF group]. A total of 255 patients died from non-cardiac-related causes, whereas 167 patients, mostly in the HFrEF, underwent heart transplantation or LVAD implantation.

Table 2 reports the univariate analysis of the main significant clinical variables with respect the pre-specified end-point at 5 years in the two study groups. Albeit with different magnitudes, most of the general, echocardiographic, laboratory and CPET data were significantly associated to cardiovascular death in both groups (age, atrial fibrillation, LVEF, Hb, Na, MDRD, AT identification, VO_2 at AT, pVO_2 also expressed as percentage of the maximum predicted, VE/VCO_2 slope) except for the lack of a protective role in the rec-HFmrEF group of male gender, high BMI and preserved chronotropic response.

TABLE 2. Univariate Cox proportional survival analysis in the study groups according to the specified end-point (CV mortality at 5 years).

	rec-HFmrEF (n. 1176)			HFrEF (n. 4535)		
	UNIVARIATE			UNIVARIATE		
	H.R. (95% C.I.)	**P values**	**C-index**	**H.R. (95% C.I.)**	**P values**	**C-index**
Age	1.06 (1.04-1.082)	<0.001	0.675	1.032 (1.026-1.039)	<0.001	0.593
Male	1.280 (0.765-2.142)	NS	--	1.562 (1.242-1.965)	<0.001	0.525
Body mass index	0.950 (0.900-1.003)	NS	--	0.963 (0.946-0.980)	<0.001	0.563
AF	1.937 (1.237-3.032)	0.004	0.562	1.579 (1.325-1.883)	<0.001	0.539
LVEF	1.081 (1.009-1.158)	0.027	0.578	0.938 (0.928-0.948)	<0.001	0.629
Haemoglobin	0.811 (0.715-0.920)	0.001	0.625	0.814 (0.776-0.855)	<0.001	0.600
Sodium	0.930 (0.877-0.986)	0.015	0.555	0.945 (0.926-0.965)	<0.001	0.567
MDRD	0.977 (0.967-0.987)	<0.001	0.659	0.979 (0.975-0.982)	<0.001	0.635
AT identified	0.341 (0.158-0.738)	0.006	0.567	0.714 (0.552-0.810)	0.032	0.513
VO_2 at AT, ml/kg/min	0.915 (0.845-0.990)	0.028	0.589	0.871 (0.845-0.897)	<0.001	0.624
pVO_2, ml/kg/min	0.872 (0.829-0.918)	<0.001	0.675	0.859 (0.842-0.876)	<0.001	0.671
pVO_2, % of predicted	0.964 (0.952-0.978)	<0.001	0.687	0.959 (0.954-0.964)	<0.001	0.679
VE/VCO_2 slope	1.061 (1.034-1.089)	<0.001	0.661	1.056 (1.048-1.084)	<0.001	0.660
pHR%, % of predicted	1.010 (0.999-1.021)	NS	--	0.990 (0.985-0.994)	<0.001	0.549

H.R.: hazard ratio; C.I. : confidence interval. See table 1 for other abbreviations

By pursuing a multivariate approach via a multivariate Cox analysis, in the HFrEF group, besides the well-known six variables included in the MECKI score (LVEF, Hb, Na, MDRD, pVO_2, VE/VCO_2 slope), also age was independently associated to cardiovascular death (C-index for the entire model 0.744) (table 3). Conversely, in the rec-HFmrEF group, just two variables, namely age and pVO_2 expressed as percentage of the maximum predicted, remained significantly associated to the outcome (C-index for the entire model 0.745) (table 3). We also sought for possible interactions between treatment and the other independent variables, but the Akaike Information Criterion (AIC) (used to perform model selection) did not speak in favor of the inclusion of any interactions.

TABLE 3. Multivariate Cox proportional survival analysis in the study groups according to the specified end-point (CV mortality at 5ys).

	rec-HFmrEF (n. 1176)			HFrEF (n. 4535)		
	MULTIVARIATE			MULTIVARIATE		
	H.R. (95% C.I.)	P values		H.R. (95% C.I.)	P values	
Age	1.044 (1.016-1.074)	0.001		1.021 (1.012-1.031)	<0.001	
LVEF	1.082 (0.989-1.184)	0.084		0.957 (0.943-0.971)	<0.001	
Haemoglobin	1.011 (0.852-1.198)	0.904		0.902 (0.846-0.958)	<0.001	
Sodium	0.965 (0.905-1.030)	0.286		0.952 (0.927-0.978)	<0.001	
MDRD	0.987 (0.974-1.001)	0.077		0.990 (0.985-0.994)	<0.001	
pVO_2, % of predicted	0.965 (0.947-0.983)	<0.001		0.971 (0.963-0.978)	<0.001	
VE/VCO_2 slope	1.010 (0.973-1.048)	0.609		1.018 (1.001-1.030)	0.003	
			C-index for the model			C-index for the model
			0.745			0.744

H.R.: hazard ratio; C.I. : confidence interval. See table 1 for other abbreviations

After the 1:1 matching the survival matched analysis confirmed the just observed favorable outcome of the rec-HFmrEF category with respect the HFrEF group ($p < 0.0001$) (Figure 2, panel B). Within the supplementary file, Table 1S shows a detailed comparison between these subgroups whereas Table 2S and Table 3S report the univariate and multivariate analysis data which substantially overlap with those obtained in the whole study groups.

Finally, focusing on the rec-HFmrEF population, the ROC curve analysis showed that the best pVO_2 threshold, expressed as % of the maximum predicted, was equal to 55% (sensitivity 65%; specificity 62%; area under the curve (AUC) 69%) whereas the best VE/VCO_2 slope cut-off value was 31 (sensitivity 56%; specificity 73%; area under the curve (AUC) 67%) (Figure 3, Panel A and B). By adopting both the abovementioned threshold values in order to identify a rec-HFmrEF patient at high risk of cardiovascular death, the model shows a sensitivity nearly to 80% with a positive predictive value of higher than 90% (table 4) (Figure 3, Panel C). Conversely, no advantage has been found in including the age into the model. Validation by bootstrap analysis confirmed the robustness of the abovementioned accuracy data (i.e. sensitivity/specificity and positive/negative predictive values).

Table 4. Accuracy of the main CPET variables in the rec-HFmrEF study sample according to the cut-off identified at ROC analysis.

CPET variables	R.R. (95% C.I.)	*P value*	Sensitivity, % (97.5% C.I.)	Specificity, % (97.5% C.I.)	PPV, % (97.5% C.I.)	NPV, % (97.5% C.I.)	A.U.C.
$pVO_2 \leq 55\%$ of predicted	3.1	<0.001	65.1	62.2	97.1	8.3	68.7
	(1.825-5.321)		(62.2-67.9)	(48.9-74.4)	(96.4-97.6)	(6.1-11.1)	(62.1-72.6)
VE/VCO_2 slope ≥ 31	3.5	<0.001	56.5	72.8	96.9	9.8	67
	(1.981-6.451)		(53.4-59.4)	(59.7-83.6)	(96.4-97.4)	(6.7-14.3)	(59.9-74.1)
$pVO_2 \leq 55\%$ and VE/VCO_2 slope ≥ 31	3.8	<0.001	78.8	50.0	96.9	10.6	---
	(2.197-6.323)		(76.3-81.2)	(36.8-63.2)	(95.9-97.6)	(8.4-13.2)	

R.R.: relative risk; C.I.: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

DISCUSSION

The present multicenter study supplied a comparison of several clinical variables between a large cohort of stable HFrEF and rec-HFmrEF outpatients on optimized drug regimen. Besides confirming the expected clinical, functional and outcome differences between groups as well as the pivotal prognostic role of CPET parameters in the HFrEF (3-5, 17-20), our data strongly supports a possible usefulness of CPET in the rec-HFmrEF management, too. Particularly, within this specific HFmrEF subset, both a reduced pVO_2 value and an impaired ventilatory efficiency (increased VE/VCO_2 slope value) were significantly associated to a long term increased risk of cardiovascular death.

Differently from HFrEF, the well-behaved "older sibling child", whose clinical features and prognosis have been extensively described, few data are available on HFmrEF, the "middle child" unloved and neglected (21-25). Indeed, with respect a possible distinct phenotype, some previous studies reported that this HF category has a peculiar clinical profile between HFrEF and HF with preserved EF (HFpEF) (26-30). Particularly, compared to those with HFrEF, HFmrEF patients are usually older, more predominantly female and more likely affected by diabetes, atrial fibrillation and chronic kidney disease. Conversely, with respect the HFpEF, this category seems to suffer more frequently from ischaemic heart disease and, by a lesser extent, from hypertension and valvular disease (21). Similarly, even from a prognostic viewpoint, patients with HFmrEF have been reported to show an "intermediate" behavior between HFrEF and HFpEF patients (21,26,31). Eventually, differently from the "older sibling child", it has been shown that HFmrEF patients are usually undertreated with the HF disease modifier drugs, namely angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor antagonists (ARBs), β-blockers and mineralocorticoid receptor antagonists (MRA) (32), most likely because of a not univocal pharmacological strategy in this new born HF setting. Adding further complexity to the HFmrEF clinical scenario, it is still debated whether the HFmrEF should be considered as a real clinical entity or just as a transition step of the dynamic functional and structural evolution of the continuous HF spectrum (24,33,34). However, another viewpoint, actually the prevalent one, distinguishes those HFmrEF patients who recovered from a depressed systolic function (rec-HFmrEF) from those who never experienced a EF lower than 40% (*de novo* HFmrEF). In such a context, Nadruz and

colleagues reported a lower risk of cardiovascular events in rec-HFmrEF than in HFrEF and, quite surprisingly, even lower than in *de novo* HFmrEF (2). Similar results have been achieved also in a large registry study by Park CS and colleagues where it has been shown a lower rate of all-cause mortality in the rec-HFmrEF subset (35). Due to the significant differences in the study design, such as the primary outcome (i.e. they explored a combined endpoint of all-cause mortality), as well as in the characteristic of the analyzed sample (i.e. they evaluated acutely decompensated patients), a comparison between our results and those presented by Park and colleagues cannot be feasible or, even, misleading (35). Conversely, with respect to the rec-HFmrEF population studied by Nadruz (2), besides the consistently larger cohort evaluated (1176 versus 170 patients), there are some aspects worthy to be discussed briefly. Notwithstanding, our sample tends to overlap for haemoglobin levels, renal function and EF, however it appears significantly older, with a higher prevalence of male sex, ischaemic heart disease and concomitant MRA treatment. Eventually, even if our survival analysis shows a lower incidence of events at 5-years (5.2% versus nearly 8%), it should be remarked that we explored pure cardiovascular death rate rather than the overall mortality analyzed in the other study.

Nadruz and colleagues characterized their cohort from a functional viewpoint through a CPET assessment, however they did not investigate a possible association between the CPET-derived parameters and the outcome. Furthermore, due to the difference in the patients' characteristics (i.e. they analyzed a younger cohort with a higher prevalence of female and a lower incidence of ischaemic heart disease than the one explored in the present study) it is difficult to compare our CPET data with those obtained in the rec-HFmrEF population analyzed by Nadruz (36). Conversely, two recent studies explored the prognostic power of CPET-derived parameters in HFmrEF, albeit in relatively small and inhomogeneous samples (11,12). Sato and colleagues found that pVO_2 lower than the observed median values, within a cohort of 254 HFmrEF patients, was the only independent predictor of cardiac and all-cause deaths (11). Compared to our HFmrEF sample, their cohort had a higher prevalence of ischemic heart disease, atrial fibrillation and renal insufficiency. In another study by Nadruz and colleagues, involving 144 HFmrEF patients, pVO_2 (expressed as ml/kg/min) and VE/VCO_2 slope were associated with a composite outcome of all-cause death,

LVAD implantation and heart transplantation (12). It should be underlined that the patients enrolled by Nadruz and colleagues were younger and with a lower male and ischemic heart disease prevalence with respect those enrolled in our study. Unfortunately, given that any of the abovementioned studies analyzed a pure rec-HFmrEF setting, it remains difficult a strict comparison with respect clinical and survival data. In fact, the present study addressed specifically a possible advantage of CPET in a rec-HFmrEF cohort and it strongly supports the pVO_2, expressed as % of the maximum predicted, as the unique instrumental parameter able to predict independently the cardiovascular death risk. Why just pVO_2, but not other key clinical and instrumental variables (i.e. those included in the MECKI score), seems to better define the cardiovascular risk in such HF category might be due proper to its multidimensional character (37). Indeed, according to the Fick law, pVO_2 represents the product between cardiac output and artero-venous O_2 difference, both factors being impaired, although with different extent, in rec-HFmrEF patients. Moreover, particularly due to the demographic characteristics, our data argue in favor of the pVO_2 expressed as the percentage of the maximum predicted rather than just corrected for the body weight (15). Noteworthy, besides the pVO_2, most of the CPET-derived variables were univariately associated to the pre-specified end-point, including the VE/VCO_2 slope, the VO_2 at the AT as well as an AT not identified, each of them known powerful outcome predictor in the "older sibling child" HFrEF. In such a context, with respect to the Sato and Nadruz studies (11,12), we propose a possible easy approach to identify and, possibly, to treat more aggressively those rec-HFmrEF at higher cardiovascular death risk by means of both pVO_2 and VE/VCO_2 slope cut-off values. Indeed, we identified a $pVO_2 \leq 55\%$ of predicted and a VE/VCO_2 slope ≥ 31 as the most accurate cut-off values able to identify a rec-HFmrEF subgroup with a cardiovascular mortality rate significantly higher than the overall rec-HFmrEF (5.2% vs 8.5%). Furthermore, by using both cut-off values contextually, we were able to identify a relatively small rec-HFmrEF population with a cardiovascular risk quite similar to the HFrEF sample (12.2% vs 11.4%) and, contextually, a huge number of rec-HFmrEF patients a cardiovascular death risk lower than 2% (those with a $pVO_2 > 55\%$ of predicted and a VE/VCO_2 slope < 31) (Figure 4). Of note, the lack of an additive prognostic role of age on top of the combined model might be due to the close relationship of this variable with both the pVO2, expressed as a percentage of its

predicted normal value and, albeit to a lesser extent, the VE/VCO2 slope (36). However, albeit easy to use in daily clinical practice, it should be underlined that it is undoubtedly more appropriate from a clinical and pathophysiological viewpoints to consider these two CPET parameters as continuous variables rather than categorical. Supporting the need of a reasoned and multidimensional rather than a CPET-centered approach, the accuracy of the model using only cut-off values, although validated by boot strapping analysis and characterized by high positive predictive values, remains suboptimal. Of note, our decision to include the ventilatory efficiency into our accuracy analysis, regardless not independently associated to the pre-specified end-point, is based not only on its well-established prognostic role both in HFrEF and HFpEF but mainly on another possible advantage. Indeed, the VE/VCO_2 slope may represent a pivotal CPET parameter in those cases (i.e. elderly and highly comorbid HF patients) where it is difficult to achieve the metabolic criteria for consider a CPET as maximal (38).

LIMITATIONS

Albeit its retrospective feature, the present study has been conducted on a sizable cohort with a nearly four years median follow-up and all the centers involved were highly experienced with HF management and CPET analysis. However, a few limitations should be acknowledged.

Firstly, we examined the prognostic impact of several variables at a single time point. Therefore, considering the long follow-up period, we cannot exclude that changes in some clinical strategies (i.e. upgrading of pharmacological treatment and/or, devices implantation) altered our survival analysis as well as a possible patients' transition to another LVEF category. Secondly, it should be reasonable that the lack of significance of some variables at multivariate analysis in the rec-HFmrEF with respect the HFrEF group, albeit coefficients similar in direction and magnitude in the stratified univariate analysis, might be driven much more by the differences in sample size between groups than to the an effective lack of clinical relationship in the rec-HFmrEF group. Conversely, even if it could be considered a little bit more than a trend, in our rec-HFmrEF population a significantly higher LVEF has been found associated to a greater cardiovascular death risk. Of note, also this somewhat paradoxical relationship disappears at multivariable analysis casting doubts about its possible pathophysiological meaning. However, in such a case, a possible

highly speculative explanation might be that it was a consequence of a further less strict therapeutic strategy in those rec-HFmrEF with a better ventricular function. Thirdly, as previously discussed, we examined only rec-HFmrEF patients and this aspect could be, at the same time, a strengthen but also a weakness of the current study. Unfortunately, because all patients came from the MECKI score database, we were not able to include a comparison with a *de novo* HFmrEF as well as a HFpEF cohort. Moreover, again due to the design of the MECKI score dataset, the lack of data with respect the timeline between disease onset and LVEF recovery does not allow us to speculate about a possible impact of the medical treatment length on the HF category interchange. Last, the pre-specified study end-point was pure cardiovascular mortality prevented us from even speculating on possible different mode of death between rec-HFmrEF and HFrEF (i.e. sudden cardiac death or HF worsening) as well as possible specific attitude of the explored variables in identifying the mode of death.

CONCLUSIONS

In conclusion, the actual retrospective analysis of data coming from the large multicenter MECKI score dataset, besides confirming the independent role of some CPET, instrumental and laboratory variables in stratifying the cardiovascular risk in HFrEF, argues in favor of the adoption of this safe and noninvasive diagnostic approach in the rec-HFmrEF category clinical management, too. Even, besides the pVO_2 which resulted independently associated, also a number of other CPET variables were univariately associated to the cardiovascular death risk. Particularly, a $pVO_2 \leq 55\%$ of the maximum as well as a VE/VCO_2 slope ≥ 31 identified a rec-HFmrEF subgroup of patients with a cardiovascular death risk similar to the one observed in the HFrEF group. Further interventional and prospective studies are needed to confirm and, possibly, to translate our results into the daily HFmrEF clinical management.

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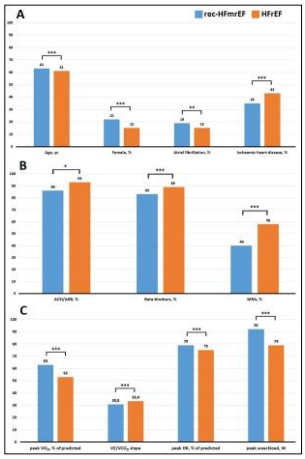

Figure 1. Clinical, therapeutic and functional characteristics of the rec-HFmrEF and HFrEF groups

Differences in clinical profile (age, gender, fibrillation and ischemic heart disease) (Panel A), treatment with disease modifier drugs (ACEi/ARB, beta-blockers and MRA) (Panel B) and cardiopulmonary exercise test parameters (pVO_2 , peak heart rate, ventilatory efficiency and peak woarkload) (Panel C) between rec-HFmrEF and HFrEF patients. See table 1 for further details.

rec-HFmrEF, heart failure with recovered mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; peak VO_2, peak oxygen uptake; VE/VCO_2 slope, ventilatory efficiency; peak HR, heart rate;

***, p-value <0.001; **, p-value <0.01; *, p-value < 0.05.

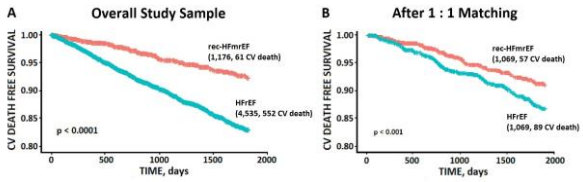

Figure 2. Cardiovascular mortality according to left ventricular ejection fraction categories.

Kaplan–Meier estimator of CV mortality at 5 years conditional on significant independent variables according to left ventricular ejection fraction in the overall study sample (Panel A) and age, gender, BMI, MDRD, NYHA class, Hb, Na and pVO_2 (% of predicted) and disease modifier drugs (angiotensin converting enzyme inhibitors /angiotensin receptor antagonists, β-blockers and mineralocorticoid receptor antagonists) (Panel B).

rec-HFmrEF, heart failure with recovered mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; CV, cardiovascular.

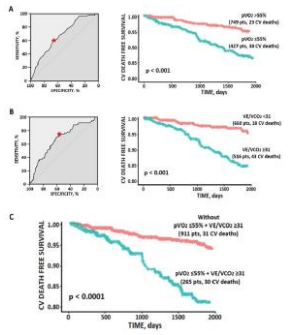

Figure 3. Cardiovascular mortality in the rec-HFmrEF sample according to CPET parameters.

Receiver-operating curves (ROC) and Kaplan–Meier estimator of CV mortality at 5 years in the rec-HFmrEF sample for peak oxygen uptake (peak VO_2 ≤55%) (Panel A), for ventilatory efficiency (VE/VCO_2 slope ≥31) (Panel B) and and Kaplan–Meier estimator of CV mortality at 5 years in the rec-HFmrEF sample for both cut-off values (Panel C). See Table 4 for the accuracy data. rec-HFmrEF, heart failure with recovered mid-range left ventricular ejection fraction; CPET, cardiopulmonary exercise test; CV, cardiovascular.

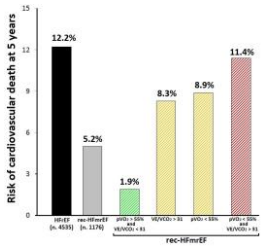

Figure 4. Incidence rate of cardiovascular mortality in different HF subgroups.

Incidence rate of CV mortality at 5 years in the overall HFrEF and rec-HFmrEF samples and in rec-HFmrEF subgroups categorized according to the best cut-off values of peak VO_2 and VE/VCO_2 slope.

HFrEF, heart failure with reduced left ventricular ejection fraction; rec-HFmrEF, heart failure with recovered mid-range left ventricular ejection fraction; CV, cardiovascular.

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