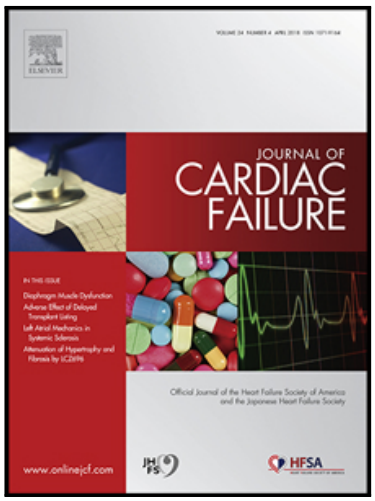

CARDIOVASCULAR DEATH RISK IN RECOVERED MID-RANGE EJECTION FRACTION HEART FAILURE: INSIGHTS FROM CARDIOPULMONARY EXERCISE TEST

Damiano Magrì MD, PhD , Massimo Piepoli MD , Ugo Corrà MD , Giovanna Gallo MD , Antonello Maruotti PhD , Carlo Vignati MD , Elisabetta Salvioni PhD , Massimo Mapelli MD , Stefania Paolillo MD, PhD , Pasquale Perrone Filardi MD , Davide Girola MD , Marco Metra MD , Angela B. Scardovi MD , Rocco Lagioia MD , Giuseppe Limongelli MD , Michele Senni MD , Domenico Scrutinio MD , Michele Emdin MD , Claudio Passino MD , Carlo Lombardi MD , Gaia Cattadori MD , Gianfranco Parati MD , Mariantonietta Cicoira MD , Michele Correale MD , Maria Frigerio MD , Francesco Clemenza MD , Maurizio Bussotti MD , Marco Guazzi , Roberto Badagliacca MD , Susanna Sciomer MD , Andrea Di Lenarda MD , Aldo Maggioni MD , Gianfranco Sinagra MD , Massimo Volpe MD , Piergiuseppe Agostoni MD, PhD , on behalf of the MECKI score Research Group (see appendix)

PII: S1071-9164(20)30031-2
DOI: https://doi.org/10.1016/j.cardfail.2020.04.021
Reference: YJCAF 4532

To appear in: *Journal of Cardiac Failure*

Received date: 10 January 2020
Revised date: 13 March 2020
Accepted date: 17 April 2020

Please cite this article as: Damiano Magrì MD, PhD , Massimo Piepoli MD , Ugo Corrà MD , Giovanna Gallo MD , Antonello Maruotti PhD , Carlo Vignati MD , Elisabetta Salvioni PhD , Massimo Mapelli MD , Stefania Paolillo MD, PhD , Pasquale Perrone Filardi MD , Davide Girola MD , Marco Metra MD , Angela B. Scardovi MD , Rocco Lagioia MD , Giuseppe Limongelli MD , Michele Senni MD , Domenico Scrutinio MD , Michele Emdin MD , Claudio Passino MD , Carlo Lombardi MD , Gaia Cattadori MD , Gianfranco Parati MD , Mariantonietta Cicoira MD , Michele Correale MD , Maria Frigerio MD , Francesco Clemenza MD , Maurizio Bussotti MD , Marco Guazzi , Roberto Badagliacca MD , Susanna Sciomer MD , Andrea Di Lenarda MD , Aldo Maggioni MD , Gianfranco Sinagra MD , Massimo Volpe MD , Piergiuseppe Agostoni MD, PhD , on behalf of the MECKI score Research Group (see appendix), CARDIOVASCULAR DEATH RISK IN RECOVERED MID-RANGE EJECTION FRACTION HEART FAILURE: INSIGHTS FROM CARDIOPULMONARY EXERCISE TEST, *Journal of Cardiac Failure* (2020), doi: https://doi.org/10.1016/j.cardfail.2020.04.021

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

Authors: Damiano Magrì[1], MD, PhD, Massimo Piepoli [2], MD, Ugo Corrà[3], MD, Giovanna Gallo[1], MD, Antonello Maruotti [4,5,6], PhD, Carlo Vignati[7] , MD, Elisabetta Salvioni[7], PhD, Massimo Mapelli[7], MD, Stefania Paolillo[8], MD, PhD, Pasquale Perrone Filardi[8], MD, Davide Girola[9], MD, Marco Metra[10], MD, Angela B. Scardovi[11], MD, Rocco Lagioia[12], MD, Giuseppe Limongelli[13], MD, Michele Senni[14], MD, Domenico Scrutinio[12], MD, Michele Emdin[15,16], MD, Claudio Passino[15,16], MD, Carlo Lombardi[10], MD, Gaia Cattadori[17], MD, Gianfranco Parati[18,19], MD, Mariantonietta Cicoira[20], MD, Michele Correale[21], MD, Maria Frigerio[22], MD, Francesco Clemenza[23], MD, Maurizio Bussotti[24], MD, Marco Guazzi[25], Roberto Badagliacca[26], MD, Susanna Sciomer[26], MD, Andrea Di Lenarda[27], MD, Aldo Maggioni[28], MD, Gianfranco Sinagra[29], MD, Massimo Volpe[1,30], MD, Piergiuseppe Agostoni[7, 31], MD, PhD, on behalf of the MECKI score Research Group (see appendix).

Affiliations:

[1] Department of Clinical and Molecular Medicine, Azienda Ospedaliera Sant'Andrea, "Sapienza" Università degli Studi di Roma, Roma, Italy.

[2] UOC Cardiologia, G da Saliceto Hospital, Piacenza, Italy.

[3] Cardiology Department, Istituti Clinici Scientifici Maugeri, IRCCS, Veruno Institute, Veruno, Italy.

[4] Dipartimento di Giurisprudenza, Economia, Politica e Lingue Moderne - Libera Università Maria Ss Assunta

[5] Department of Mathematics, University of Bergen

[6] School of Computing, University of Portsmouth

[7] Centro Cardiologico Monzino, IRCCS, Milano, Italy.

[8] Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy.

[9] Clinica Hildebrand Centro di riabilitazione Brissago, Switzerland.

[10] Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy.

[11] Cardiology Division, Santo Spirito Hospital, Roma, Italy

[12] Division of Cardiology, "S. Maugeri" Foundation, IRCCS, Institute of Cassano Murge, Bari, Italy.

[13] Cardiologia SUN, Ospedale Monaldi (Azienda dei Colli), Seconda Università di Napoli, Napoli, Italy.

[14] Department of Cardiology, Heart Failure and Heart Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy.

[15] Fondazione Gabriele Monasterio, CNR-Regione Toscana, Pisa, Italy.

[16] Life Science Institute, Scuola Superiore Sant'Anna, Pisa, Italy.

[17] Unità Operativa Cardiologia Riabilitativa, Multimedica IRCCS, Milano, Italy.

[18] Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.

[19] Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Istituto Auxologico Italiano, Milan, Italy.

[20] Section of Cardiology, Department of Medicine, University of Verona, Verona, Italy.

[21] Department of Cardiology, University of Foggia, Foggia, Italy.

[22] Dipartimento Cardiologico "A. De Gasperis", Ospedale Cà Granda- A.O. Niguarda, Milano, Italy.

[23] Department for the Treatment and Study of Cardiothoracic Diseases and Cardiothoracic Transplantation IRCCS – ISMETT, Palermo, Italy.

[24] Cardiac Rehabilitation Unit, Fondazione Salvatore Maugeri, IRCCS, Scientific Institute of Milan, Milan, Italy.

[25] Cardiology University Department, Heart Failure Unit and Cardiopulmonary Laboratory, IRCCS Policlinico San Donato, San Donato Milano, Italy.

[26] Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, "Sapienza", Rome University, Rome, Italy.

[27] Cardiovascular Center, Health Authority n°1 and University of, Trieste, Trieste, Italy.

[28] ANMCO Research Center, Firenze, Italy.

[29] Cardiovascular Department, Ospedali Riuniti and University of Trieste, Trieste, Italy.

[30] IRCCS Neuromed, Pozzilli (Isernia), Italy.

[31] Dept. Of Clinical sciences and Community health, Cardiovascular Section, University of Milano, Milano, Italy.

Disclosures: None to be declared.

Correspondence to:

Piergiuseppe Agostoni, MD, PhD

Centro Cardiologico Monzino, IRCCS

Via Parea 4, 20138, Milan, Italy

Phone: 0039 02 58002586 - Fax 0039 02 58002283

E mail: piergiuseppe.agostoni@unimi.it

ABSTRACT

BackgroundςHeart 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 ResultsςWe 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.

ConclusionsςPresent 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.

- t l·úλŜyűăΩ ŦƧtt2ø dzLJ l·yŘ ăűdzŘè ŜvŘ-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