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Predictors of outcome in heart failure patients with severe functional mitral regurgitation undergoing MitraClip treatment☆

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ABSTRACT

Background: The prognostic predictors of outcome in patients with functional mitral regurgitation (FMR) undergoing MitraClip implantation (MCi) are still poorly known. The aim of our study is to identify the baseline predictors of outcome in FMR patients candidate to MCi.
Methods: All patients with symptomatic moderate-to-severe or severe FMR undergoing MCi at our institution were consecutively and prospectively enrolled. Baseline clinical and instrumental data were collected. Primary endpoint was the occurrence of cardiac death; secondary endpoints were all-cause death and the composite of cardiac death or rehospitalization for heart failure.
Results: 74 patients (mean 71.6 ± 8.3 years) were enrolled. During follow-up (median 416.0 days), the primary endpoint occurred in 15 (20.3%), all-cause death in 26 (35.1%) and the composite endpoint in 25 (33.8%). At multivariate analysis, the left atrial volume index (LAVi; HR:1.02; $P = 0.048$) and the low peak oxygen uptake (peak VO_2; HR:0.73; $P = 0.018$) increased the risk of cardiac death at follow-up; atrial fibrillation (AF; HR:2.69; $P = 0.027$) was independently associated to all-cause death and the low level of peak VO_2 was an independent predictor of overall mortality (HR:0.70; $P < 0.001$) as well as of the composite endpoint (HR:0.73; $P < 0.001$).
The ROC analysis identified a peak VO_2 cut-off of 10.0 mL/kg/min as the best predictor for the three study endpoints; the best LAVi cut-off for cardiac death was 67 mL/m^2. Kaplan-Meier analysis for the individual and combined outcome predictors confirmed their significant stratification ability during follow-up.
Conclusions: Peak VO_2, along with LAVi and AF, identify FMR patients with the worst prognosis after MCi.

1. Introduction

Percutaneous mitral valve (MV) repair (PMVR) with MitraClip® (MC) system (Abbott Vascular, Santa Clara, CA) has become a viable therapeutic option in patients with symptomatic severe mitral regurgitation (MR) despite optimal medical therapy and judged inoperable or at high risk for surgery [1,2]. In Europe, heart failure (HF) patients with functional MR (FMR) are the main target of MC accounting for over 70% of cases [3]. Conversely, in U.S. MC treatment has been approved only for primary MR while regulatory authorities have been waiting for the results of dedicated clinical trials [2,4].

Although the indication for PMVR with MC is clinically and echocardiographically driven, the appropriateness and feasibility of the procedure, including the risk stratification and the benefit prediction, still depends on the empirical evaluation by dedicated Heart Teams [5,6]. The efforts of the scientific community have been attempted to look for the baseline features identifying the patient phenotype more suitable for MC treatment in order to outline a more effective, evidence-based, selection process [7–9].

In this scenario, the severity of left ventricular (LV) dysfunction and the high burden of comorbidities compel FMR patients in the confined area bounded by the surgical denial and the hazard of futility, an issue long away to be definitely solved. The aim of our study is to identify the baseline predictors of long-term outcome in FMR patients undergoing PMVR with MC.

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

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2. Methods

2.1. Study population

From March 2012 to February 2018, patients with symptomatic moderate-to-severe or severe functional MR (FMR), refractory to optimal medical therapy, undergoing PMVR with MC at our institution were consecutively enrolled in a prospective registry if were able to perform cardiopulmonary exercise test (CPET).

Patients were accepted as candidate to MC implantation (MCi) after Heart Team decision-making process developed on the basis of surgical risk scores [logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and EuroSCORE II], clinical assessment, evaluation of frailty and comorbidities. Main exclusion criteria were severe clinical comorbidities portending an adverse short-term outcome or unfavorable MV morphology [5,8]. Transthoracic and transesophageal echocardiography were performed to quantify MR grade and to assess anatomical suitability for MCi [5]. MR was defined functional if leaflets show normal morphology but do not properly coapt due to either LV or left atrium dilatation [10].

For all patients, baseline demographic, clinical, echocardiographic and CPET data were collected and entered on a predefined computerized data sheet. Procedural success was defined as a significant reduction of MR to grade ≤ 2+/4+ (mild to moderate) after device implantation. Patients with post-procedural MR > 2+ were excluded from the analysis. Chronic kidney disease (CKD) was defined by a glomerular filtration rate (GFR) <60 mL/min calculated by using CKD Epidemiology Collaboration equation [11]. Informed consent was obtained from all individual participants included in the study. The study was approved by the local ethics committee. The investigation conforms to the principles outlined in the Declaration of Helsinki.

2.2. Transthoracic echocardiography

All patients underwent transthoracic echocardiography (TTE) using a commercially available system (Vivid E9; GE-Vingmed Ultrasound, Horten, Norway). TTE images were obtained with a 3.5-MHz transducer. All patients were assigned a MR severity score of 1 (mild), 2 (mild-to-moderate), 3 (moderate-to-severe), or 4 (severe), according to the quantitative measure of the effective regurgitant orifice area and regurgitant volume by using proximal isovelocity surface area method. In cases with extremely eccentric jet, the vena contracta width was measured in parasternal long-axis view and measured using zoom mode at the narrowest portion of the regurgitant jet [10]. After MCi, MR severity was assessed by visual assessment of expert echocardiographers (RC, CB) using an integrative approach based on anatomical considerations, color flow Doppler jet characteristics (size, number and eccentricity of regurgitant jets), and pulmonary vein flow-pattern [12]. LV end-diastolic, end-systolic volume index and LV ejection fraction (LVEF) were calculated by apical approach using the biplane Simpson's method. Left atrial volume (LAV) was obtained using the biplane method of disks [13]. LV and left atrial volumes were indexed to body surface area under optimized medical therapy before MCi; the same values were applied for indexing volume at follow-up. Systolic pulmonary artery pressure was derived from the tricuspid regurgitant jet velocity using systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation and the addition of estimated right atrial pressure according to inferior vena cava dimension and inspiratory distensibility [10]. As a parameter of global right ventricular function, tricuspid annular plane systolic excursion was assessed by aligning the M-mode linear cursor to the lateral tricuspid annulus in the apical four-chamber view [13].

2.3. Cardiopulmonary exercise test

Symptom-limited CPET was performed on an electronically braked cycloergometer. A ramp exercise protocol was tailored to the patients in order to obtain an exercise duration of 8–12 min. In the absence of clinical events, CPET was self-terminated by the patients for fatigue when reaching the maximal effort. A breath-by-breath analysis of expiratory gases and ventilation was performed by using a mass flow sensor (Vmax Encore, CareFusion, Yorba Linda, CA, USA) and average data over 20–30-s intervals were sampled as recommended [14]. Furthermore, 12-lead ECG, blood pressure, and heart rate were monitored at rest, each minute during exercise, and for at least 5 min during recovery. Ventilatory threshold was measured by V-slope analysis of oxygen uptake (VO_2) and carbon dioxide (CO_2) production, and it was confirmed by the behavior of the ventilatory equivalents of O_2 and CO_2 [14].

Peak VO_2 was determined as the highest VO_2 normalized to body weight (VO_2, mL/kg/min) for a given 15- or 20 s interval. The percentage of predicted peak VO_2 ($ppVO_2$) was calculated by using the equation proposed by Wasserman and Hansen [15]. Each test was performed by two physicians expert in CPET blinded to patient clinical features.

2.4. Percutaneous mitral valve repair with MitraClip

Design features of the MC system and technical details of the procedure have been reported elsewhere [5]. All procedures were performed in the cardiac catheterization laboratory under general anesthesia by using transesophageal 2- and 3-dimensional echocardiographic as well as fluoroscopic guidance.

2.5. Study endpoints and follow-up

We defined three endpoints at the longest available follow-up: the primary one was cardiac death; the secondary ones were all-cause death and the composite of cardiac death or rehospitalization for HF.

Clinical follow-up was performed at 1 month after MC treatment and then every 6 months in a dedicated outpatient clinic. In some cases, informations were obtained by telephone interview of the treating physicians or next of kin.

2.6. Statistical analysis

Distribution of continuous data was tested with the Kolmogorov–Smirnov and the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation, whereas non-normal distributed ones as median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Continuous normally distributed variables were compared by using the Student *t*-test (for paired data in case of two sets of observations for each patient). Categorical variables were compared with chi-squared test, or Fisher exact test when appropriate. Differences between non-normally distributed and ordinal variables were tested with Wilcoxon signed-ranks test or Mann-Whitney *U* test for paired and unpaired data, respectively. All baseline variables were tested at univariate analysis for the primary and secondary endpoints by using Cox regressions. Furthermore, a multivariate stepwise Cox regression model was performed to identify a set of independent predictors for cardiac death, all-cause death and for the composite of HF rehospitalization or cardiac death at the longest available follow-up. In order to limit the overfitting, only variables with the best compromise between high statistical significance at univariate analysis and clinical impact were tested; we preferred to test variables from different setting (i.e. clinical, laboratory, echocardiographic, functional, risk scores) to avoid multicollinearity bias. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). The Hosmer–Lemeshow statistic was used to assess the goodness-of-fit of the logistic regression model. Time-dependent receiver operating characteristic (ROC) curve analysis was performed in order to calculate the area under the curve (AUC) of the single variables, included in multivariate analysis, and of the whole models. Moreover, the best cut-off value of the outcome predictors included in multivariate model, were calculated. The cumulative incidence of the study endpoints was estimated at various time frame using the Kaplan-Meier method and the Log-rank test was used for comparison between groups. For all test, a *P* values <0.05 was considered statistically significant. Statistical analysis was performed by using SPSS version 23.0 (SPSS Inc., Chicago, Illinois) and R (R foundation for Statistical Computing, Vienna, Austria) statistical software.

3. Results

3.1. Study population

In the study period, 74 consecutive patients (mean age 71.6 ± 8.3 years; 78.4% men) with 3+ or 4+ FMR were enrolled. Baseline demographic, clinical, TTE and CPET findings of the study population are reported in the Table 1. The median logistic EuroSCORE and EuroSCORE II at enrollment were 17.9% (9.0–29.5) and 6.1% (3.8–10.4), respectively. In the majority of cases, a New York Heart Association (NYHA) functional class ≥ III was observed (68, 91.9%). The mean values of six minute walk test (6MWT, 266.2 ± 106.8 m), LVEF (33.2 ± 6.8%) and peak VO_2 (10.5 ± 2.7 mL/kg/min) suggested a relevant impairment of the LV systolic function and of the global functional exercise capacity in the study cohort.

3.2. In-hospital outcome

Successful MCi was observed in all cases according to the study inclusion criteria. No patients died during procedure, but three in-hospital post-procedural death were observed: one for hemorrhagic shock due to recurrent, intractable, bleedings from upper respiratory airways in a patient on triple antithrombotic therapy; one for cardiogenic shock triggered by acute kidney injury in a patient suffering from severe CKD; the last one for inability of the patients to be weaned from mechanical ventilation.

3.3. Long term follow-up and predictors of events

The median follow-up was 416.0 days (IQR 138.5–994.0). No patient was lost. At 1 year, a marked improvement both in MR grade (≤2+ in 84.1%) and in NYHA class (I or II in 79.5%) was observed (Supplemental Fig. 1). The changes of the main echocardiographic parameters from baseline to 6-months follow-up is reported in Table A.1 and

Supplemental Fig. 2. Along the whole investigation time, 26 (35.1%) patients died; among them, a cardiac etiology was recognized in 15 (57.7% of deaths) patients. Three patients died within 30 days from MCi, all before discharge. The composite endpoint was observed in 25 (33.8%). A comparison of the patients' baseline features according to the occurrence of the study endpoints at 1 year is reported in the Table A.2.

The Kaplan-Meier survival free from cardiac death at 6 months, 1, 2 and 3 years were 89.5% (CI: 82.5–97.2), 87.5% (CI: 79.7–96.1), 75.5% (CI: 64.2–88.7) and 71.7% (CI: 59.3–86.7), respectively (Fig. 1). The 1 and 3 years survival free from all-cause death were 78.9% (CI: 69.6–89.5) and 57.6% (CI: 45.0–73.7), and from the composite endpoint were 73.3% (CI: 63.0–85.2) and 62.9% (CI: 51.4–77.1), respectively (Fig. 2).

The univariate and multivariate Cox analysis for the primary and secondary endpoints are reported in the Tables 2 and A.3–A.5. At multivariate analysis, LAV index (LAVi) (HR: 1.02; 95% CI: 1.00–1.03; $P = 0.048$) significantly and independently increase the risk of cardiac death, whereas the peak VO_2 (HR: 0.73; 95% CI: 0.56–0.95; $P = 0.018$) decrease the risk of cardiac death at follow-up. The regression model for all-cause death identified a number of variables significantly associated with outcome at univariate analysis: atrial fibrillation (AF, $P = 0.032$), GFR ($P = 0.024$), 6MWT ($P = 0.023$), LVEF ($P = 0.021$), TAPSE ($P = 0.003$), LAVi ($P = 0.036$) and peak VO_2 ($P < 0.001$). However, only AF (HR: 2.69; 95% CI: 1.12–6.47; $P = 0.027$) and the peak VO_2 (HR: 0.70; 95% CI: 0.59–0.85; $P < 0.001$) were significantly associated with the overall mortality at multivariate analysis. Furthermore, the peak VO_2 (HR: 0.73; 95% CI: 0.60–0.88; $P < 0.001$) emerged as the only independent predictor of the composite endpoint at follow-up. The 2-years ROC analysis for primary endpoint identified, as the best cut-off, a peak VO_2 of 10.0 mL/kg/min [AUC: 0.87] with a sensitivity and specificity of 100.0% and 73.0%, respectively. The best cut-off for LAVi was 67 mL/m2 (AUC: 0.57; sensitivity: 48.7%; specificity: 75.2%). Furthermore, a multivariate model including both peak VO_2 and LAVI showed a better accuracy in the prediction of cardiac death after MCi (AUC: 0.90; sensitivity: 90.6%; specificity: 86.4%).

Among predictors of 2-years overall mortality, the same cut-off of 10.0 mL/kg/min was identified for peak VO_2 (AUC: 0.82; sensitivity 84.6%%; specificity: 75.0%); AF showed an AUC of 0.60 (sensitivity: 69.2%; specificity: 50.0%). Moreover, the combination of these two baseline parameters, improved prognostic stratification of patients at higher risk of 2-years death (AUC: 0.84; sensitivity: 80.0%; specificity: 79.5%). Eventually, the same peak VO_2 cut-off value of 10.0 mL/kg/min showed a good accuracy in the prediction of the occurrence of the composite endpoint at 2-years follow up (AUC:0.89; sensitivity:93.7%; specificity: 80.0%).

Kaplan-Meier sub-analysis for the primary and the secondary endpoints according to the baseline predictors of outcome is reported in the Figs. 1 and 2. The individual variables were able to identify patients' subsets at higher risk of events and, of note, their combination markedly improve their prognostic stratification capability.

Table 1
Baseline characteristics of the study population (n = 74).

Age, yrs	71.6 ± 8.3
Male sex, n (%)	58 (78.4)
Hypertension, n (%)	39 (52.7)
Diabetes mellitus, n (%)	26 (35.1)
CAD, n (%)	37 (57.3)
Previous myocardial infarction, n (%)	35 (47.3)
Previous PCI, n (%)	27 (36.5)
Previous CABG, n (%)	15 (20.3)
Previous stroke, n (%)	5 (6.8)
AF, n (%)	42 (56.7)
COPD, n (%)	29 (39.19)
Chronic kidney disease, n (%)	69 (93.2)
GFR, mL/min, median (IQR)	43.9 (28.5–62.0) [1]
ICD, n (%)	35 (47.3)
CRT, n (%)	19 (25.7)
Logistic euroSCORE, %, median (IQR)	17.9 (9.0–29.5)
EuroSCORE II, %, median (IQR)	6.1 (3.8–11.5)
NYHA functional class, n (%)	
I	0 (0)
II	6 (8.1)
III	63 (85.1)
IV	5 (6.8)
6-min walk test, meters	266.2 ± 106.8 [2]
BNP, pg/mL	739.0 (346.0–1262.0) [3]
LVEF, %	33.2 ± 6.8
LVEDV index, mL/m^2	97.4 ± 37.7
LVESV index, mL/m^2	65.9 ± 29.0
TAPSE, mm	15.7 ± 4.1
sPAP, mm Hg	51.0 ± 12.2
LAVi, mL/m^2	60.0 (47.1–74.0) [4]
MR grade, n (%)	
3+	6 (8.1)
4+	68 (91.9)
Peak VO_2, mL/kg/min	10.5 ± 2.7 [5]
ppVO_2, %	49.2 ± 14.8 [5]

Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are expressed as n (%). Continuous non-normally distributed variables are expressed as median (interquartile range).
AF, atrial fibrillation; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAVi, left atrial volume index; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; ppVO_2, percentage of predicted peak VO_2; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption.

4. Discussion

The main findings of our study on FMR patients candidates to MC implantation are the following: (i) despite the successful reduction of MR after MCi, FMR patients have high incidence of events reflecting the advanced HF status and the baseline comorbidities; (ii) among all the baseline clinical and instrumental covariates evaluated, peak VO_2 at CPET is the only independent predictor for all the three study endpoints: cardiac death, all-cause death and the composite endpoint of cardiac death or HF rehospitalization; (ii) patients with high LAVi and low peak VO_2 values show a reduced survival due to cardiac death; (iii) preexisting AF and a low peak VO_2 are independently associated to an increased risk of all-cause death. Our study reports a high occurrence of events at follow-up, pointing out the role of an adequate patient selection process. In HF with reduced EF (HFrEF) patients, moderate-to-severe MR negatively impacts on short- and long-term outcome [16,17]. Being associated with higher burden of comorbidities and more severe LV systolic dysfunction, FMR shows a distinct clinical profile compared with degenerative MR [18,19]. In our study, although several parameters were significantly correlated to adverse outcome at univariate analysis, only peak VO_2 emerged as an independent predictor for all the study endpoints. Furthermore, none of the echocardiographic parameters of left and right ventricular dysfunction as well as sPAP values met statistical significance in the stepwise regression model, when including peak VO_2. Probably, in this highly selected subset of patients showing advanced LV systolic dysfunction, echocardiography depicts their global risk profile but, in comparison with peak VO_2, seems to be not able to predict the occurrence of events. Conversely, the multivariate analysis for the primary endpoint showed a significant prognostic role of LAVi, confirming the results of previous studies on HF patients [20]. In a cohort of 146 subjects hospitalized for HF, Tamura et al. observed the independent association of LAV with cardiac events at follow-up and described a stepwise increase in risk with each increment of the LAVi values [21]. Therefore, by integrating the changes of LV filling pressure, LAVi may be considered a biomarker of magnitude and duration of LV diastolic dysfunction, useful for risk stratification in HF patients. In absence of original studies addressing the prognostic role of LAVi in FMR patients candidate to MC treatment, our data seems to

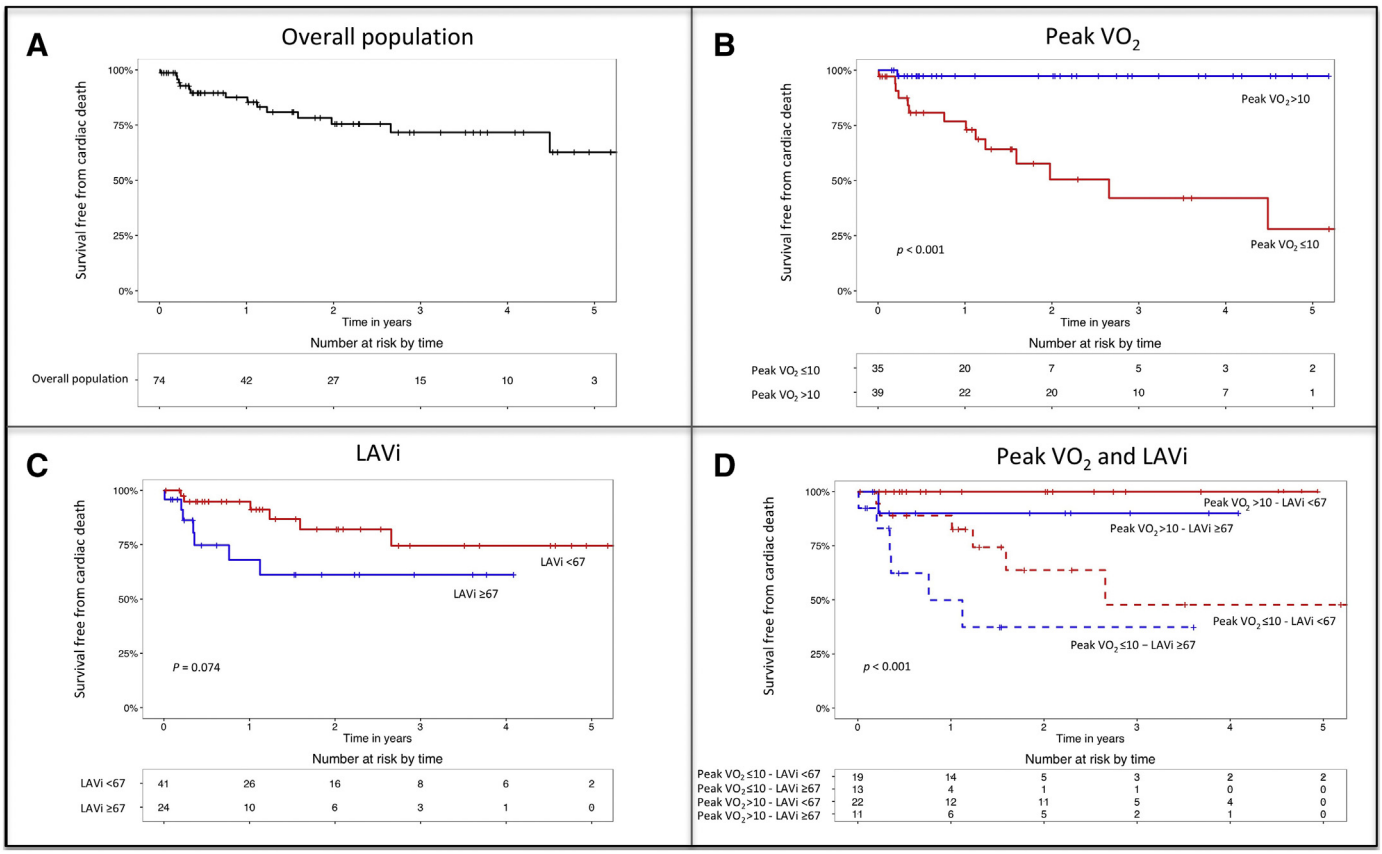

Fig. 1. Kaplan-Meier analysis of survival free from the primary endpoint. Survival free from cardiac death in the overall population (panel A) and in distinct subgroups according to the peak VO_2 cut-off of 10 mL/kg/min (panel B), to the LAVi cut-off of 67 mL/m^2 (panel C), and to the combination of the previous ones variables (panel D). LAVi, left atrial volume index (mL/m^2); VO_2, oxygen consumption (mL/kg/min).

suggest the similar identity of useful prognostic predictor of cardiac death even in this selected high-risk HF population.

In patients candidate to PMVR with MC, the role of AF has not yet well defined. Our results are consistent with TRAMI registry reporting a significantly lower 1-year survival in patients with preexisting AF [22]. In this real-word cohort, AF was not associated to a different clinical profile but resulted an independent predictor of 1-year mortality. An Italian study on 116 subjects undergoing MCi confirmed a higher incidence of death and HF rehospitalization at a median six months follow-up [23]. Furthermore, a recently published study on 618 patients undergoing MCi in five Dutch centers, showed a significantly lower 5-year overall survival in the AF cohort [24]. The discrepancies between these results and EVEREST data, reporting no differences on outcome of patients with and without AF, can be explained by the wide heterogeneity of the studies cohorts [25]. In the lower clinical risk population of the EVEREST II trial, AF seems to surrogate a worse clinical status and a more advanced HF stage. Conversely, in the TRAMI registry, which enrolled a higher risk population of patients denied for surgery, AF seems by itself to stratify prognosis. Our research provided to recruit selectively only the FMR patients, driving a higher risk profile, and was able to show the independent prognostic role of AF on all-cause mortality at long-term follow-up.

To the best of our knowledge, current study is the first evaluating the use of CPET in patients candidate to MCi. In daily practice, exercise capacity is commonly assessed both by NYHA functional class, too much subjective and insensitive, and by 6MWT, mainly affected by patient's motivation and unable to correlate the exercise performed to the individual maximal performance [13]. CPET, reliably addressing to cardiopulmonary fitness, is the most objective method to quantify the exercise capacity, but not routinely used. In systolic HF patients, the maladaptive response of the components involved in the oxygen uptake functional system (lungs, heart, vessels, blood and mitochondria) decreases the exercise tolerance. The imbalance between impaired muscle oxygen supply and the increasing demands during effort drives to low VO_2 values at peak exercise providing an accurate appraisal of the maximal achievable exercise capacity [26]. In our study, the peak VO_2 was significantly and independently associated to the occurrence of all the three study endpoints at follow-up. The cut-off of 10 mL/kg/min was able to distinguish two subgroups with markedly different survival rate at long-term; moreover the combination with the LAVi and AF further increased its prognostic stratification performance. In 1991, in a cohort of 114 patients with advanced HF, subjects with peak $VO_2 \leq 14$ mL/kg/min showed a low survival rate if denied for transplant, and a better outcome if accepted; patients with peak $VO_2 > 14$ mL/kg/min could be safely deferred [27]. Progress in HF medical therapy, including the wide use of beta-blockers in HF patients, has improved the overall survival, redefining at 10 mL/kg/min the peak VO_2 cut-off value associated with worse prognosis in HF patients with reduced LV EF [28,29]. Of note, our study included patients treated with beta-blockers in the vast majority of cases. In a recently published position paper of HF association, an even lower cut-off of 8 mL/kg/min has been proposed to identify high-risk patients on beta-blockers treatment [30]. However, such peak VO_2 value derives from an end-stage HFrEF population evaluating a different composite endpoint of death or heart transplantation [31].

CPET has been included in the diagnostic workup of HF patients, not only for selection of candidates to heart transplantation, but also in patients with preserved LV EF or LV assistance device recipients [30]. Our study seems to add a new indication for a subgroup of patients with severe FMR undergoing PMVR with MC. In the prognostic stratification chart for patients with HFrEF, the peak $VO_2 < 10$ mL/kg/min adjudges subject to a "red zone" encompassing a clinical area at increased risk of hard and soft events, and achieves a primary criterion for cardiac

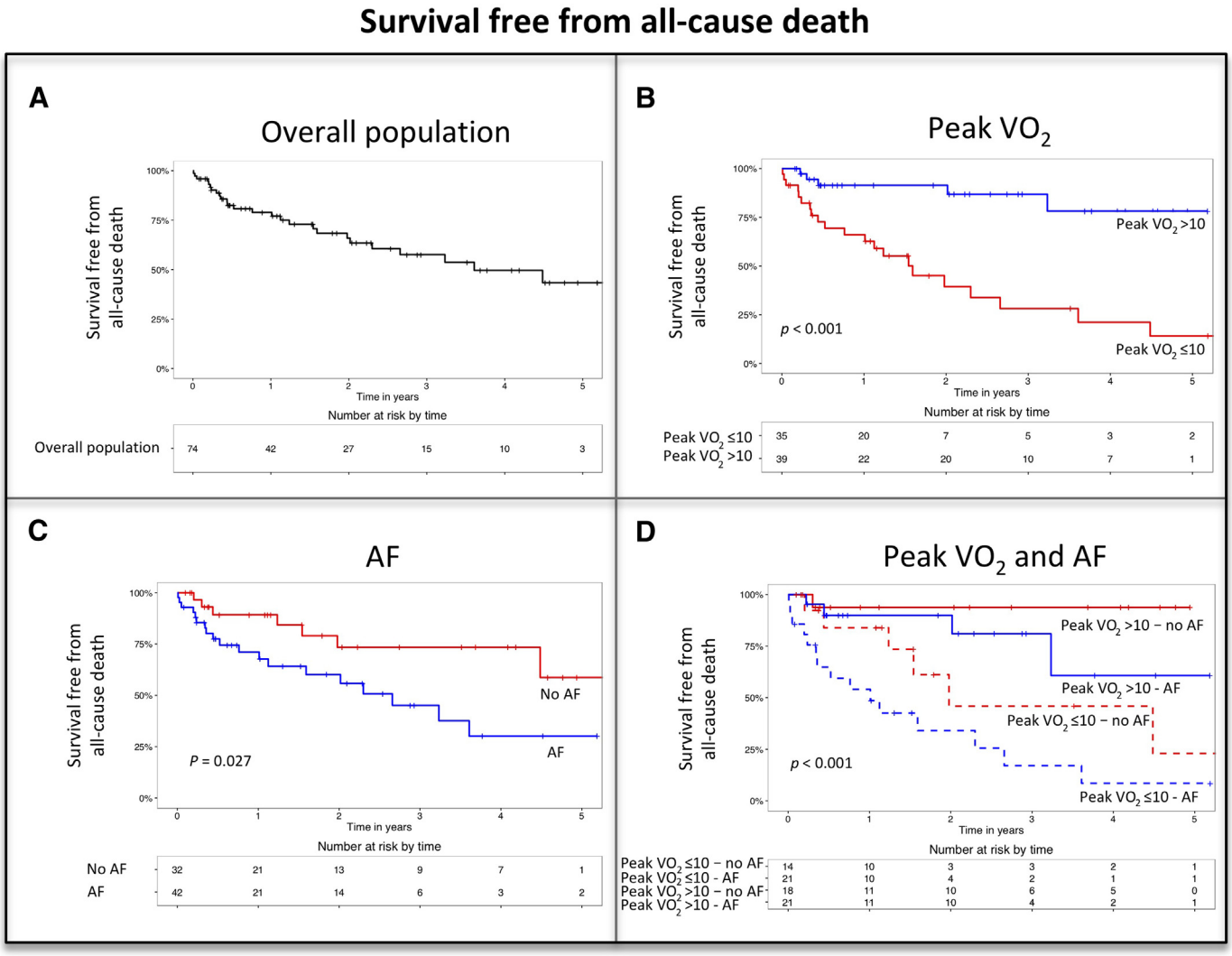

Fig. 2. Kaplan-Meier analysis of survival free from the secondary endpoints. Overall survival probability in the overall population (panel A) and in distinct subgroups according to the peak VO_2 cut-off of 10 mL/kg/min (panel B), to the presence of AF (panel C), and to the combination of AF and peak VO2 cut-off of 10 mL/kg/min (panel D). Panel E and F show the Kaplan-Meier survival free from the composite endpoint in the overall population (panel E) and in distinct subgroups according to the peak VO_2 cut-off of 10 mL/kg/min (panel E). AF, atrial fibrillation; VO2, oxygen consumption (mL/kg/min).

Table 2
Predictors of outcome in the study population (n = 74).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Cardiac death						
Peak VO_2, mL/kg/min	0.67	0.51–0.86	0.002	0.73	0.56–0.95	0.018
LAVi, mL/m^2	1.02	1.01–1.04	0.010	1.02	1.00–1.03	0.048
All-cause death						
Peak VO_2, mL/kg/min	0.70	0.58–0.85	<0.001	0.70	0.59–0.85	<0.001
TAPSE, mm	0.88	0.79–0.98	0.003	–	–	n.s.
LVEF, %	0.93	0.88–0.99	0.021	–	–	n.s.
6-min walk test, meters	0.99	0.99–1.00	0.023	–	–	–
GFR, mL/min	0.98	0.96–1.00	0.024	–	–	n.s.
AF	2.59	1.09–6.19	0.032	2.69	1.12–6.47	0.027
LAVi, mL/m^2	1.02	1.00–1.03	0.036	–	–	–
Composite endpoint						
Peak VO_2, mL/kg/min	0.73	0.60–0.88	<0.001	0.73	0.60–0.88	<0.001
LAVi, mL/m^2	1.02	1.00–1.03	0.041	–	–	n.s.

Abbreviations are reported in Table 1.

transplant eligibility [28]. Current analysis found the peak VO_2 cut-off value in FMR patients eligible to MCi exactly as in the latter population. However, in our context, the discriminative power of this finding works at the opposite. MC treatment is proved to be effective in reducing mitral regurgitant volume but, although associated in a number of patients to significant reverse remodeling [9,32], it is not a definitive therapy of LV dysfunction such as heart transplantation. Therefore, in patients candidate to MC treatment, the evidence of peak VO_2 < 10 mL/kg/min at CPET resulted as a good and accurate predictor of outcome thus defining the potential futility of MCi.

In this perspective, our results may contribute to optimize the choice of the good candidate, excluding HF patients too much severely compromised in their clinical status. The selection of patients seems to be the key to solving the discrepancies between the conflicting results of the recently published COAPT and MITRA-FR trials comparing MCi vs guidelines-directed medical therapy alone in FMR patients [33,34]. The lack of benefit of MCi in the MITRA-FR may be related by the enrollment of patients too late in the progression toward end-stage HF suggested by the higher LV volumes in spite of less severe MR grade as compared to COAPT. The proper recruitment provided in the latter study seems to explain the lower rates of mortality and HF rehospitalization. These results are consistent with previous studies and in line with a recently published metanalysis [3,35].

5. Study limitations

Current study has a several limitations. First of all, the relatively small sample size of the study population. Nevertheless, we have preferred to include in the analysis only patients with FMR in order to obtain a selected and homogeneous population of HF patients at high risk. The relevant number of events due to the long-term median follow-up allowed us to develop a multivariate regression model to explore the predictors of outcome. The study is deliberately focused on hard clinical endpoints and does not report echocardiographic and CPET data at follow-up. Another limitation concerns the heart rhythm definition. In order to make easier the interpretation of results, AF was defined according to the ECG at enrollment without considering its duration. This approach does not distinguish AF types and might underestimate the paroxysmal forms. The conversion rate to sinus rhythm during follow-up was not reported.

6. Conclusions

The selection of the ideal patient to schedule for MCi should be based on a multiparametric approach. CPET provides essential informations to stratify FMR patients at higher mortality risk and should be systematically performed before MCi. Peak VO_2 < 10 mL/kg/min, along with high LAVi values and AF, carried the worst prognosis after MCi, and should be taken into account to avoid futile procedure.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.055.

Conflict of interest

No conflict of interest or any financial support to declare.

Appendix A

Table A.1
Echocardiographic changes from baseline to 6-months follow-up.

	Baseline (n = 49)	6 months (n = 49)	*P*-value
MR grade, n (%)			<0.001
1+	0 (0)	30 (61.2)	
2+	0 (0)	19 (38.8)	
3+	5 (10.2)	0 (0)	
4+	44 (89.8)	0 (0)	
LVEF, %	34.0 (7.2)	36.4 (8.6)	0.013
LVEDV index, mL/m2	94.1 (35.4)	87.5 (35.4)	0.005
LVESV index, mL/m2	62.9 (27.4)	57.5 (27.5)	0.005

Abbreviations are reported in Table 1.

Table A.2
Baseline characteristics of the study population according to the occurrence of the study endpoints at 1 year (n = 54).

	Cardiac death			Overall death			Composite endpoint		
	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
	39	7		42	12		39	15	
Age, yrs	71.19 ± 8.20	73.29 ± 8.48	0.533	71.50 ± 8.11	71.33 ± 8.80	0.951	70.82 ± 8.39	73.13 ± 7.62	0.357
Male sex, n (%)	36 (76.6)	5 (71.4)	1	31 (73.8)	10 (83.3)	0.766	31 (79.5)	10 (66.7)	0.528
Hypertension, n (%)	24 (51.1)	3 (42.9)	1	22 (52.4)	5 (41.7)	0.743	19 (48.7)	8 (53.3)	1
Diabetes mellitus, n (%)	18 (38.3)	2 (28.6)	0.938	15 (35.7)	5 (41.7)	0.970	14 (35.9)	6 (40.0)	1
CAD, n (%)	24 (51.1)	5 (71.4)	0.547	21 (50.0)	8 (66.7)	0.488	20 (51.3)	9 (60.0)	0.787
Previous MI, n (%)	23 (48.9)	6 (85.7)	0.157	20 (47.6)	9 (75.0)	0.177	20 (51.3)	9 (60.0)	0.787

(continued on next page)

Table A.2 (*continued*)

	Cardiac death			Overall death			Composite endpoint		
	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
	39	7		42	12		39	15	
Previous PCI, n (%)	16 (34.0)	4 (57.1)	0.446	13 (31.0)	7 (58.3)	0.164	14 (35.9)	6 (40.0)	1
Previous CABG, n (%)	10 (21.3)	2 (28.6)	1	9 (21.4)	3 (25.0)	1	8 (20.5)	4 (26.7)	0.903
Previous stroke, n (%)	4 (8.5)	0 (0.0)	0.977	4 (9.5)	0 (0.0)	0.627	3 (7.7)	1 (6.7)	1
AF, n (%)	24 (51.1)	6 (85.7)	0.189	21 (50.0)	9 (75.0)	0.227	17 (43.6)	13 (86.7)	0.011
COPD, n (%)	20 (42.6)	2 (28.6)	0.772	16 (38.1)	6 (50.0)	0.684	16 (41.0)	6 (40.0)	1
Chronic kidney disease, n (%)	44 (93.6)	7 (100.0)	1	39 (92.9)	12 (100.0)	0.812	36 (92.3)	15 (100.0)	0.658
GFR, mL/min	47.68 (23.01)	39.51 (25.76)	0.394	48.57 (23.70)	39.25 (21.23)	0.244	47.92 (24.07)	43.30 (21.79)	0.524
ICD, n (%)	18 (38.3)	5 (71.4)	0.213	16 (38.1)	7 (58.3)	0.358	14 (35.9)	9 (60.0)	0.195
CRT, n (%)	9 (19.1)	2 (28.6)	0.941	7 (16.7)	4 (33.3)	0.391	8 (20.5)	3 (20.0)	1
Logistic euroSCORE, %	21.64 (15.21)	32.42 (21.95)	0.105	21.52 (14.64)	28.37 (21.36)	0.205	21.53 (15.69)	26.96 (18.05)	0.280
EuroSCORE II, %	7.97 (5.60)	13.95 (9.63)	0.021	7.56 (5.16)	12.90 (8.83)	0.010	7.87 (5.79)	11.04 (7.72)	0.107
NYHA class, n (%)			0.497			0.261			0.465
II	5 (10.6)	0 (0.0)		5 (11.9)	0 (0.0)		3 (7.7)	2 (13.3)	
III	39 (83.0)	7 (100.0)		34 (81.0)	12 (100.0)		33 (84.6)	13 (86.7)	
IV	3 (6.4)	0 (0.0)		3 (7.1)	0 (0.0)		3 (7.7)	0 (0.0)	
6-min walk test, meters	260.21 ± 100.15	240.33 ± 113.22	0.658	264.83 ± 93.68	232.10 ± 124.98	0.371	267.82 ± 98.63	229.33 ± 105.73	0.262
BNP, pg/ml	947.70 ± 905.90	1380.43 ± 1283.17	0.275	944.87 ± 958.33	1209.08 ± 993.45	0.413	925.06 ± 962.16	1202.47 ± 970.63	0.356
LVEF, %	33.46 ± 6.57	31.29 ± 5.68	0.412	33.76 ± 6.70	31.12 ± 5.21	0.213	33.62 ± 6.93	32.03 ± 5.01	0.423
LVEDV index, mL/m2	93.50 ± 31.50	132.33 ± 62.90	0.011	93.52 ± 32.87	116.08 ± 51.82	0.073	94.78 ± 32.78	108.31 ± 50.54	0.251
LVESV index, mL/m2	62.73 ± 24.01	91.04 ± 49.92	0.017	62.41 ± 24.95	80.35 ± 40.25	0.063	63.47 ± 25.28	74.01 ± 38.61	0.244
TAPSE, mm	15.62 ± 4.39	14.57 ± 4.35	0.558	16.10 ± 4.31	13.33 ± 3.96	0.052	15.51 ± 4.36	15.40 ± 4.50	0.933
sPAP, mm Hg	50.28 ± 13.00	57.14 ± 10.81	0.190	50.00 ± 13.24	55.25 ± 10.94	0.215	51.59 ± 13.51	50.07 ± 11.37	0.701
LAVi, mL/m2	58.53 ± 15.89	80.43 ± 35.99	0.010	57.96 ± 16.21	74.33 ± 30.02	0.022	58.14 ± 15.80	70.39 ± 29.10	0.068
MR grade 4+, n (%)	43 (91.5)	7 (100.0)	0.977	38 (90.5)	12 (100.0)	0.627	36 (92.3)	14 (93.3)	1
Peak VO2, mL/kg/min	10.81 ± 2.94	9.03 ± 2.03	0.129	10.96 ± 2.98	9.22 ± 2.11	0.065	11.07 ± 2.95	9.29 ± 2.34	0.040
ppVO2, %	52.27 ± 15.14	41.29 ± 9.53	0.069	53.19 ± 15.18	42.63 ± 11.02	0.029	52.68 ± 14.97	46.06 ± 14.21	0.146

Abbreviations are reported in Table 1.

Table A.3
Predictors of cardiac death in the study population (n = 74).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, age	1.02	0.95–1.08	0.615	–	–	–
Male sex	2.32	0.51–10.45	0.273	–	–	–
Hypertension	0.98	0.35–2.73	0.964	–	–	–
Diabetes mellitus	1.36	0.48–3.85	0.557	–	–	–
CAD	1.03	0.37–2.84	0.961	–	–	–
Previous MI	1.51	0.54–4.26	0.434	–	–	–
Previous PCI	1.68	0.60–4.67	0.322	–	–	–
Previous CABG	1.28	0.406–4.03	0.673	–	–	–
Previous stroke	1.02	0.13–7.82	0.985	–	–	–
AF	2.59	0.82–8.19	0.104	–	–	–
COPD	1.09	0.39–3.06	0.872	–	–	–
GFR, ml/min	0.98	0.96–1.01	0.182	–	–	–
NYHA functional class	0.21	0.38–4.00	0.727	–	–	–
6-min walk test, meters	1.00	0.99–1.00	0.416	–	–	–
BNP[a]	1.27	0.86–1.86	0.228	–	–	–
LVEF, %	0.94	0.87–1.01	0.105	–	–	ns
TAPSE, mm	0.95	0.84–1.08	0.460	–	–	–
sPAP, mm Hg	1.02	0.98–1.05	0.404	–	–	–
LAVi, mL/m^2	1.02	1.01–1.04	0.010	1.02	1.00–1.03	0.048
Peak VO_2, mL/kg/min	0.67	0.51–0.86	0.002	0.73	0.56–0.95	0.018

Abbreviations are reported in Table 1.
[a] Expressed in ng/ml (instead of pg/mL) to get results simpler to read.

Table A.4
Predictors of all-cause mortality in the study population (n = 74).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, yrs	1.01	0.96–1.06	0.719	–	–	–
Male sex	2.04	0.70–6.01	0.193	–	–	–
Hypertension	0.74	0.33–1.65	0.460	–	–	–
Diabetes mellitus	1.12	0.49–2.53	0.786	–	–	–
CAD	1.16	0.53–2.54	0.705	–	–	–
Previous MI	1.34	0.611–2.91	0.469	–	–	–
Previous PCI	1.34	0.61–2.94	0.463	–	–	–
Previous CABG	1.53	0.66–3.53	0.317	–	–	–
Previous stroke	0.54	0.07–3.99	0.546	–	–	–

Table A.4 (*continued*)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AF	2.59	1.09–6.19	**0.032**	2.69	1.12–6.47	0.027
COPD	1.94	0.89–4.20	0.093	–	–	–
GFR, ml/min	0.98	0.96–1.00	**0.024**	–	–	n.s.
NYHA functional class	1.29	0.53–3.10	0.574	–	–	–
6-min walk test, meters	0.99	0.99–1.00	**0.023**	–	–	–
BNP[a]	1.27	0.95–1.70	0.107	–	–	–
LVEF, %	0.93	0.88–0.99	**0.021**	–	–	n.s.
TAPSE, mm	0.88	0.79–0.98	**0.003**	–	–	n.s.
sPAP, mm Hg	1.00	0.98–1.04	0.364	–	–	–
LAVi, mL/m^2	1.02	1.00–1.03	**0.036**	–	–	–
Peak VO_2, mL/kg/min	0.70	0.58–0.85	<**0.001**	0.70	0.59–0.85	<0.001

Abbreviations are reported in Table 1.
[a] Expressed in ng/ml (instead of pg/mL) to get results simpler to read.

Table A.5
Predictors of the composite endpoint in the study population (n = 74).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, yrs	0.99	0.95–1.04	0.776	–	–	–
Male sex	0.90	0.36–2.25	0.818	–	–	–
Hypertension	1.09	0.48–2.43	0.840	–	–	–
Diabetes mellitus	1.25	0.56–2.78	0.590	–	–	–
CAD	0.94	0.43–2.08	0.883	–	–	–
Previous MI	1.01	0.46–2.22	0.986	–	–	–
Previous PCI	0.91	0.39–2.09	0.821	–	–	–
Previous CABG	1.66	0.72–3.85	0.237	–	–	–
Previous stroke	1.35	0.32–5.76	0.684	–	–	–
AF	2.12	0.91–4.93	0.082	–	–	–
COPD	0.98	0.44–2.19	0.970	–	–	–
Chronic kidney disease	2.37	0.32–17.61	0.400	–	–	–
GFR, ml/min	0.99	0.98–1.01	0.458	–	–	–
NYHA functional class	1.36	0.52–3.54	0.531	–	–	–
6-min walk test, meters	1.00	0.99–1.00	0.117	–	–	–
BNP[a]	1.33	0.99–1.78	0.056	–	–	n.s.
LVEF, %	0.95	0.89–1.00	0.084	–	–	n.s.
TAPSE, mm	0.98	0.89–1.07	0.624	–	–	–
sPAP, mm Hg	0.98	0.96–1.02	0.389	–	–	–
LAVi, mL/m^2	1.02	1.00–1.03	0.041	–	–	n.s.
MR grade 4+	1.96	0.26–14.54	0.511	–	–	–
Peak VO_2, mL/kg/min	0.73	0.60–0.88	<**0.001**	0.73	0.60–0.88	<**0.001**

Abbreviations are reported in Table 1.
[a] Expressed in ng/ml (instead of pg/mL) to get results simpler to read.

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