Prognostic value of cardiopulmonary exercise testing repetition during follow-up of clinically stable patients with severe dilated cardiomyopathy. A preliminary study

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ARTICLE INFO

Keywords:
Cardiopulmonary exercise test
Dilated cardiomyopathy
Prognosis
Follow-up

ABSTRACT

Background: Cardiopulmonary exercise testing (CPET) is a recognized tool for prognostic stratification in patients with dilated cardiomyopathy (DCM). Given the lack of data currently available, the aim of this study was to test the prognostic value of repeating CPET during the follow-up of patients with DCM.
Methods: This multicenter, retrospective study, analyzed DCM patients who consecutively performed two echocardiographies and CPETs during clinical stability. The study end-point was a composite of death from all causes, heart transplantation, left ventricular assist device implantation, life-threatening ventricular arrhythmias or hospitalization for heart failure.
Results: 216 DCM patients were enrolled (52 years, 78% male, NYHA I-II 82%, LVEF 32%, 94% on ACE inhibitors/ARNI, 95% on beta-blockers). The interval between CPETs was 15 months. During a median follow-up of 38 months from the second CPET, 102 (47%) patients experienced the study end-point. Among them, there was stability of echocardiographic values but a significant worsening of functional capacity.
Among the 173 patients (80%) who did not show echocardiographic left ventricular reverse remodeling (LVRR), the 1-year prevalence of the study-end point was higher in patients who worsened vs patients who maintained stable their functional capacity at CPET (38 vs. 15% respectively, *p*-value: 0.001).
These results were consistent also when excluding life-threatening ventricular arrhythmias from the composite end-point.
Conclusion: In clinically stable DCM patients with important depression of LVEF, the repetition of combined echocardiography and CPET might be recommended. When LVRR fails, 1-year repetition of CPET could identify higher-risk patients.

1. Introduction

Dilated Cardiomyopathy (DCM) is a primary heart muscle disease defined by non-ischemic left ventricular dilatation and systolic dysfunction with the eventual affection of the right ventricle and diastolic function. DCM results in a heterogeneous group of patients with heart failure, firstly about the etiology (idiopathic, autoimmune, post-myocarditis, etc..) but also in onset and clinical course [1,2].

Despite a significant prognostic improvement during the last decades [3,4], DCM still represents one of the main causes of heart failure (HF) and heart transplantation (HTx). Some patients may develop rapidly progressive HF; conversely, in response to medical therapy, up to 40% of

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DCM patients undergo favorable left ventricular reverse remodeling (LVRR), defined as an improvement in systolic function and reduction in left ventricular dimensions [5,6]. For this reason, DCM is considered a dynamic disease, requiring a continuous and individualized long-term follow-up, with clinical and echocardiographic systematic evaluations [7,8].

Cardiopulmonary exercise testing (CPET) provides an objective evaluation of patients' functional capacity and represents a cornerstone in defining clinical severity and predicting outcomes in HF patients [9,10]. A previous study demonstrated that the peak VO_2, expressed in % of predicted value (ppVO_2 peak) and the VE/VCO_2 slope are strong prognostic variables in the specific evaluation of DCM patients [11]. These CPET variables are as well included in the strong and effective "Metabolic Exercise test data combined with Cardiac and Kidney Indexes" (MECKI) score [12]. As a dynamic disease, DCM needs initial diagnostic evaluation and long-term surveillance, to recognize disease progression or LVRR. Despite that, data about the prognostic usefulness of repeating CPET in parallel to echocardiography during follow-up (and at what timeline) in these patients, are still lacking [7,13].

Therefore, the aim of this study was to investigate the prognostic role of repeating CPET (in addition to an echocardiographic exam) among a large, well-characterized cohort of patients with clinically stable DCM on optimal evidence-based therapy.

2. Methods

2.1. Study population

In this multicenter, retrospective study, we enrolled patients with DCM who underwent at least two CPET from 2004 to 2020 in two Italian referral centers for cardiomyopathies, the Heart Muscle Registry of Trieste and the Monzino IRCCS Cardiological Center in Milan. DCM was defined as left ventricular ejection fraction (LVEF) $< 50\%$ in the absence of any possible cause of systolic impairment, as previously reported [11,12,14]. For the proposal of the study, the secondary causes of DCM (tachy-induced, infective diseases, alcohol abuse, peripartum, etc..), were excluded.

All patients received optimized medical therapy according to guidelines that were in effect at the time of enrollment [15,16].

Both CPET and echocardiography have been performed in a phase of clinical stability of the disease, (i.e., at least 6 months after hospitalization for heart failure, invasive procedures and changes in pharmacological therapy). The two CPETs had to be separated by a time interval ranging from 6 to 24 months and CPETs and echocardiographies had to be separated from 0 to 10 days. If a patient underwent more than two CPETs, the first two closest to the diagnosis of DCM were selected.

Informed consent was obtained from all participants according to the policy of the institutional review board of the two enrolling centers' administration. The investigation complies with the Declaration of Helsinki.

2.2. CPET

CPET was performed using an individualized cycle-ergometer ramp protocol. Before each test, the equipment used was calibrated in a standard manner using reference gases and volumes [17]

The exercise protocol ramp was personalized and set on a clinical basis (age, weight, sex, symptoms, or degree of training) to achieve peak exercise between 8 and 12 min. In the absence of clinical events, CPET was symptom-limited and self-interrupted by patients, regardless of the peak respiratory exchange ratio (RER) achieved. A "Breath-by-breath" analysis of expiratory gases and ventilation was performed. A 12-lead electrocardiogram and transcutaneous oxygen saturation were also continuously monitored throughout the exam and blood pressure were determined manually every 2 min. The peak VO_2 was defined as the highest VO_2 rate measured during the last 30s of exercise. Anaerobic threshold (AT) was calculated by V-slope graphic analysis of VCO_2 and VO_2 and therefore confirmed by analyzing the ventilatory equivalents and the end-tidal pressure of CO_2 and O_2. Premature AT was defined by values $<40\%$ of predicted peak VO_2 [18].

Exercise Oscillatory Ventilation (EOV) was defined as a cyclic fluctuation of ventilation in accordance with the most used diagnostic criteria [19]. VE/VCO_2 Slope was calculated as the slope of the linear relationship between ventilation and VCO_2 from 1 min after the beginning of the loaded exercise to the end of the isocapnic buffering period, as previously described. Peak oxygen pulse (VO_2/HR) was considered as the VO_2 peak/Heart Rate peak. Predicted peak (maximal) heart rate values were calculated by 220 - age (if female 210 - Age). Wasserman equation, adjusted for age and sex, was used for calculating the percentage of predicted peak VO_2 (peak VO_2pp) [20]. The most used equipment for our study was Vmax 29C Sensormedics. CPET data were collected by re-analyzing the related reports by independent operators (NB, DZ, BP, PA), without being aware of the patient's status at the time of reanalysis.

2.3. Echocardiography

All patients underwent complete transthoracic echocardiographic evaluation at rest.

The echocardiographic equipment consisted of Vivid l9 GE, Vivid E95 GE, Vi-vid Q GE and ie33 Philips.

The M-mode, two-dimensional and standard Doppler variables were measured in accordance with international guidelines [21–23]. All echocardiographic examinations were performed and reviewed by a third-level trained echocardiographer with specific expertise in cardiomyopathy imaging. LV volumes and LVEF were assessed using the Simpson biplane method. Chamber diameters, areas and volumes were normalized to body surface area (BSA).

The pulsed-wave Doppler-derived transmitral velocity and tissue Doppler mitral annular velocity were obtained from the apical 4-chamber view. LV filling pattern was classified as restrictive in the presence of *E*-wave deceleration time < 120 msec or E/A > 2 associated with E-wave deceleration time < 150 msec. The E/e' ratio was calculated to estimate LV filling pressure. Functional mitral regurgitation was assessed using a multiparametric approach. All measurements were obtained from the mean of 3 beats (patients with sinus rhythm) or 5 beats (in case of atrial fibrillation). The reproducibility of echocardiographic data has been published previously [24].

As our study began before the extensive use of Global Longitudinal Strain (GLS), it was not included in the echocardiographic data analyses."

2.4. Study outcomes and definitions

The primary study outcome was defined as a composite of death, HTx, implantation of durable left ventricular assist device (LVAD), life-threatening ventricular arrhythmias (i.e., documented sustained ventricular tachycardia, ventricular fibrillation or appropriated ICD interventions) and hospitalizations for HF. If a patient experienced more than one event, the first one was considered. As a secondary, HF-related study outcome, we considered a composite of death, HTx, implantation of a durable left ventricular assist device (LVAD) and hospitalizations for HF.

For the purposes of the study, the date of study enrolment was the date of the first CPET but the follow-up started after the second CPET until the achievement of the primary endpoint or the last medical contact.

To create a cohort of clinically stable patients with DCM, those who experienced any event through 1st and 2nd evaluation (CPET and echocardiography) were excluded.

LV reverse remodeling (LVRR) was defined as an increase of LVEF >10 points % (or LVEF $>50\%$) associated with a decrease of Left

Ventricular End-Diastolic Volume indexed (LVEDVi) >10% [21–23].

In the absence of specific cut-offs in literature, we defined a significant worsening in functional capacity at CPET a relative decrease of peak VO_2 as peak VO_2pp ≥ 10% [10,25].

2.5. Statistical analysis

Summary statistics of clinical and instrumental variables were expressed as mean SD, median (interquartile range, IQR), or counts and percentage, as appropriate. Comparisons between groups were made by an analysis of variance (ANOVA), on continuous variables, using the robust Brown–Forsythe test when appropriate; Mann–Whitney test was used for continuous variables with the non-Gaussian distribution. The Chi-square test was calculated for discrete variables using the Fisher exact test when necessary.

In the case of repeated variables (i.e., at first and second CPET), the T-student test for paired samples was chosen for Gaussian data, the Wilcoxon test for non-Gaussian data and the McNemar test for categorical variables. The Chi-square test was calculated for discrete variables.

Relative percentage variation was calculated for continuous variables using the formula [(2nd evaluation – 1st evaluation)/1st evaluation]*100.

Kaplan-Meier survival curves were estimated between subgroups of patients, and then compared thanks to the log-rank test (p-value of statistical significance set at a value lower than 0.05). The arbitrary choice of a cut-off for guiding the Kaplan-Meier event-free curve estimation is discussed above.

Results were regarded as statistically significant when the p value was <0.05. All calculations were performed using IBM SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA) and the R package 3.10, library 'survival'.

3. Results

The study cohort included 216 patients (149 from the Heart Muscle Registry of Trieste, 69 from Monzino IRCCS Cardiological Center in Milan). The main clinical parameters for the overall study population, collected respectively at the first and second CPET, are described in Table 1. Most of the patients were middle-aged men with few symptoms of HF despite severe systolic dysfunction (52 years, 78% male, NYHA class I-II 82%, LVEF 32%). At baseline, the mean peak VO_2/Kg was 18.8 ± 5 ml/min/kg (66 ± 17% of VO_2pp) and the VE/VCO_2 slope was 30 ± 6. 94% of patients were on ACE inhibitors/Angiotensin Receptor-Neprilisin Inhibitors (ARNI) and 95% were on β-blockers.

The duration of the disease at the time of the first CPET was 68 months. The median distance between the first and the second CPET was 15 months. The median follow-up of the study population from the second CPET evaluation was 38 months. During this period, 102 patients (47%) experienced the primary endpoint; 7 (7%) of them died from refractory heart failure, 5 (5%) underwent HTx or LVAD implant, 23 (22%) had life-threatening ventricular arrhythmias and 67 (66%) was hospitalized for HF.

Patients who experienced the study outcome, compared to those who did not, showed baseline significantly worse LV systolic and diastolic function and chambers dimensions (LVEF 31 vs 34%, p 0.007; E/e' 13 vs. 11, p 0.029; LVEDVi 100 vs 84 ml/m2, p 0.004), lower peak VO_2 (17.7 vs. 19.7 ml/kg/min; p 0.006) and higher VE/VCO_2 slope (30 vs 28, p 0.023; Supplementary Table 1).

3.1. Evaluation of echocardiographic and CPET parameters

Despite the average, we observed a significant improvement in echocardiographic values (LVEDVi from 91 to 84 ml/m2, *p*-value <0.001; LVEF from 32% to 35%, p-value <0.001; Table 1), 173 patients (80%) did not develop a complete LVRR process (148 showed stable parameters and only 25 [11.5% of the total population] had a > 10-points worsened LVEF). These were significantly at higher risk of events with respect to patients presenting LVRR (*p*-value: 0.024; Fig. 1, panel A). Of note, in the subgroup of DCM patients who did not develop a complete LVRR process, a worsened CPET characterized those with a significantly further poorer outcome: in fact, the prevalence of the study end-point was 38% vs. 15% (at 1 year) and 50% vs. 22% (at 2 years) in patients with CPET worsening (n = 54) vs. stable CPET (n = 119) respectively (*p*-value: 0.001; Fig. 2, panel A). These results were consistent also when excluding life-threatening ventricular arrhythmias from the composite end-point (Figs. 1 and 2, panels B).

In particular, in patients experiencing the study outcome, LVEF remained at 30% (p-value: 0.96) and LVEDVi went from 100 to 99 ml/m^2 (p-value: 0.98) between the 1st and 2nd evaluations. Conversely, the percentage of predicted peak VO_2 ($ppVO_2$ peak) moved from 63% to 59% (p-value: 0.008; Table 2). See Supplementary Table 2 for the relative variation of all CPET and echocardiography parameters through 1st and 2nd evaluation.

Table 1
Characteristics of the overall population at 1st and 2nd evaluation.

N° of Patients: 216	1st Evaluation	2nd Evaluation	p-value
Age (years)	52.5 (12)	53 (12)	<0.001
BMI (m^2/kg)	27.2 (5)	27.1 (5)	0.891
SBP (mmHg)	114 (14)	112 (14)	0.003
NYHA class I-II – (n°, %)	178 (82%)	143 (81%)	0.607
Creatinine (mg/dl) -median (IQR)	1 (0.87–1.18)	1.01 (0.87–1.29)	0.097
Hb (g/dl)	14 (1.5)	14 (1.5)	0.201
Na^+ (mmol/L)	139 (3)	139 (2)	0.330
Beta-blocker (%)	95%	97%	1.000
ACE-i/ARB/ARNI (n°, %)	94%	97%	0.267
MRAs (n°, %)	56%	54%	0.458
Diuretics (n°, %)	60%	62%	0.503
ICD/CRT (n°, %)	73%	73%	1.000
AFib (n°, %)	9%	10%	0.774
LBBB (n°, %)	32%	31%	0.710
LVEDVi (ml/m^2) – median (IQR)	91 (76–117)	84 (70–109)	0.002
LVEF (%)	32 (9)	35 (10)	<0.001
MR, moderate-severe (n°, %)	26%	26%	1.000
E/e' – median (IQR)	12 (9–15)	11 (8–16)	0.147
VO_2 peak/Kg (ml/kg/min)	18.8 (5)	18.5 (6)	0.199
$ppVO_2$ peak (%)	66.5 (17)	66.6 (18)	0.490
ppHR peak (%)	76 (13)	76 (15)	0.926
VE/VCO_2 slope	30 (6)	30 (7)	0.439
RQ peak	1.13 (0.1)	1.12 (0.1)	0.418
Periodic breathing pattern (n, %)	10 (5%)	3 (1%)	0.289
AT identified (n, %)	188 (89%)	183 (92%)	0.571
$ppVO_2$ AT (%)	54 (17)	53 (19)	0.645

BMI: body mass index; SBP: Systolic Blood Pressure; NYHA: New York Heart Association functional classification; Hb: Hemoglobin; ACE-i: ACE-inhibitors; ARBs: Angiotensin Receptors Blockers; ARNI: Angiotensin Receptor-Neprilisin Inhibitor; MRAs: Mineralocorticoid Receptor Antagonist; ICD: Implantable Cardioverter Defibrillator; CRT: Cardiac Resynchronization Therapy; HR: Heart Rate; AFib: Atrial Fibrillation; LBBB: Left Bundle Branch Block; LVEDVi: Left Ventricular End-Diastolic Volume indexed; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; $ppVO_2$ peak: percentage of predicted VO_2 peak; RQ: Respiratory Quotient; AT: Anaerobic Threshold; ppHR: percentage of predicted HR; $ppVO_2$ AT: percentage of predicted VO_2 AT. VE: ventilation; VCO_2: carbon dioxide production; VO_2: oxygen consumption. IQR: Inter-Quartile Ratio.

4. Discussion

To the best of our knowledge, this is the first study demonstrating the prognostic value of repeating CPET during follow-up in patients with clinically stable DCM carrying on average, most importantly depressed LVEF. Indeed, despite its clear usefulness in a single evaluation [11], no studies have investigated yet the role of repeated (and at what time) CPET in patients with DCM, especially as a potential complementary tool of repeated echocardiographic evaluation.

Despite a large proportion (82%) of subjects classified as in NYHA I

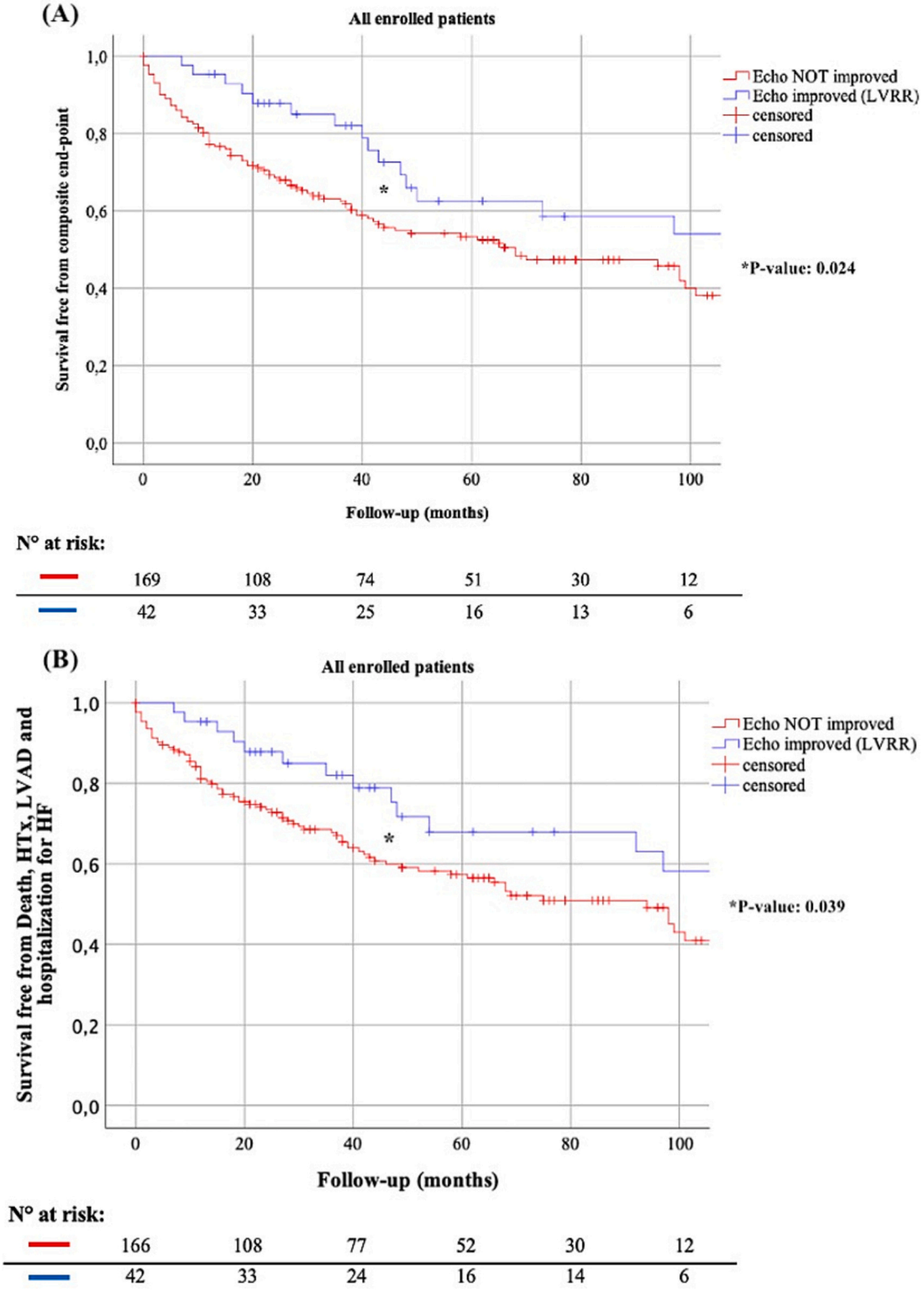
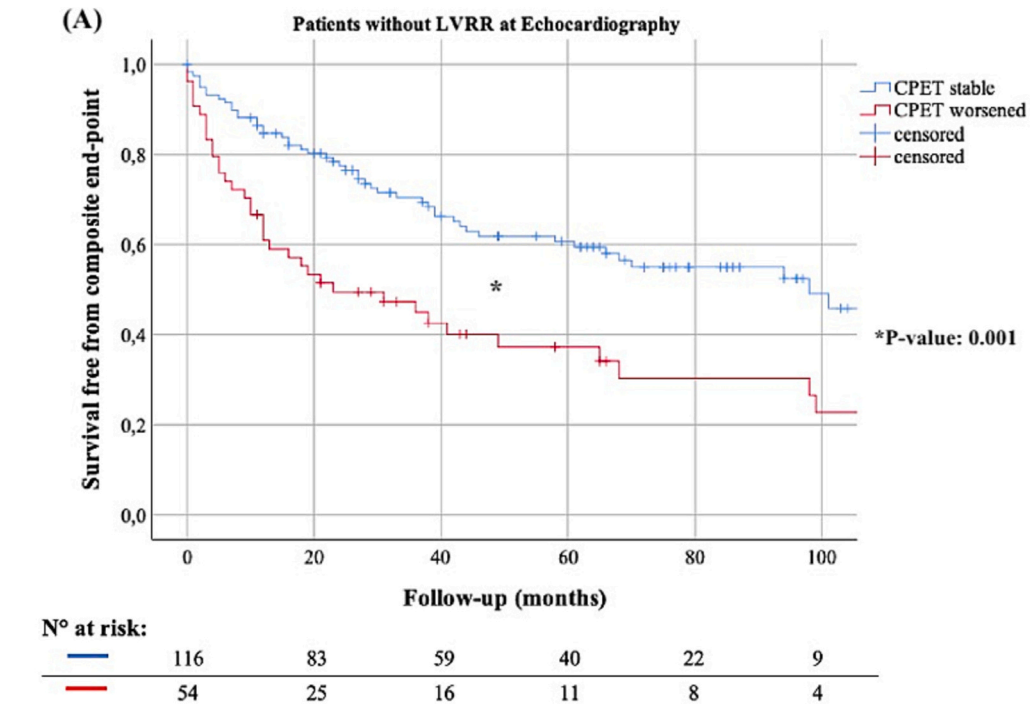


Fig. 1. Prognostic role of LVRR at echocardiography at Kaplan-Meier survival analysis.
Patients who did not show LVRR ("Echo not improved" was defined as an improvement in LVEDVi or LVEF <10%) were at significantly higher risk of events. The Panel A Kaplan-Meier curve tested the survival from the composite end-point. The panel B Kaplan-Meier curve tested survival from death from all causes, heart transplantation, implantation of a durable left ventricular assist device or hospitalization for heart failure.

and II, the mean ppVO2 peak was 66% reflecting a moderate reduction in exercise performance. The median value of the VE/VCO_2 slope was 30, without significant change from the 1st to 2nd evaluation (Table 1). To our knowledge, the most accurate threshold values for outcome prediction in DCM were < 60% for the ppVO_2 peak and > 29 for VE/VCO_2 slope [26]. Furthermore, this indicates the stable phase of the disease in which is often more difficult to determine an accurate prognostic stratification.

This suggests that, despite a mild pulmonary vascular impairment at 1st CPET evaluation (as seen by mean VE/VCO_2 slope values), functional



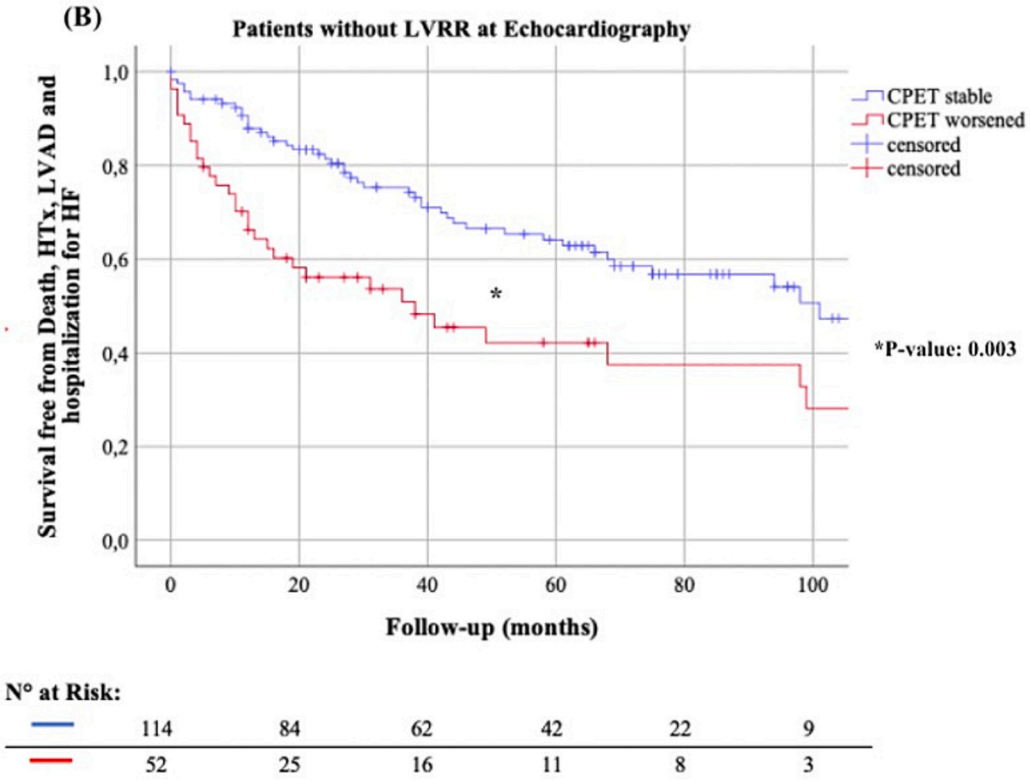


Fig. 2. Additive prognostic role of CPET at Kaplan-Meier survival analysis.
Patients who did not showed LVRR presented a significantly poorer outcome in case of contemporary worsening functional capacity at CPET ("CPET worsened" was defined as a reduction in VO_2 peak/Kg or $ppVO_2$ peak higher than 10%). The panel A Kaplan-Meier curve tested the survival from the composite end-point, while the panel B Kaplan-Meier curves showed the survival from death from all causes, heart transplantation, implantation of durable left ventricular assist device or hospitalization for heart failure.

capacity could have a greater prognostic power than VE/VCO_2 slope in stratifying patients who will experience events and who will not.

As expected, the most prevalent event of the primary end-point was hospitalization for heart failure (66%). Interestingly, the second most prevalent event was life-threatening arrhythmias (22%), followed by death for refractory HF (7%) and HTx or LVAD implantation (5%). This reinforces the importance of the CPET repetition in the specific HF model represented by DCM, which may also aid in preventing malignant ventricular arrhythmias. Further studies focused on this perspective will be necessary to confirm and to better understand the underlying mechanism.

Interestingly, especially in events-free patients, LVRR was possible in a minority of patients (20%) even after a median time of 68 months from diagnosis, well beyond the 12–24 months assessed in previous studies [26]. This demonstrates that LVRR in DCM is a complex phenomenon influenced by several factors (genetic background, medical drugs, the

Table 2
Evolution of the main CPET and echocardiography parameters through 1st and 2nd evaluation.

	EVENTS (n° 102)			NON EVENTS (n° 114)		
VARIABLE	1st CPET	2nd CPET	P-value	1st CPET	2nd CPET	P-value
LVEDVi (median, IQR)	100 (80–120)	99 (80–127)	0.979	84 (71–111)	75 (66–90)	<0.001
LVEF (median, IQR)	30 (25–36)	30 (25–36)	0.963	34 +/− 9	38 +/− 9	<0.001
VO_2 peak/kg (median, IQR)	17 (14–20)	15.9 (12–20)	0.014	19 (15–23)	19 (15–24)	0.498
ppVO_2 peak (median, IQR)	63 (56–70)	59 (49–73)	0.008	69 ±18	72 +/− 17	0.088

Abbreviations as in Table 1.

removal of the cardiac insult, CRT, edge-to-edge mitral valve repair), that might continue even in the long term, as recently suggested in some reports and that could be assessed by a multi-modality approach [27].

As a confirmation of that, in our patients, we found a significant rise in LVEF (from 34% to 38%) and a lowering in LVEDVi (from 84 to 75 ml/m^2) respectively among the group without the experience of the composite endpoint. Therefore, a persistent improvement in LVEF is here confirmed as one of the major therapeutic goals for DCM patients [28,29]. Finally, patients who experimented with the composite endpoint during follow-up showed a worsening of CPET parameters despite echocardiographic stability (Table 2).

These results consist of the hypothesis that CPET and echocardiography could provide complementary information and therefore the repetition of CPET during the follow-up appears useful for an adequate overall prognostic assessment of clinically stable DCM patients with relevant depression of LVEF. Indeed, in these patients, mostly when characterized by a lack of significant echocardiographic improvement, a relevant worsening in functional capacity at CPET could be a useful tool for the detection of patients developing HF-related events at follow-up. For this reason, CPET, in addition to echocardiography, might be a remarkable clinical tool for addressing a personalized follow-up (see Fig. 2).

We found that the first CPET was conducted >5 years after the diagnosis, indicating that CPET is not widely used in clinical practice despite its growing evidence-based recommendations for HF. Based on our results, we suggest of considering CPET as a tool for early assessment of the trajectory over time of functional capacity in patients with DCM. It seems also reasonable to wait for 12–18 months of follow-up before performing both echocardiography and CPET. Further studies are needed to confirm this timeframe. Finally, it emerges the importance of increasing the availability of CPET among clinical cardiologists and improving their interpretation skills to better stratify patients with DCM.

Therefore, specific networks should be enhanced and, in skilled centers, CPET could be proposed for clinically stable DCM patients who haven't reached echocardiographic improvement maintaining importantly reduced LVEF.

5. Limitations

This study has the intrinsic limits of retrospective studies, so no definitive conclusion can be taken; prospective and focused studies are requested to confirm the hypotheses that arose.

The cohort of the study reflects the medical therapy commonly used from 2004 to 2020.

Since the lack of literature referrals, the interval between the 1st and the 2nd CPET has been arbitrarily chosen based on the clinical practice of participating centers.

The variability in CPET and echocardiographic measurements over time could have influenced the results.

The study population has been enrolled in an Italian referral center for cardiomyopathies; also, only patients able to perform CPET were included in the study. This could generate a selection bias.

Given the limited sample size and the number of events, a multivariate analysis was not feasible. For this reason, this has to be considered a preliminary study that serves as a basis for future larger studies to confirm our results.

Despite such limitations, we are firmly convinced of the novelty of our results, because, to our knowledge, this is the largest study of DCM patients in which repeated CPET performance has been analyzed. This represents a clinical need in the era of the multimodality approach of HF (in particular for DCM).

6. Conclusions

In a large population of clinically stable DCM patients with importantly depressed LVEF, an integrated complementary evaluation of echocardiography and CPET during follow-up might be recommended: in fact, repeated CPET at a mean distance of at least 12 months appeared to be a useful tool in identifying those higher-risk patients, mostly when echocardiographic LVRR was not identified.

The data underlying this article are available in the article and in its online supplementary material.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

Acknowledgments

This research did not receive any specific grant from public, commercial or non-profit funding agencies.

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