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Estimating maximum work rate during cardiopulmonary exercise testing from the six-minute walk distance in patients with heart failure

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A R T I C L E I N F O

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A B S T R A C T

Background: Exercise is recommended for patients with chronic heart failure (CHF) and its intensity is usually set as a percentage of the maximal work rate (MWR) during cardiopulmonary exercise testing (CPX) or a symptom-limited incremental test (SLIT). As these tests are not always available in cardiac rehabilitation due to logistic/cost constraints, we aimed to develop a predictive model to estimate MWR at CPX (estMWR@CPX) in CHF patients using anthropometric and clinical measures and the 6-min walk test (6 MWT), the most widely used exercise field test.
Methods: This is a multicentre cross-sectional retrospective study in a cardiac rehabilitation setting. Six hundred patients with HF in New York Heart Association (NYHA) functional class I-III underwent both CPX and 6 MWT and, through multivariable linear regression analysis, we defined several predictive models to define estMWR@CPX.
Results: The best model included 6 MWT, sex, age, weight, NYHA class, left ventricular ejection fraction (LVEF), smoking status and chronic obstructive pulmonary disease COPD (adjusted $R^2 = 0.55$; 95% LoA −39 to 33 W). When LVEF was excluded as a predictor, the resulting model performed only slightly worse (adjusted $R^2 = 0.54$; 95% LoA −42 to 34 W). Only in 34% of cases was the percentage difference between estMWR@CPX and real MWR@CPX <10% in absolute value. EstMWR@CPX tended to overestimate low values and underestimate high values of true MWR@CPX.
Conclusions: Our results showed a lack of accuracy in the predictive model evaluated; therefore, for an accurate prescription of cycle-ergometer exercise training, it is necessary to assess MWR by CPX or SLIT.

1. Introduction

A large body of evidence supports the role of exercise training as a tool for improving functional capacity and quality of life and reducing hospitalization in patients with chronic heart failure (CHF) [1]. Because of these proven benefits, exercise rehabilitation is recommended as a class 1 intervention in the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure [2,3]. Currently, the exercise intensity is usually recommended as a percentage of the patient's maximal aerobic capacity [usually assessed by maximal oxygen uptake (VO_2 max), maximal work rate (MWR)] [4].

The gold-standard assessment of maximal aerobic capacity and training intensity is the cardiopulmonary exercise testing (CPX), typically performed on a treadmill or cycle ergometer, with incremental increases in exercise workload up to the maximal effort, usually limited by symptoms or fatigue [5]. However, CPX is not widely used in the cardiorespiratory rehabilitation setting due to the cost of equipment and

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List of abbreviations

6 MWT	6-min walk test
BMI	body mass index
CHF	chronic heart failure
COPD	Chronic Obstructive Pulmonary Disease
CPX	cardiopulmonary exercise testing
estMWR@CPX	estimate MWR at CPX
ICS =	Istituti Clinici Scientifici
LoA	Limits of agreement
LVEF	left ventricular ejection fraction
MWR	maximal work rate
MWR@CPX	MWR at CPX
NHYA	New York Heart Association
RER	respiratory exchange ratio
RPE	Rating of Perceived Exertion
SLIT	symptom-limited incremental test
VE	ventilation
VCO_2	carbon dioxide production
VO_2	oxygen uptake
W	Watt

the need for specialized staff to perform and interpret the CPX [6–8]. As a result, exercise capacity is often measured using field-based walking tests [6–8] which are easy to perform and interpret and inexpensive. The 6-min walk test (6 MWT), which measures the distance walked by the patient in 6 min at a self-selected pace, is currently the most widely used exercise field test [9].

Several studies in COPD patients have investigated the relationship between 6 MWT and the MWR at CPX (MWR@CPX) [10–13]. These have led to the development of some regression equations to estimate MWR@CPX from the distance walked and other anthropometric parameters in order to set the correct workload during cycle-ergometer exercise training [13]. In CHF patients, the distance walked during the 6 MWT was found significantly related to peak VO2 at CPX ($r = 0.63$) [14] and some studies have estimated peak VO_2 from 6 MWT for prognostic and clinical purposes [15–17]. However, to our knowledge, no studies have directly estimated the MWR@CPX for exercise prescription purposes. Considering the above studies in patients with COPD, we hypothesized that if a significant relationship between 6 MWT and MWR was also found in patients with CHF, this would facilitate the prescription of cycle ergometer training in a rehabilitation setting.

Therefore, the aim of this cross-sectional study was to develop a predictive model to estimate the MWR@CPX (estMWR@CPX) in a large cohort of CHF patients using the distance walked at 6 MWT and a set of anthropometric and clinical measures as covariates.

2. Materials and methods

In this multicentre cross-sectional study, we retrospectively analyzed data from patients with CHF who underwent both CPX and 6 MWT at the Istituti Clinici Scientifici (ICS) Maugeri of Lumezzane, Montescano, and Veruno (Italy) and at the Istituto Cardiologico Monzino (Milano, Italy) between October 2008 and November 2020.

2.1. Patients

We selected CHF patients aged 40–80 years in NYHA class I-III who had undergone 6 MWT and CPX, for the assessment of functional capacity, with less than a 1-week interval between the two tests. The CPX was performed in the absence of established absolute and relative contraindications [18]. Thus, patients were clinically stable on optimal medical therapy with standard HF medications. Exclusion criteria were the use of long-term oxygen therapy, previous heart transplantation or left ventricular assist device, severe aortic stenosis, neuromuscular or orthopaedic co-morbidities, and concomitant moderate or more severe chronic obstructive pulmonary disease. The presence of a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy was not exclusion criteria.

2.2. Outcome measure

The CPX was performed and interpreted according to current international guidelines [19,20] using a stationary ergo spirometer (Quark PFT, COSMED, Rome, Italy) with an electronically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany). The load increase protocol was set at 10 W/min and patients pedalled at 60 rpm. In the absence of clinical events (including ECG abnormalities, attainment of maximal HR, hypertensive crisis, hemodynamic instability, and significant desaturation with SpO_2 <85%), CPX was stopped when patients reported reaching maximal effort due to muscle fatigue or dyspnea. The MWR achieved (Wmax) was the parameter we used as the dependent variable in our estimation equations.

From the breath-by-breath analysis of expiratory gases and ventilation (VE), the respiratory exchange ratio (RER) was measured as VCO_2/VO_2, and the exercise performance achieved was defined as maximal or near maximal, based on a cut-off value of 1.05 [20–22].

The 6 MWT was performed, according to the ATS/ERS guidelines [23,24], along a flat corridor of at least 20 m. Each patient received standardized pre-test instructions and verbal encouragement at every minute during the test. Two tests were performed: the first was for familiarization and was not included in the analysis.

A standard 2D-echocardiography was performed in all patients as recommended by the American Society of Echocardiography [25].

The following patient data were also taken into account: demographic (age, sex), anthropometric [weight, height, body mass index (BMI)], and clinical data (hemoglobin, ejection fraction, and presence of any comorbidities and risk factors).

2.3. Statistical analysis

Descriptive statistics are reported as mean ± SD or N (percentage frequency) for continuous and categorical variables, respectively. The association between pairs of variables was assessed by Pearson's correlation coefficient or Kendall's rank correlation coefficient, as appropriate.

Simple and multivariable linear regression analyses were performed to develop predictive models for estimating Wmax at CPET (response variable) using the distance walked at 6 MWT, demographic, anthropometric, and clinical variables as predictors. Specifically, a first very simple model including only the 6 MWT was developed, then a multivariable model including sex, age, and weight in addition to the 6 MWT was developed. Finally, a backward stepwise regression analysis with elimination at the 0.05 significance level was performed including all available candidate predictors to obtain the best possible model.

The agreement between the predicted and the true values of Wmax was assessed using Bland-Altman plots, with computation of the nonparametric 95% limits of agreement (95%LoA, the 2.5-th and 97.5-th percentiles of the difference between paired measurements), which provide an estimate of the interval within which 95% of the differences are expected to lie.

All statistical tests were two-tailed and statistical significance was set at $p < 0.05$. All analyses were carried out using MATLAB, release 2014a (The MathWorks, Natick, MA, U.S.A.) and the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, U.S.A.).

3. Results

Of the 728 HF patients screened, 600 (mean age 63 ± 10 years, mean left ventricular ejection fraction 34 ± 10%, NYHA class I-III) met the inclusion/exclusion criteria and were included in this analysis.

Of these, 533 were men (89%), 43% had hypertension, 27.5% had diabetes and 10% had COPD as a comorbidity. Regarding medications, 94% were taking β-blockers, 92% were taking diuretics and 58% were taking statins (Table 1SM in the supplementary material).

The association (Pearson's r) between true MWR@CPX and relevant variables is shown in Table 1. MWR@CPX was significantly associated with 6 MWT, 6MWTwork (obtained as the distance walked at 6 MWT * weight) [26] and anthropometric and clinical data. Fig. 1SM in the supplementary material shows a scatterplot of the relationship between true MWR@CPX and 6 MWT, together with the linear regression line (equation: estMWR@CPX=4.43 + 0.191*6 MWT, adjusted $R^2 = 0.28$).

We then built a simple model including, in addition to 6 MWT, sex, age and weight: the equation obtained was estMWR@CPX = −18.77 + 0.16*6 MWT +9.1*sex (1 Male, 0 Female) - 0.25*Age + 0.55*Weight (Fig. 1). All variables included in the model were significant (i.e. independent predictors of MWR@CPX). The adjusted coefficient of determination (R^2) was 0.38. The 95% LoA ranged from −56 to 37 W.

We then performed a backward stepwise regression analysis including all available variables: 6 MWT, age, weight, sex, NYHA class, left ventricular ejection fraction (LVEF), smoking status, and COPD were retained at the 0.05 significance level. The resulting model equation was: estMWR@CPX = 8.83 + 0.14*6 MWT +12.74*sex (1 Male, 0 Female) - 0.32*Age + 0.51*Weight - 19.97*NYHA2 (1 if NYHA class = 2, 0 otherwise) - 31.43*NYHA3 (1 if NYHA class = 3, 0 otherwise) + 0.33*LVEF - 5.58*Smoke (0 Non-smoker, 1 Ex-smoker, 2 Smoker) - 6.55*COPD (0 no COPD, 1 COPD). The adjusted R^2 was 0.55 and the 95% LoA ranged from −39 to 33 W.

Because LVEF may not be readily available in all clinical settings, we also run the backward stepwise regression analysis without this variable (Fig. 1). The resulting equation was: MWR@CPX = 17.57 + 0.14*6 MWT +11.50*sex (1 Male, 0 Female) - 0.30*Age + 0.53*Weight - 21.01*NYHA2 (1 if NYHA class = 2, 0 otherwise) - 33.43*NYHA3 (1 if NYHA class = 3, 0 otherwise) - 5.95*Smoke (0 Non-smoker, 1 Ex-smoker, 2 Smoker) - 6.17*COPD (0 no COPD, 1 COPD). The adjusted R^2 was 0.54 with 95% LoA ranging from −42 to 34 W.

Focusing on the Bland-Altman plots, it can be seen that for all models developed, the predicted values of MWR@CPX tended to overestimate low values of true MWR@CPX (positive error) and underestimate high values of MWR@CPX (negative error).

The error (estMWR@CPX – true MWR@CPX) obtained with the last model described (i.e. the one without LVEF), was, in absolute value, less than 5 Watts in 21.7% of patients, between 5 and 10 Watts in 21.6% of patients and greater than 10 Watts in 56.7% of patients. The histogram showing the distribution of patients according to the percentage error (100*(estMWR@CPX – true MWR@CPX)/true MWR@CPX) is shown in Fig. 3. The absolute percentage error was smaller than 10% in 34.2% of patients, between 10% and 25% in 37.9% of patients and greater than 25% in the remaining 27.9% of patients.

For the sake of comparison with previous findings reported in COPD patients, we also tested 6MWTwork as a predictor instead of the distance walked at 6 MWT, but no improvement in the predictive ability was observed.

4. Discussion

Our results show that the models we developed to estimate MWR@CPX in CHF patients using the 6 MWT and a set of anthropometric and clinical measures were not sufficiently accurate. In only 34% of our CHF patients was the difference between estimated and actual MWR@CPX less than 10%. Using the estMWR@CPX regression equations would lead to an overestimation or underestimation of the true MWR@CPX. This means that if we applied the regression calculated

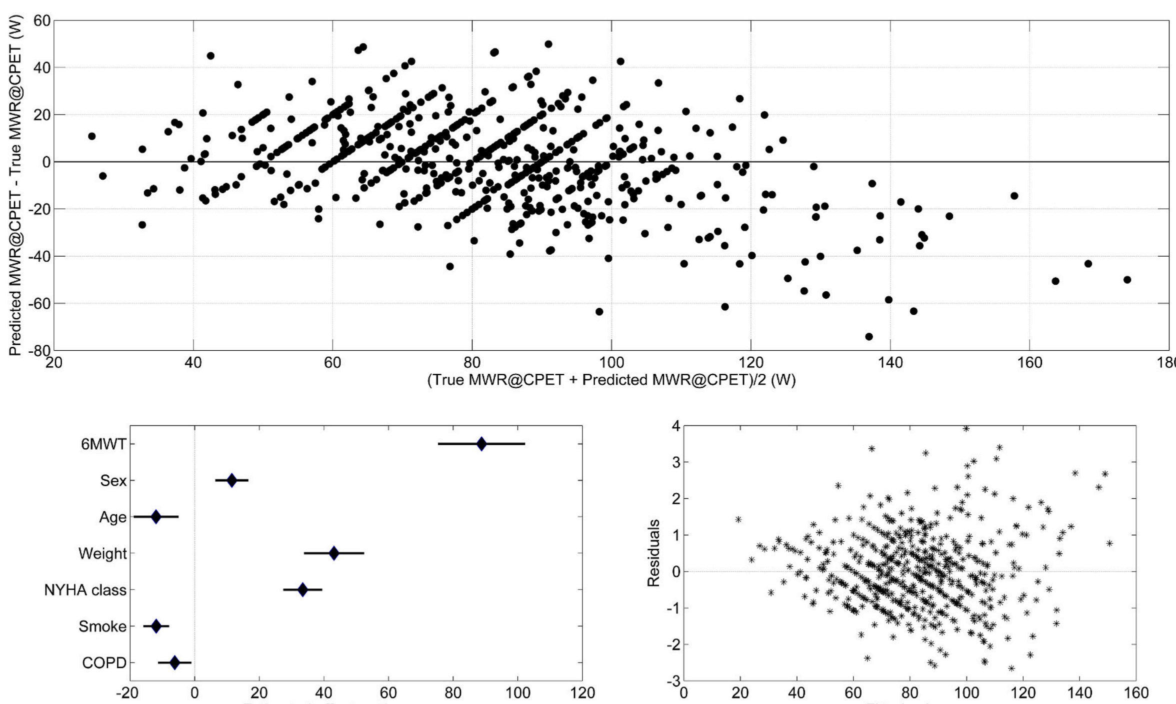

Fig. 1. Results for model: estMWR@CPX = 17.57 + 0.14*6 MWT +11.50*sex - 0.30*age +0.53*weight - 21.01*NYHA2 - 33.43*NYHA3 - 5.95*smoking - 6.17*COPD.

Legend: Top panel: Bland-Altman plot (difference between the mean values of estimated and true MWR@CPX). Bottom left panel: graphical representation of the effect of the considered predictors on estimated MWR@CPX. Diamonds represent the expected average change in estMWR@CPX moving from one extreme value to the other of each variable in the model, adjusting for all other variables. The lines around the circles represent the 95% confidence interval: crossing the zero effect line indicates a lack of significance. Bottom right panel: plot of the residuals as a function of predicted values. Sex: 1 male, 0 female; NYHA2: 1 if NYHA class = 2, 0 otherwise; NYHA3: 1 if NYHA class = 3, 0 otherwise; smoking: 0 non-smoker, 1 ex-smoker, 2 smoker; COPD: 0 no COPD, 1 COPD.

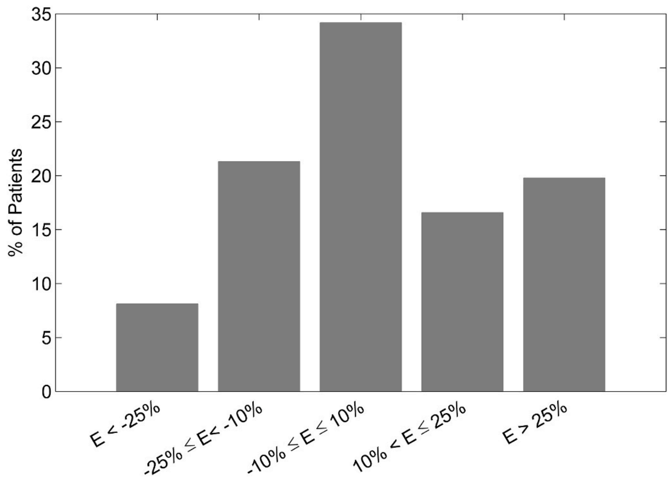

Fig. 2. Histogram showing the distribution of patients according to the percentage difference (E) between estimated and true MWR@CPX.

with the present data set, most HF patients would not start cycle-ergometer training with an optimal workload. Therefore, in our opinion, in HF patients it is mandatory to assess the MWR directly by CPX or a symptom-limited incremental test (SLIT) to accurately define a tailored cycle-ergometer training program.

In addition, the performance of our best model ($R^2 = 0.55$) was worse than reported in COPD patients, both in studies with small cohorts ($R^2 = 0.67$ and $R^2 = 0.80$) [11,13] and in a study with a very large cohort (N = 2096, $R^2 = 0.67$) [27]. Of note, despite the better coefficient of determination reported in COPD patients, Sillen et al. [27] also concluded that this estimation method was not accurate enough to be used in practice.

A possible explanation for the low accuracy of the 6 MWT in estimating MWR@CPX is that the CPX and 6 MWT measure different aspects of exercise tolerance. From a physiological point of view, this could be explained by the principle of exercise specificity [28]: the muscles involved, the movement and the type of tasks required are different between the two tests. In addition, the 6 MWT is a constant exercise test, whereas the CPX usually uses a ramp exercise protocol, and gas exchange and ventilatory kinetics are therefore different [29]. In fact, in patients with severe CHF, peak aerobic capacity is higher on the 6 MWT than on the CPX in almost half of the patients, as is ventilation and heart rate [30]. As the 6 MWT has a constant VO_2 for at least 5 min of exercise, these data clearly show that the 6 MWT elicits a greater effort than the CPX in patients with severe HF and therefore the data between the two are not easily comparable.

Therefore, our results suggest that the 6 MWT cannot be used to estimate training work rate when this is calculated as a percentage of peak exercise capacity. Accordingly, a pre-rehabilitation CPX is necessary especially when the focus is on high-intensity cycle-ergometer training. In this regard, the American Heart Association [31], the American Association of Cardiovascular and Pulmonary Rehabilitation [32], the Canadian Association of Cardiac Rehabilitation [33], and the European Association of Preventive Cardiology [34–37] all recommend an ECG-monitored exercise testing as a pre-rehabilitation assessment. Moreover, in order to facilitate interventions on lifestyle and during phase II/phase III cardiac rehabilitation programs, the Italian Alliance for Cardiovascular Rehabilitation and Prevention (ITACARE-P) has recently developed a CPX reporting form specifically oriented to exercise prescription [38].

Despite the recommendations of these leading cardiovascular societies, in Australasia and the UK a lower standard is used to determine functional capacity, based on less technical exercise testing in the form of either the 6 MWT or a shuttle walk test [38]. However, the authors acknowledge that an ECG-monitored exercise stress test should be performed in high-risk patients (those with decompensated HF, uncontrolled arrhythmias, or experiencing angina at rest or on minimal exercise) and in those who wish to participate in a high-intensity exercise program (>75% of maximal heart rate) [39].

Thus, we confirm that it is important to perform a CPX or, at least, a functional sign/symptom-limited exercise test before starting a rehabilitation program using the cycle ergometer for training [3]. Of note, programs based on walking as the main exercise modality are also beneficial for patients with CHF [40] and, for (brisk) walking programs, the use of an incremental shuttle walk test [41] or a 6 MWT has been suggested.

If logistic constraints (unavailability of equipment or skilled personnel) or the setting (e.g. home maintenance programs after cardiac rehabilitation) prevent the assessment of MWR with CPX or an ECG-monitored exercise test, the optimal training intensity should be defined according to current guidelines. Further studies are needed to investigate whether the use of some equations to estimate maximal work rate using the distance walked on the 6 MWT (even if not precise), in combination with the rating of perceived exertion (RPE) and close monitoring could be useful to safely set the correct workload target in these contexts. Further studies will also evaluate whether the assessment of oxygen consumption on the 6 MWT can help to improve the estimation of target exercise load.

4.1. Study limitation

The main limitation of this study is its retrospective nature: however, we are confident in the accuracy of the data collected as our laboratories are equipped with advanced technological devices and highly qualified experts in exercise evaluation.

5. Clinical implication and conclusions

The use of the 6 MWT to prescribe the intensity of exercise to be performed during cycle ergometer training in patients with HF is becoming increasingly common. This is because, compared with cardiopulmonary exercise testing, the 6 MWT is easier to perform, less time-consuming and does not require specialized personnel and equipment to perform and interpret the test. In this study, we investigated the feasibility of building a model that provides an equation to predict the watts in the CPT using the meters walked in the 6 MWT, using anthropometric, demographic and clinical parameters as adjusting factors.

Unfortunately, the results were negative, as the estimation of MWR@CPX using the 6 MWT in patients with HF lacks accuracy, even when conventional clinical variables are added to the model.

The study highlights the importance of the cardiopulmonary testing (at least one exercise test) when prescribing exercise to patients with HF and suggests caution against using the 6 MWT to prescribe exercise training intensity.

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CRediT authorship contribution statement

Giancarlo Piaggi: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mara Paneroni:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Roberto Maestri:** Formal analysis, Visualization, Writing – review & editing. **Elisabetta Salvioni:** Data curation, Investigation, Writing – review & editing. **Ugo Corrà:** Data curation, Investigation, Writing – review & editing. **Angelo Caporotondi:** Data curation, Investigation, Writing – review & editing. **Simonetta Scalvini:** Data curation, Supervision, Writing – review & editing. **Piergiuseppe Agostoni:** Data curation, Supervision, Writing – review & editing. **Maria Teresa La Rovere:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

All Authors declare no conflict of interest relevant to the research, analysis, or interpretation presented in the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200247.

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