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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Old and new equations for maximal heart rate prediction in patients with heart failure and reduced ejection fraction on beta-blockers treatment: results from the MECKI score data set

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Aims Predicting maximal heart rate (MHR) in heart failure with reduced ejection fraction (HFrEF) still remains a major concern. In such a context, the Keteyian equation is the only one derived in a HFrEF cohort on optimized β-blockers treatment. Therefore, using the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) data set, we looked for a possible MHR equation, for an external validation of Keteyien formula and, contextually, for accuracy of the historical MHR formulas and their relationship with the HR measured at the anaerobic threshold (AT).

Methods and results Data from 3487 HFrEF outpatients on optimized β-blockers treatment from the MECKI data set were analyzed. Besides excluding all possible confounders, the new equation was derived by using HR data coming from maximal cardiopulmonary exercise test. The simplified derived equation was [109–(0.5*age) + (0.5*HR rest) + (0.2*LVEF)–(5 if haemoglobin <11 g/dL)]. The R^2 and the standard error of the estimate were 0.24 and 17.5 beats min^{-1} with a mean absolute

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percentage error (MAPE) = 11.9%. The Keteyian equation had a slightly higher MAPE = 12.3%. Conversely, the Fox and Tanaka equations showed extremely higher MAPE values. The range 75–80% of MHR according to the new and the Keteyian equations was the most accurate in identifying the HR at the AT (MAPEs = 11.3–11.6%).

Conclusion The derived equation to estimate the MHR in HFrEF patients, by accounting also for the systolic dysfunction degree and anaemia, improved slightly the Keteyian formula. Both formulas might be helpful in identifying the true maximal effort during an exercise test and the intensity domain during a rehabilitation programme.

Keywords Heart failure • Maximal heart rate • Chronotropic incompetence • Cardiopulmonary exercise test • MECKI score

Introduction

Predicting maximal heart rate (MHR) represents the first step to define the chronotropic incompetence. Both the MHR prediction and the chronotropic incompetence definition are unsolved issues in clinical practice of heart failure (HF) evaluation, being influenced by therapy, specific disease features and patients' fitness.[1] An equation able to predict accurately the MHR in HF patients might be useful for a number of clinical reasons, i.e. ischaemia threshold detection, functional capacity assessment, and rehabilitation programmes' prescription.[2–6] At present, to define the MHR, the historical equation by Fox.[7] i.e. MHR predicted = (220–age), is still routinely used albeit it has not been validated in specific clinical settings including HF.[8,9] Similarly, the equation by Tanaka *et al.*[10], i.e. MHR predicted = 208–(0.7 * age), acknowledges the same limitations of the Fox one given it has been obtained in a large but healthy population free of any medication. Accordingly, many authors attempted to develop alternative formulas for the MHR prediction but the resulting equations are not applicable in the general HF population, likely due to different methodological issues (i.e. sample size, type of stress test, inhomogeneous drug regimen).[11] In such a context, Keteyian et al.[12] supplied an interesting equation for predicting the MHR in 767 HF patients with a left ventricular ejection fraction <35% and on optimized β-blockers treatment. Noteworthy, for their study purpose, the authors analyzed HR data coming from a symptomlimited cardiopulmonary exercise test (CPET) maximal from a metabolic viewpoint (i.e. respiratory exchange ratio >1.10), this methodological approach strengthening their equation.[12]

Up to now, to our knowledge, there are no other studies which attempted neither to build an alternative and possibly more accurate equation to predict the MHR in stable heart failure with reduced ejection fraction (HFrEF) on β-blockers regimen nor to validate externally the Keteyian formula. Furthermore, since the intensity domains' identification represents a crucial step in prescribing the exercise intensity during the HF patients rehabilitation programmes,[13–19] it would be appealing to investigate possible correspondence between the MHR predicted and the HR at the anaerobic threshold (AT) as identified by CPET analysis.

Therefore, using the Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) data set,[20,21] likely the world largest repository of clinical data, including those from CPET, coming from consecutive measurements in stable HF patients, we sought to investigate the following items: (i) a new and possibly more accurate equation to predict the MHR; (ii) the accuracy of the historical formulas, including the one proposed by Keteyian *et al.*, in predicting the MHR; (iii) the relationship between the HR measured at the AT and the MHR predicted according to the different available formulas as well according to the new one derived.

Methods

Study sample

We retrospectively analyzed data of patients with HFrEF (left ventricular ejection fraction, LVEF, <40%) from the MECKI Score database which includes consecutive stable HF patients recruited and followed by MECKI Score Research Group in 27 Italian HF centres. The design, patients' eligibility criteria, and methods of MECKI score study have been previously described.[20,21]. Briefly, primary inclusion criteria were stable clinical conditions with unchanged medications for at least 3 months and no major cardiovascular treatment or intervention scheduled. Conversely, the exclusion criteria were history of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive/restrictive lung disease, primary pulmonary hypertension, significant peripheral vascular disease, and exercise-induced angina, and/or ST changes. Furthermore, for the actual study purpose (i.e. evaluation of the MHR predicted response during a maximal strength), we excluded from the analysis also the following HF patients' categories: HF patients with atrial fibrillation at the CPET examination ($n = 1036$), with a pacemaker-dependent HR ($n = 566$) and those not taking β-blockers ($n = 638$) (*Figure 1*). Moreover, those HF patients who performed a CPET with respiratory exchange ratio ≤ 1.05 whose maximality is uncertain were excluded ($n = 375$). Thereafter, within the remaining patients, we also excluded a small group of patients ($n = 156$, 4.2%) who performed a CPET on treadmill and who were enrolled in a single centre to analyze a homogeneous HFrEF cohort in terms of stress test protocols and avoid confounders.

To avoid possible confounding with respect to the different β-blockers agents, the doses were converted to equivalent doses of carvedilol. Briefly, the daily dosage in those taking atenolol, metoprolol, or metoprolol XL was divided by two, whereas the dose for bisoprolol or nebivolol was multiplied by five.[22]

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. The data underlying this article will be shared on reasonable request to the corresponding author.

Cardiopulmonary exercise testing

A maximal, symptom-limited CPET was performed on an electronically braked cycloergometer (100% of the cases) connected to a metabolic chart. A personalized ramp exercise protocol was chosen, aiming at a test duration of 10 ± 2 min.[23,24] The minimum duration of the test did not represent an inclusion criteria, since a metabolic viewpoint (i.e. RER >1.05) was used to identify maximal exercise performances. In all the centres contributing to the study, the exercise was preceded by an appropriate resting breath-by-breath gas exchange monitoring

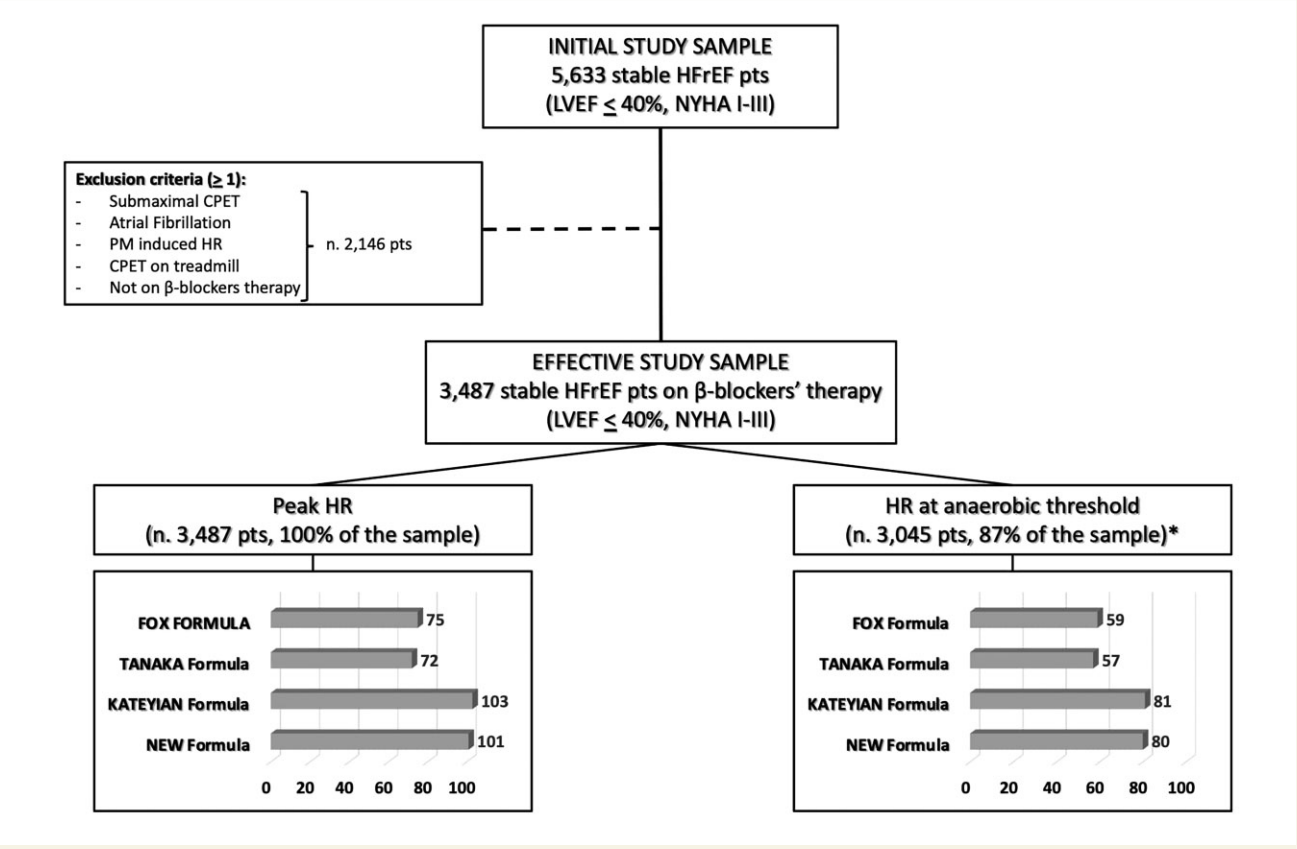

Figure 1 Diagram showing the step-by-step screening procedures of the population studied and heart rate (HR) values measured at peak exercise and at the anaerobic threshold expressed as percentage according to the different formulas for predicting maximal HR (MHR).* The anaerobic threshold was not identifiable in the 13% of the study sample. HFrEF, heart failure with reduced ejection fraction; Pts, patients; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; R.E.R., respiratory exchange ratio; PM, pacemaker; CPET, cardiopulmonary exercise test.

and unloaded warm-up (2 min). The exercise was followed by a 2 min unloaded recovery phase. A 12-lead electrocardiogram, blood pressure, and HR were also recorded. CPET was self-terminated by the subjects when they claimed that they had achieved maximal effort. 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.[25] Anaerobic threshold 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 O_2 (VE/VO_2) and CO_2 (VE/VCO_2), as well as through the end-tidal pressure of O_2 and CO_2.[23,24] The relation between VE and VCO_2 was analyzed as the slope (VE/VCO_2 slope) of the linear relationship between VE and VCO_2 from 1 min 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 programme at Centro Cardiologico Monzino.

Classification of the exercise-induced HR response

Baseline HR (HR rest), peak HR, and ΔHR (peak HR–HR rest) were collected during CPETs, HR rest being measured after at least 2 min of rest in a seated position on the cycloergometer. Peak HR data were also analyzed as a percentage of maximum predicted values according to the following standard formulas:

- Fox formula[7]:

$$\%MHR_{FOX} = [\text{peak HR}/(220 - \text{age})] \times 100$$

- Tanaka formula[10]:

$$\%MHR_{TANAKA} = \{\text{peak HR}/[208 - (0.7*\text{age})]\} \times 100$$

- Keteyian formula[12]:

$$\%MHR_{KETEYIAN} = \{\text{peak HR}/[114 + (0.5*\text{HR rest}) - (0.5*\text{Age})]\} \times 100$$

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 (75th percentile−25th 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.

A list of the main demographic and resting clinical variables were analyzed as possible predictors of MHR (age, gender, body mass index, aetiology, HR rest, LVEF, haemoglobin, renal function, sodium, carvedilol dose equivalent). We aim at building a parsimonious model, by retaining a subset of the predictors and discarding the rest. We use a shrinkage method, namely the lasso, to perform subset selection and produce a model that is interpretable and has possibly lower prediction error than the full model. The resulting model, although parsimonious from a statistical perspective, may not be straightforwardly applied by clinicians. Thus, we simplified it by further reducing the number of independent variables in the model, retaining all variables with a partial $R^2 \geq 0.01$ only. A model inclusive of the remaining variables with the associated overall R^2, standard error of the estimate (SEE), and the *P*-value and partial R^2 value for each parameter was rendered. Thereafter, we focused on the accuracy of the historical models (Fox, Tanaka, and Kateyian) and a number of possible candidate equations for estimating the MHR in the actual study cohort. Consistent with the statistical method adopted in the Keteyian study,[12] a comprehensive list of demographic and resting clinical variables (see *Table 1*) were assessed as predictors of MHR. Multiple linear regression was used with variable selection in two stages. First, a stepwise backwards selection algorithm was used in which the variable with the highest *P*-value was removed, the model was then re-fit and the variable with the highest P-value in the new model was removed. This process was repeated until all remaining covariates had $P < 0.05$. The second stage removed, in a single step, all variables with a partial $r^2 < 0.01$.

We compared them in terms of mean absolute percentage errors (MAPEs) = (average absolute percent error for each time period−actual values)/(actual values). The same approach has been used to analyze the accuracy of abovementioned formulas (in terms of a number of different percentages) with respect the HR measured at the AT. To avoid a possible overfitting, which is a common problem in the development of predictive models (i.e. too optimistic estimation of apparent model performance), we proceeded with an internal validation using bootstrapping techniques which allows one to quantify the optimism of a predictive model and provide a more realistic estimate of its performance measures. Statistical analysis was performed using the R software (R Development Core Team, 2020).

Table 1 Main clinical variables of the overall HF study ($n = 3487$)

General data	
Age, years	59 ± 12
Male, *n* %	2931 (84.1)
Body mass index, kg/m^2	26.7 ± 4.3
NYHA, *n* (%)	
I	697 (20)
II	1987 (57)
III	803 (23)
Ischaemic etiology, *n* (%)	1531 (44)
Haemoglobin, g/dL	13.6 ± 1.8
LVEF, %	29.4 ± 6.9
MDRD, ml/min*1.73 m^2	74.2 ± 23.6
CPET variables	
AT not identified, *n* (%)	512 (14.6)
VO_2 AT, ml/kg/min	10.5 ± 3.2
VO_2 AT, % of max predicted	34 ± 17
Peak VO_2, ml/kg/min	15.5 ± 4.7
Peak VO_2, % of predicted	57 ± 17
RER	1.12 ± 0.03
Length, min	9.5 ± 1.5
Treatment	
ACEi or ARBs, *n* (%)	3158 (91)
β-blockers, *n* (%)	3487 (100)
Carvedilol dose equivalent, mg	29 ± 17
MRA, *n* (%)	1897 (54.4)

Data are expressed as mean ± SD, as absolute number of patients (% on total sample) or as median (25th–75th percentile). NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MDRD, Modification of diet in renal disease; HR, heart rate; VO_2, oxygen uptake; AT, anaerobic threshold; RER, respiratory exchange ratio; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

Table 2 Main clinical variables independently associated at peak heart rate in the overall study sample ($n = 3487$ HFrEF patients)

	Parameter estimate	*P* values	Partial R^2
Intercept	109.006	<0.001	
Age	−0.553	<0.001	0.116
HR rest	0.560	<0.001	0.096
LVEF, %	0.223	<0.001	0.010
Haemoglobin ≤ 11 g/dL	−4.729	0.001	0.014
MDRD ≤ 30 ml/min	−5.613	0.048	0.012
BMI < 18 or > 30 kg/m^2	−2.626	0.035	0.016

See *Table 1* for abbreviations. Note that only variables with a $R^2 \geq 0.01$ are reported.

Results

Starting from an initial study sample of 5633 stable HFrEF outpatients, 3487 patients met the inclusion/exclusion criteria and were considered for the present study (*Figure 1*). *Table 1* summarizes the main clinical and CPET data as well as concomitant therapeutic strategies with disease modifier drugs collected at the study run-in in the overall study group. Particularly, the study population consisted mostly of middle-aged male patients in NYHA functional Class I-III, with significantly depressed LVEF and moderate-to-severe exercise limitation (peak VO_2 averagely 60% of the maximum predicted). Of note, there was a meaningful percentage of patients with the AT not identified (nearly 15% of the total sample). HF treatment was in accordance with the guidelines applied at the time of the CPET.[26] The β-blocker treatment was considered optimized by the HF cardiologist in charge of the patient. Since the combination of β-blockers and non-dihydropyridine calcium-channel-blockers is not recommended, this latter pharmacological class was not prescribed in our population. A small percentage of subjects (<1%) received ivabradine, similar prevalence being for those treated with digoxin (<1%).

Table 3 Historical and possible candidate equations for estimating maximal heart rate (MHR) and related accuracy data

		R^2	SSE,beats·min^{-1}	MAPE,%
Historical equations				
MHR_{FOX}	220–age			37.6
MHR_{TANAKA}	208–0.7*age			42.6
$MHR_{KETEYIAN}$	114 + (0.5*HR rest) – (0.5*age)			12.4
Attempted equations				
One variable (age) regression	157.04–(0.62*age)	0.12	19.4	13.0
One variable (resting HR) regression	77.17 + (0.63*HR rest)	0.11	19.6	13.2
Two variables (age and resting HR)	114.45–(0.52*age) + (0.53*HR rest)	0.20	18.4	12.2
Proposed new equation				
Regression equation	108.68 + (0.554*HR rest) – (0.550*Age) + (0.222*LVEF) – 5.312 (if Hb < 11 g/dL)	0.24	17.5	11.8
Simplified equation	109 + (0.5*HR rest) – (0.5*age) + (0.2*LVEF) – 5 (if Hb < 11 g/dL)			11.9

Hb, haemoglobin; SEE, standard error of the estimate; MAPE, mean absolute percentage error. For other abbreviations, see *Table 1*.

Table 4 Heart rate data at peak exercise and at anaerobic threshold (AT) expressed as absolute values and as percentages of maximum predicted according different equations

Variables	
Exercise test variables	
HR rest, bpm	67 ± 9
Peak HR, bpm	120 ± 21
Peak HR (Fox), %	75 ± 12
Peak HR (Tanaka), %	72 ± 12
Peak HR (Keteyian), %	103 ± 16
Peak HR (new formula), %	101 ± 9
AT identified, *n* (%)	3045 (87)
HR AT, bpm	96 ± 16
HR AT (Fox), %	59 ± 10
HR AT (Tanaka), %	57 ± 9
HR AT (Keteyian), %	81 ± 12
HR AT (new formula), %	80 ± 12

For abbreviations, see *Table 1*.

Table 5 Possible cut-off values to identify the anaerobic threshold (AT) intensity domain and related accuracy data

	MAPE, %
HR_{FOX}	
50%	16.5
55%	13.1
60%	13.6
HR_{TANAKA}	
50%	14.7
55%	13.0
60%	13.9
$MHR_{KeTEYIAN}$	
70%	14.2
75%	11.6
80%	11.5
MHR_{NEW}	
70%	13.5
75%	11.3
80%	11.6

For other abbreviations, see *Table 1*.

The four candidate variables independent predictors of MHR with a partial $R^2 > 0.01$ in the full multivariable model are shown in *Table 2*, whereas the resulting equation is extensively supplied in *Table 3* with its accuracy data ($R^2 = 0.24$; SEE = 17.5 beats·min^{-1}; MAPE = 11.8%), as well as the simplified formula (MAPE = 12%). *Table 3* shows a detailed comparison between the MAPEs values of the three historical formulas (i.e. Fox, Tanaka, and Keteyian) with the attempted equations derived from (i) one variable (i.e. age or HR rest), (ii) two variables (i.e. age and HR rest), (iii) all the four variables resulting from the multivariable analysis (i.e. age, HR rest, LVEF, and Hb levels). The new equation, even when simplified, showed a significantly lower MAPE with respect to the Fox and Tanaka equation, whereas a slightly lower MAPE than the one obtained for the Keteyian formula (11.9 vs. 12.4%). Validation of our main simplified equation using 1000 bootstrap samples yielded a mean $R^2 = 0.23 \pm 0.01$ with a SEE of 18 beats min^{-1}.

Table 4 reports all the HR data either expressed as absolute values and as percentages of maximum predicted according to each of the different equations analyzed in the actual study. Of note, the peak HR values expressed as percentage were nearly 30% lower according to the Fox and Tanaka formulas than when calculated adopting the Keteyian or the new equation. Eventually, *Table 5* reports the most accurate percentages range of MHR according to the four tested equations with respect the identification of the HR at the

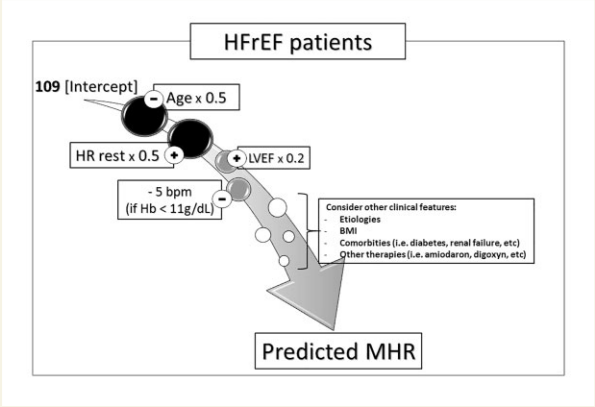

Figure 2 Explicative figure showing the main variables included in the derived equation for maximal heart rate (MHR) prediction and other clinical features possibly influencing the effective MHR in patient with heart failure and reduced ejection fraction (HFrEF) on optimized β-blockers therapy. HR, heart rate; LVEF, left ventricular ejection fraction; Hb, haemoglobin; BMI, body mass index.

AT. Besides a significantly lower percentage range of MHR (55–60 vs. 75–80%), the Fox and Tanaka equations were less accurate than the Keteyian and the new formula in terms of MAPEs values.

Discussion

The present analysis has been conducted on the MECKI Score data set, the world largest repository of clinical data coming from consecutive measurements in stable HFrEF patients on optimized medical treatment.[20,21] Our main finding, from a sizeable cohort of 3487 stable HFrEF outpatients on optimized β-blockers treatment, is a new equation for the MHR prediction, i.e. MHR = [109 +(0.5*HR rest)–(0.5*age) + (0.2*LVEF) (–5 if Hb <11 g/dL)], which performed significantly better than the Fox[7] and Tanaka[10] formulas and, even, it slightly improved the Keteyian equation[12] accuracy. Another finding, likely more important from a clinical/rehabilitative viewpoint, is that the 75–80% range of MHR calculated with the new and the Keteyian formulas[12] identifies accurately the HR at the AT factually measured at a maximal symptom-limited CPET in this setting of patients.

A reliable prediction of the MHR in the HFrEF population might be extremely useful for a huge number of clinical reasons. Indeed, in absence of a simultaneous collection of gas exchange, as it is possible only during a CPET execution, the knowledge of the MHR in a HFrEF patient might be helpful to be sure that the maximum exercise effort is achieved and, consequently, to consider the test reliable to detect inducible ischaemia, to derive a rehabilitation plan or, more in general, to assess quite accurately the functional capacity.[2–6] In such a context, the high prevalence of chronotropic incompetence, to some extent due to the concomitant treatments with negative chronotropic agents (i.e. β-blockers), add further complexity to the matter.[27–29] Notwithstanding, the historical equation by Fox, i.e. MHR_{FOX} = (220–age), still remains the most frequently used equation in daily practice, even in HFrEF patients. Nonetheless, it should be noted that the Fox equation has been derived from a diagram plotting of a number of studies (n = 35) executed on different healthy populations, as well as using different exercise test mode and protocols.[7] Similarly, also the Tanaka and colleagues equation, i.e. MHR_{TANAKA} = [208–(0.7*age)], resulted from a large meta-analysis of 351 studies mostly involving healthy subjects free of any medication.[10] Furthermore, an additional limitation of both studies was the absence of certainty of a maximal exercise test. In such a context, to our knowledge, only Keteyian *et al.*[12] derived a population-specific formula for the MHR prediction in HF patients with LVEF <35% on optimized β-blockers treatment, i.e. $MHR_{KETEYIAN}$ = [119 + (0.5*HR rest)–(0.5*age) (−5 if bike test)]. Of note, to be reassured that the peak HR values pertained to maximal exercise test, the authors analyzed only data from symptom-limited CPET maximal from a metabolic viewpoint (i.e. RER ≥ 1.10) and, further strengthening their results, they validated internally the proposed equation (i.e. bootstrapping). The present analysis from the MECKI Score data set confirms a poor reliability of the MHR_{FOX} and MHR_{TANAKA} in the HFrEF patients taking β-blockers and, contextually, it supplies for the first time an external validation of the $MHR_{KETEYIAN}$ on an independent cohort nearly five-fold larger than the original one (3487 vs. 767 patients). Thus, albeit the characteristics of the patients enrolled in our study were different compared with the population originally analyzed by Keteyian et al. (i.e. LVEF <40 vs. <35%, white race 100 vs. 59, female prevalence 16 vs. 30, bike mode 100 vs. 11%), a satisfactory accuracy of the $MHR_{KETEYIAN}$ was achieved also in our analysis. However, in a so large study cohort as we analyzed, it was unavoidable that the Keteyian equation accuracy would have been improved when corrected by some clinical markers of an advanced HF stage. Indeed, the HFrEF represents a highly heterogeneous category, and the chronotropic incompetence degree tends to increase proportionally to the disease severity.[30,31] Albeit far from being elucidated, particularly in the HFrEF setting, the chronotropic incompetence has been attributed to a reduced myocardial sensitivity to sympathetic modulation together with a β-receptor down-regulation[32] and to the anatomical and functional changes in the sinus node properties.[33] All these conditions are known to play an important role in the most advanced HFrEF stages which are usually characterized from a reduced exercise capacity and a poor outcome. In such a context, we tried primarily to derive a more 'clinical' MHR equation and we identified the systolic dysfunction degree, as well as a concomitant moderate-to-severe anaemic condition as significant correction factors for the MHR prediction. Specifically, in the new simplified formula, the predicted MHR increases by one beats·min^{-1} for every 5% LVEF increase (i.e. LVEF 5% = +1 beats·min^{-1}; LVEF 40% = +8 beats·min^{-1}). On the other hand, a reduction of 5 beats·min^{-1} is applied in case of a moderate-to-severe anaemic state (Hb <11 g/dL). Why just these two variables achieved the threshold significance in the model is clearly beyond the actual study purpose but, besides accurately mirroring the HFrEF severity, a great impact on the autonomic nervous balance might be conceivable for both of them. However, it should be noted that we identified also other variables possibly related to MHR [i.e. Modification of Diet in Renal Disease (MDRD) and BMI] but, due to their marginal contribute to the final equation and to the tight statistical approach adopted, they were excluded to avoid a correction factors' overaload.[34] This datum, anyway, further supports the complexity of the MHR prediction in each single HFrEF patient, whose exercise performance may be influenced by a number of possible specific clinical

features (see *Figure 2*). Conversely, although apparently unexpected, the lack of a statistical significance of the carvedilol dose equivalent could be related both to a possible collinearity with a strong variable such as the HR rest, as well as to potential differences in sensitivity to the β-blockers.[28]

Another clinically relevant point we tried to address in the present article was to provide some insights about the rehabilitation plans to be adopted in the HFrEF patients. Indeed, the exercise training represents one of the core components of the cardiovascular rehabilitation programmes, most important targets being not only a reduction of events but also an improvement of symptoms as well as of the psychosocial well-being.[35–37] In such a context, a key question remains the identification of the true exercise intensity domains, the AT achievement being the most important metabolic watershed in any type of exercise. Usually, it is common practice to set the exercise intensity aiming to achieve/maintain a range between the 70 and 80% of the MHR in terms of predicted or, better, of observed values at a maximal exercise test.[37,38] However, without performing an exercise test combined with a gas exchange measurement, as it happens too much frequently in the real world, it is impossible to identify correctly both the AT achievement and, possibly, the respiratory compensation point. Furthermore, it should be remarked a high incidence of unidentifiable AT in the most advanced HFrEF stages[39] which could further complicate the exercise intensity prescription. Although the intensity domains (i.e. moderate, moderate-to-high) and the exercise mode (i.e. continuous, interval, etc) to be prescribed in the HFrEF are arguments falling outside the present paper purpose, the present analysis originally showed, for each of the four MHR formulas, the most accurate percentage ranges predicting the HR values factually measured at the AT during a CPET. Specifically, the 75–80% percentage range for the $MHR_{KETEYIAN}$ and MHR_{NEW} identifies the HR values measured at the AT more accurately than the 55–60% percentage range for MHR_{FOX} and MHR_{TANAKA}. Thus, although we advise against the use of this equation to determine *a priori* the HR range for exercise training, being a CPET-tailored exercise training intensity greatly preferable,[40,41] we believe that our finding still deserves a somewhat attention in those cases when a metabolic chart is not available or, even, when a maximal exercise test cannot be performed.

Limitations

Despite we analyzed a sizeable cohort and several demographics, as well as clinical variables at rest, our new proposed equation still suffers from a SEE equal to 17.5 beats min^{-1} which is undoubtedly not so small. However, as we discussed previously, it should be underlined that the HFrEF category represents an enormous pool where patients flow with all their differences in disease-severity[42] and, possibly, in sensitivity to β-blockers therapy. Thus, our study simply confirms the need of a well-reasoned and, possibly, multidimensional approach to the HFrEF setting, even in this field. Noteworthy, no significant differences were detected between genders but although the small percentage of women enrolled in our study (16%) might represent a limitation, our data seems consistent with previous reports.[43,44]

Another important limitation comes from the fact that we focused our attention only on those HR data derived from CPET performed on a cycle-ergometer, thus excluding from the actual analysis a limited amount of tests executed on a treadmill. Our decision has been made mainly for the following three reasons: (i) too small number of usable HR data deriving from CPET using a treadmill (less than 5%); (ii) some uncertainties in the AT point identification during an exercise test on a treadmill (standardized ramp protocol rarely implemented); (iii) treadmill data came all from a single centre on a total of 27 and this could be *per se* a bias. Thus, we could hypothesize that our formula might underestimate slightly the peak HR during a maximal exercise test on treadmill.

Finally, it must be remarked that, due to significant differences in HR kinetics during effort and peak exercise values, patients with atrial fibrillation were excluded from the present analysis. Accordingly, albeit atrial fibrillation is frequently observed in HF patients and particularly in those with severe exercise limitation, our new formula cannot be applied in this specific setting of HF patients. Indeed, besides several possible confounders related to different pharmacological strategies in this setting of patients, we have previously demonstrated significantly higher HR values both at peak exercise and at the AT in HF patients on atrial fibrillation.[45,46]

Conclusions

The present study, conducted on a sizeable cohort of stable HFrEF patients on optimized β-blockers therapy, derived a possible 'clinical' and accurate equation for predicting MHR. Specifically, besides the age and the HR rest, we found both the systolic dysfunction degree and the anaemic state as significant predictors of MHR in this setting of patients. Contextually, besides confirming a poor accuracy of the historical MHR equations by Fox and Tanaka, we supplied the first external validation of the Keteyian formula which performed well in the actual study sample. Eventually, we showed the 75–80% percentage range for both the Keteyian and the new MHR equation as the most accurate percentage ranges for identifying the HR values factually measured at the AT, thus supplying a possibly useful HR target for the exercise intensity prescription during cardiac rehabilitation.

Authors' contributions

D.M. and P.A. contributed to the conception of the work. D.M., G.G., and A.M. contributed to data analysis and interpretation. D.M. and G.G. drafted the manuscript. M.P. and P.A. critically revised the manuscript. All the authors contributed to data collection and finally approved the version to be published.

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Appendix

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Data availability

Data are available upon reasonable request.

References

1. Arena R, Myers J, Kaminsky LA. Revisiting age-predicted maximal heart rate: can it be used as a valid measure of effort? *Am Heart J* 2016;**173**:49–56.
2. Cubbon RM, Ruff N, Groves D, Eleuteri A, Denby C, Kearney L, Ali N, Walker AM, Jamil H, Gierula J, Gale CP, Batin PD, Nolan J, Shah AM, Fox KA, Sapsford RJ, Witte KK, Kearney MT. Ambulatory heart rate range predicts mode-specific mortality and hospitalisation in chronic heart failure. *Heart* 2016;**102**:223–229.
3. Benhorin J, Pinsker G, Moriel M, Gavish A, Tzivoni D, Stern S. Ischemic threshold during two exercise testing protocols and during ambulatory electrocardiographic monitoring. *J Am Coll Cardiol* 1993;**22**:671–677.
4. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, Rees K, Singh SJ, Gluud C, Zwisler AD. Exercise based rehabilitation for heart failure: cochrane systematic review, meta-analysis, and trial sequential analysis. *JACC Heart Fail* 2019;**7**:691–705.
5. Gulati M, Shaw LJ, Thisted RA, Black HR, Bairey Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women: the St. James women take heart project. *Circulation* 2010;**122**:130–137.
6. Morris C, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol* 1993;**22**:175–182.
7. Fox SM III, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. *Ann Clin Res* 1971;**3**:404–432.
8. Forman DE, Clare R, Kitzman DW, Ellis SJ, Fleg JL, Chiara T, Fletcher G, Kraus WE. Relationship of age and exercise performance in patients with heart failure: the HF-ACTION study. *Am Heart J* 2009;**158**:S6–S15.
9. Witte KKA, Cleland JGF, Clark AL. Chronic heart failure, chronotropic incompetence, and the effects of B-blockade. *Heart* 2006;**92**:481–486.
10. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;**37**:153–156.
11. Sakamoto M, Fukuda H, Kim J, Ide T, Kinugawa S, Fukushima A, Tsutsui H, Ishii A, Ito S, Asanuma H, Asakura M, Washio T, Kitakaze M. The impact of creating mathematical formula to predict cardiovascular events in patients with heart failure. *Sci Rep* 2018;**8**:3986.
12. Keteyian SJ, Kitzman D, Zannad F, Landzberg J, Arnold JM, Brubaker P, Brawner CA, Bensimhon D, Hellkamp AS, Ewald G. Predicting maximal HR in heart failure patients on β-blockade therapy. *Med Sci Sports Exerc.* 2012;**44**:371–376
13. Hirsh DS, Vittorio TJ, Barbarash SL, Hudaihed A, Tseng CH, Arwady A, Goldsmith RL, Jorde UP. Association of heart rate recovery and maximum oxygen consumption in patients with chronic congestive heart failure. *J Heart Lung Transplant* 2006;**25**:942–945.
14. Forman DE, Sanderson BK, Josephson RA, Raikhelkar J, Bittner V; American College of Cardiology's Prevention of Cardiovascular Disease Section. Heart failure as a newly approved diagnosis for cardiac rehabilitation: challenges and opportunities. *J Am Coll Cardiol* 2015;**65**:2652–2659.
15. Harwood AE, Russell S, Okwose NC, McGuire S, Jakovljevic DG, McGregor G. A systematic review of rehabilitation in chronic heart failure: evaluating the reporting of exercise interventions. *ESC Heart Fail* 2021;**8**:3458–3471.
16. Taylor RS, Dalal HM, McDonagh STJ. The role of cardiac rehabilitation in improving cardiovascular outcomes. *Nat Rev Cardiol* 2022;**19**(3):180–194.
17. Taylor RS, Dalal HM, McDonagh STJ. The role of cardiac rehabilitation in improving cardiovascular outcomes. *Nat Rev Cardiol* 2021;**16**:1.
18. Richardson CR, Franklin B, Moy ML, Jackson EA. Advances in rehabilitation for chronic diseases: improving health outcomes and function. *BMJ* 2019;**365**:l2191.
19. Tsuji M, Saito S, Ando T, Moriuchi M, Tamura Y, Tanigawa N, Ozawa Y, Hatano M, Horie T, Ookawa N. The clinical role of anaerobic threshold in physical training of patients with recent myocardial infarction. *J Cardiol* 1990;**20**:275–282.
20. Agostoni P, Corrà U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magrì D, Fiorentini C, Mezzani A, Salvioni E, Scrutinio D, Ricci R, Bettari L, Di Lenarda A, Pastormerlo LE, Pacileo G, Vaninetti R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Confalonieri M, Giannuzzi P, Passantino A, Cas LD, Piepoli MF, Passino C; on behalf of the MECKI Score Research Group. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013;**167**:2710–2718.
21. Corrà U, Agostoni P, Giordano A, Cattadori G, Battaia E, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magrì D, Fiorentini C, Cicoira M, Salvioni E, Giovannardi M, Veglia F, Mezzani A, Scrutinio D, Di Lenarda A, Ricci R, Apostolo A, Iorio AM, Paolillo S, Palermo P, Contini M, Vassanelli C, Passino C, Giannuzzi P, Piepoli MF, MECKI Score Research G, Other Members of the MECKI Score research G, Antonioli L, Segurini C, Bertella E, Farina S, Bovis F, Pietrucci F, Malfatto G, Roselli T, Buono A, Calabrò R, De Maria R, Santoro D, Campanale S, Caputo D, Bertipaglia D,

Berton E. The metabolic exercise test data combined with Cardiac And Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study. *Int J Cardiol* 2016;**203**:1067–1072.
22. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, Piña IL, Whellan D, O'Connor CM. Relationship of betablocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-action (heart failure: a controlled trial investigating outcomes of exercise training) trial. *J Am Coll Cardiol* 2012;**60**:208–215.
23. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. *Int J Cardiol* 2019;**288**:107–113.
24. Piepoli MF, Corrà U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, Vanhees L. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendation for performance and interpretation. I. Definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:150–164.
25. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Clinical exercise testing. principles of exercise testing and interpretation including pathophysiology and clinical applications*. Lippincott Williams & Wilkins: Philadelphia; 2005:38–139.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;**42**:3599–3726.
27. Al-Najjar Y, Witte KK, Clark AL. Chronotropic incompetence and survival in chronic heart failure. *Int J Cardiol* 2012;**157**:48–52.
28. Magrì D, Palermo P, Cauti FM, Contini M, Farina S, Cattadori G, Apostolo A, Salvioni E, Magini A, Vignati C, Alimento M, Sciomer S, Bussotti M, Agostoni P. Chronotropic incompentence and functional capacity in chronic heart failure: no role of β-blockers and β-blocker dose. *Cardiovasc Ther* 2012;**30**:100–108.
29. Magrì D, Corrà U, Di Lenarda A, Cattadori G, Maruotti A, Iorio A, Mezzani A, Giannuzzi P, Mantegazza V, Gondoni E, Sinagra G, Piepoli MF, Fiorentini C, Agostoni P. Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. *Eur J Heart Fail* 2014;**16**:201–209.
30. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* 1999;**281**:524–529.
31. Schmid JP, Zurek M, Saner H. Chronotropic incompetence predicts impaired response to exercise training in heart failure patients in sinus rhythm. *Eur J Prev Cardiol* 2013;**20**:585–592.
32. Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH. Impaired chronotropic response to exercise in patients with congestive heart failure: role of postsynaptic beta-adrenergic desensitization. *Circulation* 1989;**80**:314–323.
33. Sanders P, Kistler PM, Morton JB, Spence SJ, Kalman JM. Remodeling of sinus node function in patients with congestive heart failure: reduction in sinus node reserve. *Circulation* 2004;**110**:897–903.
34. Jorde UP, Vittorio T, Kasper ME, Arezzi E, Colombo PC, Goldsmith RI, Ahuja K, Tseng CH, Haas F, Hirsh DS. Chronotropic incompetence, beta-blockers, and functional capacity in advanced congestive heart failure: time to pace? *Eur J Heart Fail* 2008;**10**:96–101.
35. Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. *J Am Coll Cardiol* 2012;**60**:1521–1528.
36. Cattadori G, Schmid JP, Brugger N, Gondoni E, Palermo P, Agostoni P. Hemodynamic effects of exercise training in heart failure. *J Card Fail* 2011;**17**:916–922.
37. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020:2047487320913379.
38. Mezzani A, Corrà U, Giordano A, Cafagna M, Adriano EP, Giannuzzi P. Unreliability of the %VO2 reserve versus %heart rate reserve relationship for aerobic effort relative intensity assessment in chronic heart failure patients on or off beta-blocking therapy. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:92–98.
39. Agostoni P, Corrà U, Cattadori G, Veglia F, Battaia E, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magrì D, Fiorentini C, Cicoira M, Salvioni E, Giovannardi M, Mezzani A, Scrutinio D, Di Lenarda A, Mantegazza V, Ricci R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Vassanelli C, Passino C, Piepoli MF; MECKI Score Research Group. Prognostic value of indeterminable anaerobic threshold in heart failure. *Circ Heart Fail*. 2013;**6**:977–987.
40. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, Laukkanen JA, Pedretti R, Simonenko M, Wilhelm M, Davos CH, Doehner W, Iliou MC, Kränkel N, Völler H, Piepoli M. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2022;**29**:230–245.
41. Halasz G, Piepoli MF. Editor comments: focus on Cardiac rehabilitation and exercise training. *Eur J Prev Cardiol* 2021;**28**:687–689.
42. Rosano GMC, Allen LA, Abdin A, Lindenfeld J, O'Meara E, Lam CSP, Lancellotti P, Savarese G, Gottlieb SS, Teerlink J, Wintrich J, Böhm M. Drug layering in heart failure: phenotype-guided initiation. *JACC Heart Fail* 2021;**9**:775–783.
43. Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol* 2019;**73**:29–40.
44. Sciomer S, Moscucci F, Salvioni E, Marchese G, Bussotti M, Corrà U, Piepoli MF. Role of gender, age and BMI in prognosis of heart failure. *Eur J Prev Cardiol* 2020;**27**:46–51.
45. Agostoni P, Emdin M, Corrà U, Veglia F, Magrì D, Tedesco CC, Berton E, Passino C, Bertella E, Re F, Mezzani A, Belardinelli R, Colombo C, La Gioia R, Vicenzi M, Giannoni A, Scrutinio D, Giannuzzi P, Tondo C, Di Lenarda A, Sinagra G, Piepoli MF, Guazzi M. Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J* 2008;**29**:2367–2372.
46. Magrì D, Agostoni P, Corrà U, Passino C, Scrutinio D, Perrone-Filardi P, Correale M, Cattadori G, Metra M, Girola D, Piepoli MF, Iorio A, Emdin M, Raimondo R, Re F, Cicoira M, Belardinelli R, Guazzi M, Limongelli G, Clemenza F, Parati G, Frigerio M, Casenghi M, Scardovi AB, Ferraironi A, Di Lenarda A, Bussotti M, Apostolo A, Paolillo S, La Gioia R, Gargiulo P, Palermo P, Minà C, Farina S, Battaia E, Maruotti A, Pacileo G, Contini M, Oliva F, Ricci R, Sinagra G. Deceptive meaning of oxygen uptake measured at the anaerobic threshold in patients with systolic heart failure and atrial fibrillation. *Eur J Prev Cardiol* 2015;**22**:1046–1055.