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ORIGINAL RESEARCH ARTICLE

Determinants of maximal oxygen uptake in patients with heart failure

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Abstract

Aims Maximum oxygen uptake (VO_{2max}) is an essential parameter to assess functional capacity of patients with heart failure (HF). We aimed to identify clinical factors that determine its value, as they have not been well characterized yet.

Methods We conducted a retrospective, observational, single-centre study of 362 consecutive patients with HF who underwent cardiopulmonary exercise testing (CPET) as part of standard clinical assessment since 2009–2019. CPET was performed on treadmill, according to Bruce's protocol (n = 360) or Naughton's protocol (n = 2). We performed multivariable linear regression analyses in order to identify independent clinical predictors associated with peak VO_{2max}.

Results Mean age of study patients was 57.3 ± 10.9 years, mean left ventricular ejection fraction was 32.8 ± 14.2%, and mean VO_{2max} was 19.8 ± 5.2 mL/kg/min. Eighty-nine (24.6%) patients were women, and 114 (31.5%) had ischaemic heart disease. Multivariable linear regression analysis identified six independent clinical predictors of VO_{2max}, including NYHA class (B coefficient = −2.585; $P < 0.001$), age (B coefficient per 1 year = −0.104; $P < 0.001$), tricuspid annulus plane systolic excursion (B coefficient per 1 mm = +0.209; $P < 0.001$), body mass index (B coefficient per 1 kg/m^2 = −0.172; $P = 0.002$), haemoglobin (B coefficient per 1 g/dL = +0.418; $P = 0.007$) and NT-proBNP (B coefficient per 1000 pg/mL = −0.142; $P = 0.019$).

Conclusions The severity of HF (NYHA class, NT-proBNP) as well as age, body composition and haemoglobin levels influence significantly exercise capacity. In patients with HF, the right ventricular systolic function is of greater importance for the physical capacity than the left ventricular systolic function.

Keywords Maximum oxygen uptake; Heart failure; Prognostic value; Cardiopulmonary exercise testing

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Introduction

Exercise intolerance is one of the main symptoms of heart failure (HF) and a major factor conditioning a patient's quality of life.[1] Moreover, the aetiopathogenesis of exercise intolerance is multifactorial, because it involves central factors[2] related to cardiopulmonary system disorder and also peripheral factors related to both the vascular and musculoskeletal systems.[3,4]

Maximum oxygen uptake (VO_{2max}) or aerobic power is the best single parameter to measure a person's capacity to perform aerobic exercise. This parameter is defined as the maximum amount of oxygen that the body can absorb, transport and consume per unit of time.[5]

In clinical practice, VO_{2max} is determined in a protocolized way using the cardiopulmonary exercise testing (CPET) on a cycle ergometer or on a treadmill.[6] This parameter represents an objective estimation of the functional capacity in patients

with cardiovascular disease, and, in addition, it allows prognostic stratification in patients with HF, having been included in some of the most used mortality risk prediction scores such as HFSS[7] or UCLA four-variable risk score.[8] In this sense, one of the main uses of VO_{2max} is to serve as a guide for the selection of candidates for advanced therapies, including heart transplant.[9] CPET allows the additional determination of other parameters that complement the diagnostic and prognostic value of VO_{2max} such as VO_{2peak}, VO_{2max}/percentage of predicted VO_2 ratio (%pp VO_2), VO_{2max}/body mass index (BMI) ratio, pulmonary ventilator efficiency slope ratio (VE) /maximum carbon dioxide uptake (VCO_2) and oxygen uptake efficiency slope (OUES).[11]

To date, there is little information on the clinical factors that determine the exercise capacity of patients with HF[12]; the role of some co-morbidities such as obesity, anaemia or chronic kidney disease (CKD) in this regard has not been completely clarified.[13]

The main objective of this study was to identify clinical factors associated with VO_{2max} in a cohort of consecutive patients with HF who underwent CPET at a Spanish university hospital. As a secondary objective, we set out to evaluate the impact of the main co-morbidities associated with HF on VO_{2max}.

Methods

Study design and population

We carried out a retrospective observational study that included patients with HF seen in the specialized cardiology unit of the Complexo Hospitalario Universitario de A Coruña (CHUAC) who underwent a CPET between 2009 and 2019 as part of the standard clinical protocol of diagnostic and prognostic evaluation. For the purposes of this study, the follow-up of the vital status of the patients was extended until 13 March 2020.

The study protocol was approved by A Coruña and Ferrol Ethics Committee in Clinical Research.

Cardiopulmonary exercise testing

All CPET tests of the patients included in the study were carried out in the laboratory of the Cardiac Imaging and Functional Unit of the Cardiology Service of CHUAC using a treadmill and the Bruce or Naughton protocols, depending on the specific characteristics of the patient.[14,15] In cases where the patient had more than one CPET during the study period, the first one performed was considered.

Sources of data

The data presented in this manuscript were obtained from the clinical data system of the Heart Failure Unit of the CHUAC (Intelligent Heart Failure Monitoring System, SiMON-IC), complemented with the individual review of medical records, both in electronic and in paper formats.

Variable definition

For this study, the demographic, clinical, analytical and functional variables related to common functional studies were collected to describe a population of patients with HF, as well as specific variables in relation to CPET. The main variable of the study was VO_{2max} determined by CPET.

Regarding co-morbidities, anaemia was defined as any haemoglobin value $<$ 13 g/dL in men and $<$12 g/dL in women, CKD as a glomerular filtration rate (GFR) $<$ 60 mL/min/m2 and obesity as a BMI $\geq$ 30 kg/m^2.

Statistical analysis

In this study, quantitative variables are described by mean ± standard deviation, whereas variable categories are expressed as absolute and relative frequency. The chi-square test and Student's *t*-test were used to compare groups, depending on the variable being analysed.

A multivariable linear regression model through backward steps was used to identify baseline clinical variables that are independently associated with VO_{2max} by selecting a P_{out} value $<$ 0.05. Candidate variables for entering the first step of the backward stepwise analysis were those who showed a statistically significant or near-significant univariate association with VO_{2max} (univariate *P* value $<$ 0.15). Variables with $>$20% missing values were not considered for these analyses.

A comparison of the VO_{2max} value and VO_{2max}/%pp VO_2 ratio was proposed in seven subgroups selected according to the presence of clinical characteristics of special interest, such as age ($\geq$60 years vs. $<$60 years), sex, left ventricular ejection fraction (LVEF) ($<$40% vs. $\geq$40%), GFR ($<$60 mL/min vs. $\geq$60 mL/min), BMI ($<$30 vs. $\geq$30), anaemia and tricuspid annular plane systolic excursion (TAPSE) ($<$15 mm vs. $\geq$15 mm).

A significance level $P < 0.05$ was assumed for all the contrasts proposed. The analysis was performed with SPSS 20.

Results

Study population

Three hundred sixty-two patients were studied, of which 89 (24.6%) were female. The mean age of the population was

Table 1 Baseline clinical characteristics of 362 patients with heart failure who underwent cardiopulmonary exercise test

Demographics and clinical status[a]	
Age (years), mean ± SD	57.3 ± 10.9
Male sex, *n* (%)	273 (75.4%)
Body mass index (kg/m^2), mean ± SD	28.1 ± 4.8
Systolic blood pressure (mm Hg), mean ± SD	112.1 ± 17.3
Resting heart rate (beats per min), mean ± SD	67.3 ± 11.5
NYHA class, *n* (%)	
I	25 (6.9%)
II	203 (56.1%)
III	125 (34.5%)
IV	9 (2.5%)
Co-morbidities and aetiology [b]	
Hypertension, *n* (%)	161 (44.5%)
Anaemia, *n* (%)	117 (32.3%)
Ischemic heart disease, *n* (%)	114 (31.5%)
Type 2 diabetes mellitus, *n* (%)	98 (27.1%)
Chronic kidney disease, *n* (%)	111 (30.7%)
COPD, *n* (%)	14 (3.9%)
Obesity, *n* (%)	118 (32.6%)
Laboratory variables[c]	
Creatinine (mg/dL), mean ± SD	1.3 ± 0.9
Glucose (mg/dL), mean ± SD	111.9 ± 47.2
Urea (mg/dL), mean ± SD	65.7 ± 33.3
Sodium (mEq/L), mean ± SD	139 ± 6.6
GGT (u/L), mean ± SD	76.2 ± 99.7
ALT (u/L), mean ± SD	30.7 ± 28.4
Bilirubin (mg/dL), mean ± SD	0.8 ± 0.6
Uric acid (mg/dL), mean ± SD	7.8 ± 2.2
LDH (u/L), mean ± SD	383.2 ± 154.8
Albumin (g/dL), mean ± SD	4.3 ± 0.3
NT-proBNP (pg/mL), mean ± SD	2794.1 ± 4165.1
Haemoglobin (g/L), mean ± SD	13.7 ± 1.7
Haematocrit (%), mean ± SD	40.8 ± 5.8
Ferritin (ng/mL), mean ± SD	170.9 ± 144.6

ALT, alanine aminotransferase; COPD, chronic obstructive pulmonary disease; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard Deviation.
[a]Missing values: body mass index (*n* = 3), resting heart rate (*n* = 1), systolic blood pressure (*n* = 1).
[b]Missing values: chronic kidney disease (*n* = 3), obesity (*n* = 5).
[c]Missing values: creatinine (*n* = 1), glucose (*n* = 2), urea (*n* = 13), sodium (*n* = 2), GGT (*n* = 46), ALT (*n* = 35), bilirubin (*n* = 69), uric acid (*n* = 132), LDH (*n* = 233), albumin (*n* = 247), NT-proBNP (*n* = 48), ferritin (*n* = 339).

Table 2 Baseline electrocardiography, echocardiography, implantable electrical devices and treatments (*n* = 362)

ECG cardiac rhythm at rest	
Sinus rhythm, *n* (%)	241 (66.6%)
Atrial fibrillation, *n* (%)	88 (24.3%)
Atrial flutter, *n* (%)	4 (1.1%)
Paced rhythm, *n* (%)	29 (8%)
Implantable electrical devices	
ICD, *n* (%)	181 (50%)
CRT-D, *n* (%)	49 (13.5%)
CRT-P, *n* (%)	5 (1.4%)
Pacemaker, *n* (%)	12 (3.3%)
No device, *n* (%)	115 (31.8%)
Echocardiography[a]	
LVESD (cm), mean ± SD	5.2 ± 1.3
LVEDD (cm), mean ± SD	6.2 ± 1
LVEF (%), mean ± SD	32.8 ± 14.2
TAPSE (mm), mean ± SD	17.4 ± 5.3
Medications	
Beta-blockers, *n* (%)	341 (94.2%)
Diuretics, *n* (%)	308 (85.1%)
ACEI or ARB, *n* (%)	248 (68.5%)
Sacubitril-valsartan, *n* (%)	30 (8.3%)
MRA, *n* (%)	265 (73.2%)
Ivabradine, *n* (%)	36 (9.9%)
Digoxin, *n* (%)	20 (5.5%)
Amiodarone, *n* (%)	25 (6.9%)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; TAPSE, tricuspid annular plane systolic excursion.
[a]Missing values: LVEDD (*n* = 28), LVESD (*n* = 56), TAPSE (*n* = 74).

57.3 +/− 10.9 years. Most (*n* = 203, 56.1%) of the patients were in New York Heart Association (NYHA) functional class II. Anaemia was observed in 117 (32.3%), arterial hypertension in 161 (44.5%), ischaemic heart disease in 114 (31.5%), CKD in 111 (30.7%), and obesity in 118 (32.6%). *Table 1* provides baseline clinical characteristics, co-morbidity and laboratory values in the study patients.

Table 2 shows the data referring to complementary studies and pharmacological treatment. The majority (*n* = 240, 66.2%) was in sinus rhythm and almost a quarter in atrial fibrillation (*n* = 88, 24.3%). A total of 261 (72.1%) patients presented HF with reduced LVEF (<40%), 58 (16%) patients presented HF with mid-range LVEF (40%–49%), and 43 (11.9%) patients presented HF with preserved LVEF (≥50%).

Beta-blockers were prescribed to 330 (91.2%) patients, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) to 248 (68.5%), sacubitril-valsartan to 30 (8.3%), and mineralocorticoid receptor antagonists to 265 (73.2%). Overall, 181 (50%) patients carried a defibrillator, 49 (13.5%) patients carried a cardiac resynchronization therapy-defibrillator device, and 5 (1.4%) patients carried a cardiac resynchronization therapy-pacemaker device.

Cardiopulmonary exercise testing

All CPET studies were performed according to Bruce's protocol, except two, which were performed according to Naughton's one. The CPET parameters are shown in *Table 3*. The mean VO_{2max} achieved was 19.8 mL/kg/min (±5.2 SD), with a mean VO_{2max}/%pp VO_2 ratio of 75.9% (±21, 0 SD)

Table 3 Cardiopulmonary exercise testing parameters in 362 patients with heart failure

CPET parameters	
$VO_{2\ peak}$ (mL/kg/min), mean ± SD	19.8 ± 5.2
%pp VO_2, mean ± SD	75.9 ± 21.0
VE/VCO_2, mean ± SD	37.8 ± 8.1
% maximum HR, mean ± SD	77.7 ± 16.3
RER, mean ± SD	1.09 ± 0.1
Exercise time (min), mean ± SD	8.4 ± 3.9
METs, mean ± SD	5.7 ± 2.2

% maximum HR, percentage of maximum predicted heart rate; % pp VO_2, percentage of predicted peak oxygen uptake; CPET, cardiopulmonary exercise testing; METs, metabolic equivalents of task; RER, respiratory exchange ratio; VE/VCO_2, ventilatory equivalent ratio for carbon dioxide; VO_{2peak}, peak oxygen uptake.

and a mean duration of exercise of 8.4 (±3.9 SD) min. VO_{2max} was <14 mL/kg/min in 45 (12.4%) patients.

Determining factors of VO_{2max}

Table 4 shows the results of the linear regression analyses used to identify the clinical factors that determine VO_{2max} value in the study patients. Twelve variables that showed a univariate *P* value < 0.15 were selected for entering the first step of the backward stepwise process. Among them, six variables remained as independent predictors of VO_{2max} in the final multivariable linear regression model.

Older age (B coefficient for 1 year = −0.104; $P < 0.001$), worse NYHA functional class (B coefficient for one functional class −2.585; $P < 0.001$), higher plasma *N*-terminal pro-brain natriuretic peptide (NT-proBNP) value (B coefficient per 1000 pg/mL = −0.142; $P = 0.019$) and a higher BMI (B coefficient −0.172; $P = 0.002$) were statistically significantly and independently associated with a lower VO_{2max}.

On the other hand, a higher TAPSE (B coefficient per 1 mm = +0.209; $P < 0.001$) and a higher haemoglobin plasma value (B coefficient per 1 g/dL = +0.418; $P = 0.007$) were associated, also statistically significant and independently, with a higher VO_{2max} value.

Univariate linear regression coefficients for all explored variables are presented in *Table S1*.

Subgroup analysis

Table 5 shows the comparison of the VO_{2max} values and the VO_{2max}/%pp VO_2 ratio in seven subgroups of patients defined based on clinical variables of interest.

Male patients presented in absolute terms a higher VO_{2max} than female patients (20.4 ± 5.3 mL/kg/min vs. 18.1 ± 4.2 mL/kg/min; $P = 0.027$); however, the VO_{2max}/%pp VO_2 ratio was significantly higher in women (72.8% ± 18.9 vs. 85.4% ± 18.9; $P < 0.001$).

VO_{2max} in patients with anaemia (16.8 ± 3.9 mL/kg/min) was significantly lower than that of the rest of the population (20.3 ± 5.4 mL/kg/min) ($P < 0.001$); however, VO_{2max}/%pp VO_2 ratio showed no significant differences between these two groups.

VO_{2max} value was higher in patients under 60 (21.6 ± 5.2 mL/kg/min) compared with those over 60 (17.9 ± 4.7 mL/kg/min; $P < 0.001$). However, the difference between both groups in relation to the VO_{2max}/%pp VO_2 ratio did not reach statistical significance ($P = 0.087$).

Patients without CKD showed a superior response to exercise than those with CKD, both in VO_{2max} values (20.1 ± 5.4 mL/kg/min vs. 17.2 ± 4.2 mL/kg/min; $P < 0.001$) as in the VO_{2max}/%pp VO_2 ratio (77.7 ± 21.9 vs. 71.5 ± 17.9; P = 0.001).

Table 4 Clinical factors associated with peak VO_2: multivariable linear regression analysis

	Univariate analysis[a]		Multivariate analysis[b]	
	B coefficient	*P*	B coefficient	*P*
Age (years)	−0.259	<0.001	−0.104	<0.001
BMI (kg/m^2)	−0.235	0.131	−0.172	0.002
Atrial fibrillation/flutter	−2.781	0.106	–	–
Hypertension	−3.162	0.001	–	–
Diabetes mellitus	−2.582	0.123	–	–
NYHA class	−2.184	0.059	−2.585	<0.001
Creatinine (mg/dL)	−1.228	0.135	–	–
Urea (mg/dL)	−0.045	0.049	–	–
Haemoglobin (g/L)	+0.642	0.137	+0.418	0.007
NT-proBNP (1000 pg/mL)	−0.328	0.107	−0.142	0.019
TAPSE (mm)	+0.248	0.002	+0.209	<0.001
Ivabradine use	+7.933	0.001	–	–

BMI, body mass index; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA; New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
[a]Variables presented are only those that showed a univariate association with VO2 with a *P*-value < 0.15, as assessed by linear regression. These 10 variables entered the first step of multivariable backward stepwise linear regression analysis. The complete relationships of variables assessed, as well as their univariate regression coefficients, are presented as *Supporting Information*.
[b]Variables presented are only those that were selected in the final step of multivariable backward stepwise linear regression analysis.

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Table 5 Comparison of peak VO_2 and % predicted VO_2 in selected clinical subgroups

Subgroups	VO_2 peak (mL/kg/min) Mean ± SD	*P*	%pp VO_2	*P*
Gender		0.027		<0.001
Female (*n* = 89)	18.1 ± 4.2		85.4 ± 18.9	
Male (*n* = 273)	20.4 ± 5.3		72.8 ± 20.7	
Anaemia		<0.001		0.215
Without anaemia (*n* = 51)	20.3 ± 5.4		76.5 ± 21.9	
With anaemia (*n* = 311)	16.8 ± 3.9		72.7 ± 19.9	
Left ventricular ejection fraction (%)		0.690		0.454
LVEF < 40 (*n* = 261)	20.1 ± 5.2		75.6 ± 21.6	
LVEF ≥ 40 (*n* = 101)	19.6 ± 5.5		77.4 ± 19.6	
Chronic kidney disease[a]		<0.001		0.006
GFR ≥ 60 mL/min/m^2 (*n* = 246)	20.1 ± 5.4		77.7 ± 21.9	
GFR < 60 mL/min/m^2 (*n* = 111)	17.2 ± 4.2		71.5 ± 17.9	
Age (years)		<0.001		0.087
<60 (*n* = 186)	21.6 ± 5.2		74.1 ± 20.1	
≥60 (*n* = 176)	17.9 ± 4.7		77.9 ± 20.1	
Obesity[b]		0.073		<0.001
BMI < 30 kg/m^2 (*n* = 241)	20.5 ± 5.6		72.4 ± 18.9	
BMI ≥ 30 kg/m^2 (*n* = 118)	18.3 ± 5.4		82.8 ± 23.3	
Right ventricular function[c]		0.001		<0.001
TAPSE < 15 mm (*n* = 100)	17.5 ± 4.2		69.1 ± 18.0	
TAPSE ≥ 15 mm (*n* = 188)	19.9 ± 5.1		79.4 ± 19.9	

%pp VO_2, percentage of predicted peak VO_2; BMI, body mass index; GFR, glomerular filtration rate; peak VO_2, peak oxygen uptake; **SD, standard deviation**; TAPSE, tricuspid annular plane systolic excursion.
[a]Missing data in 3 (0.8%) patients.
[b]Missing data in 5 (1.4%) patients.
[c]Missing data in 74 (20.4%) patients.

Patients with a TAPSE ≥ 15 presented a higher VO_{2max} value (19.9 ± 5.1 vs. 17.5 ± 4.2; $P < 0.001$) and a higher VO_{2max}/%pp VO_2 ratio (79.4 ± 18.0 vs. 69.1 ± 18.0; $P < 0.001$) than patients with TAPSE < 15.

We did not observe statistically significant differences in VO_{2max} based on the presence or absence of obesity or the presence or absence of an LVEF > 40%.

Discussion

VO_{2max} is an essential parameter for the functional and prognostic assessment of patients with HF that depends on central and peripheral factors. In our research, in which we have studied a cohort of patients with HF followed in a specialized cardiology unit, we have identified six independent clinical predictors of VO_{2max}, including age, NYHA functional class and the presence of obesity, haemoglobin and NT-proBNP plasma levels and TAPSE.

The relationship between ageing and a progressive reduction in exercise capacity is well known. As in our study, the literature has referenced that younger patients present higher absolute VO_{2max} values in CPET.[16] This trend towards a decrease in the theoretical VO_2 as age increases may result in a less prognostic value of VO_{2max} in patients with HF and older age. Therefore, the use of VO_{2max}/%pp VO_2 ratio is recommended in this subgroup with the intention of, for example, selecting candidates for advanced therapies.[10]

The association observed between a higher NYHA functional class and a lower VO_{2max} value in patients with HF is evident. The NYHA functional class, although conditioned by a subjective evaluation, is a good initial approach to the global symptom burden of patients with HF[17] and has shown a significant prognostic value in these individuals.[18] The findings of lower VO_{2max} values in patients with higher plasma levels of NT-proBNP are consistent with the known diagnostic and prognostic value of this biomarker as an indicator of the degree of congestion and severity of HF.[19]

An interesting finding of our study is the independent association observed between an indicator of right ventricular function, TAPSE and VO_{2max}. This relationship is more interesting, if possible, taking into account that in our series we have not been able to evidence an impact of LVEF on this parameter. These results seem to suggest that in patients with HF, the preservation of the contractile function of the right ventricle would be a more determining factor for keeping the ability to exercise than the systolic function of the left ventricle itself. The prognostic importance of the parameters that assess right ventricular function in patients with HF, even in those with preserved LVEF, has been previously demonstrated.[20] It should be noted, however, that a study with a slightly larger sample size than ours, Nadruz et al.,[21] did observe a significant impact of LVEF on VO_{2max}, so patients with LVEF > 40% had higher values than patients with LVEF < 40%.

Obesity[22] and anaemia[23] are two frequent co-morbidities in patients with HF that significantly affect their exercise capacity. Other authors have previously described an association between a higher BMI[24] or a lower haemoglobin plasma value[25] and a lower VO_{2max} value in CPET. Patients with anaemia experience a decline in mitochondrial oxidative function, reduced adenosine triphosphate production and a decline of the capacity of muscular contraction that affects notably its exercise tolerance.[26]

In our study, the univariate analysis showed that patients with CKD had significantly lower VO_{2max} and VO_{2max}/%pp VO_2 values than patients with preservation of renal function. CKD is a known factor of poor prognosis and poor functional capacity in patients with HF, which can affect exercise capacity through inflammatory mechanisms, loss of muscle mass and increased oxidative stress.[27,28] However, CKD was not founded as an independent predictor of VO_{2max} in the multivariable analysis, a result that we attribute, as the most likely explanation, to its tendency to coexist in the same patient with other independent risk markers such as age and advanced NYHA functional class, anaemia or elevated NT-proBNP, as well as the limited sample size of our study.

The present study has several limitations. Firstly, it is an observational and retrospective study, so it is exposed to the typical biases of this type of research. Secondly, CPETs were performed within the framework of routine clinical care, and not according to a predefined research protocol. Finally, it should be noted that the sample size of the study, even being relevant, may have been insufficient to detect as statistically significant other risk associations that do may be clinically relevant

Conclusions

The severity HF (NYHA class, NT-proBNP) and age, body composition and haemoglobin levels influence significantly exercise capacity. In patients with HF, the right ventricular systolic function is of greater importance for the physical capacity than the left ventricular systolic function.

Our work highlights the importance of associated clinical conditions as determinants of exercise tolerance in patients with HF and reinforces the importance of appropriate handling of co-morbidities to improve functional capacity in these individuals.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting information.

References

1. Ponikowski P, Poland C, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891–975.
2. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. *Circ Heart Fail* 2015; **8**: 278–285.
3. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of

skeletal muscle in chronic heart failure. *Circulation* 1992; **85**: 1751–1759.
4. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem. *J Geriatr Cardiol* 2015; **12**: 294–304.
5. Chicharro JL, Vaquero VF. *Fisiología del ejercicio*, 2nd ed. Madrid: Editorial Médica Panamericana SA; 1998.
6. Balady G, Arena R, Sietsema K, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; **122**: 191–225.
7. Aaronson K, Schwartz J, Chen T, Wong K, Goin JMD. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; **95**: 2660–2667.
8. Sartipy U, Goda A, Mancini DM, Lund LH. Assessment of a University of California, Los Angeles 4-variable risk score for advanced heart failure. *J Am Heart Assoc* 2014; **3**: e000998.
9. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; **83**: 778–786.
10. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EAM, Zuckermann A. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transpl* 2016; **35**: 1–23.
11. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000; **36**: 194–201.
12. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol* 2015; **119**: 739–744.
13. van der Wal HH, Deursen van Deursen VM, van der Meer P, Voors AA. Comorbidities in heart failure. *Handb Exp Pharmacol* 2017; **243**: 35–66.
14. Strzelczyk TA, Cusick DA, Pfeifer PB, Bondmass MD, Quigg RJ. Value of the Bruce protocol to determine peak exercise oxygen consumption in patients evaluated for cardiac transplantation. *Am Heart J* 2001; **142**: 466–475.
15. Harb SC, Bhat P, Cremer PC, Wu Y, Cremer LJ, Berger S, Cho L, Menon V, Gulati M, Jaber WA. Prognostic value of functional capacity in different exercise protocols. *J Am Heart Assoc* 2020; **9**: e015986.
16. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas bedrest and training study I. Effect of age on the cardiovascular response to exercise. *Circulation* 2001; **104**: 1350–1357.
17. Yap J, Lim FY, Gao F, Teo LL, Lam CS, Yeo KK. Correlation of the New York Heart Association classification and the 6-minute walk distance: a systematic review. *Clin Cardiol* 2015; **38**: 621–628.
18. Bredy C, Ministeri M, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Diller GP, Gatzoulis MA, Dimopoulos K. New York Heart Association (NYHA) classification in adults with congenital heart disease: relation to objective measures of exercise and outcome. *Eur Heart J Qual Care Clin Outcomes* 2018; **4**: 51–58.
19. Krüger S, Graf J, Kunz D, Stickel T, Hanrath P, Janssens U. Brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *J Am Coll Cardiol* 2002; **40**: 718–722.
20. Murninkas D, Alba AC, Delgado D, McDonald M, Billia F, Chan WS, Ross HJ. Right ventricular function and prognosis in stable heart failure patients. *J Card Fail* 2014; **20**: 343–349.
21. Nadruz W, West E, Sengeløv M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H, Shah AM. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. *J Am Heart Assoc* 2017; **6**: e006000.
22. Lavie CL, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013; **1**: 93–102.
23. Triposkiadis F, Skoularigis J. Prevalence and Importance of comorbidities in patients with heart failure. *Curr Heart Fail Rep* 2012; **9**: 354–362.
24. Mondal H, Mishra SP. Effect of BMI, body fat percentage and fat free mass on maximal oxygen consumption in healthy young adults. *J Clin Diagnostic Res* 2017; **11**: CC17–CC20.
25. Kalra PR, Bolger AP, Francis DP, Genth-Zotz S, Sharma R, Ponikowski PP, Poole-Wilson PA, Coats AJS, Anker SD. Effect of anemia on exercise tolerance in chronic heart failure in men. *Am J Cardiol* 2003; **91**: 888–891.
26. Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, Rodenburg RJ, van Veldhuisen DJ, de Boer RA, van der Meer P. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. *Eur J Heart Fail* 2018; **20**: 910–919.
27. Damman K, Valente MAE, Voors AA, O'Connor CM, Van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014; **35**: 455–469.
28. Scrutinio D, Agostoni P, Gesualdo L, Corrà U, Mezzani A, Piepoli M, Di Lenarda A, Iorio A, Passino C, Magrì D, Masarone D, Battaia E, Girola D, Re F, Cattadori G, Parati G, Sinagra G, Villani GQ, Limongelli G, Pacileo G, Guazzi M, Metra M, Frigerio M, Cicoira M, Minà C, Malfatto G, Caravita S, Bussotti M, Salvioni E, Veglia F, Correale M, Scardovi AB, Emdin M, Giannuzzi P, Gargiulo P, Giovannardi M, Perrone-Filardi P, Raimondo R, Ricci R, Paolillo S, Farina S, Belardinelli R, Passantino A, La Gioia R. Metabolic Exercise test data combined with CArdiac and Kidney Indexes (MECKI) Score Research Group. Renal function and peak exercise oxygen consumption in chronic heart failure with reduced left ventricular ejection fraction.*Circ J* 2015; **79**: 583–591.