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ORIGINAL ARTICLE

Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure

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Abstract

Aims Right ventricular (RV) dysfunction, pulmonary hypertension, and exercise intolerance have prognostic values, but their interrelation is not fully understood. We investigated how RV function alone and its coupling with pulmonary circulation (RV-PA) predict cardio-respiratory fitness in patients with heart failure and reduced ejection fraction (HFrEF).

Methods and results The Evaluation of Resynchronization Therapy for Heart Failure (EARTH) study included 205 HFrEF patients with narrow (n = 85) and prolonged (n = 120) QRS duration undergoing implantable cardioverter defibrillator implantation. All patients underwent a comprehensive evaluation with exercise tolerance tests and echocardiography. We investigated the correlations at baseline between RV parameters {size, function [tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV-FAC), and RV myocardial performance index (RV-MPI)], pulmonary artery systolic pressure (PASP), and tricuspid regurgitation}; left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume index (LVEDVi), and left atrial volume index (LAVi); and cardiopulmonary exercise test (CPET) [peak VO_2, minute ventilation/carbon dioxide production (VE/VCO_2), 6 min walk distance (6MWD), and submaximal exercise duration (SED)]. We also studied the relationship between RV-PA coupling (TAPSE/PASP ratio) and echocardiographic parameters in patients with both data available. Univariate and multivariate linear regression models were used. Patients enrolled in EARTH (overall population) were mostly male (73.2%), mean age 61.0 ± 9.8 years, New York Heart Association class II–III (87.8%), mean LVEF of 26.6 ± 7.7%, and reduced peak VO_2 (15.1 ± 4.6 mL/kg/min). Of these, 100 had both TAPSE and PASP available (TAPSE/PASP population): they exhibited higher BNP, wider QRS duration, larger LVEDVi, with more having tricuspid regurgitation compared with the 105 patients for whom these values were not available (all $P < 0.05$). RV-FAC (β = 7.5), LAVi (β = −0.1), and sex (female, β = −1.9) predicted peak VO_2 in the overall population (all P = 0.01). When available, TAPSE/PASP ratio was the only echocardiographic parameter associated with peak VO_2 (β = 6.8; $P < 0.01$), a threshold ≤0.45 predicting a peak $VO_2 \leq 14$ mL/kg/min (0.39 for $VO_2 \leq 12$). RV-MPI was the only echocardiographic parameter associated with ventilatory inefficiency (VE/VCO_2) and 6MWD (β = 21.9 and β = −69.3, respectively, both $P \leq 0.01$) in the overall population. In presence of TAPSE/PASP, it became an important predictor for those two CPET (β = −18.0 and β = 72.4, respectively, both $P < 0.01$), together with RV-MPI (β = 18.5, $P < 0.01$) for VE/VCO_2. Tricuspid regurgitation predicted SED (β = −3.2, P = 0.03).

Conclusions Right ventricular function assessed by echocardiography (RV-MPI and RV-FAC) is closely associated with exercise tolerance in patients with HFrEF. When the TAPSE/PASP ratio is available, this marker of RV-PA coupling becomes the stronger echocardiographic predictor of exercise capacity in this population, highlighting its potential role as a screening tool to identify patients with reduced exercise capacity and potentially triage them to formal peak VO_2 and/or evaluation for advanced HF therapies.

Keywords Right ventricular function; RV to pulmonary arterial coupling; Heart failure with reduced ejection fraction; Exercise tolerance; Echocardiography

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Introduction

Evaluation of exercise tolerance whether clinically or using cardiopulmonary exercise tests (CPET) is at the basis of routine assessment and prognostication of heart failure (HF) patients,[1] including at the time of consideration for advanced HF therapies[2]; a peak $VO_2 \leq 14$ mL/kg/min is commonly used as cut-off for transplantation, but a threshold of $\leq$12 seems more reliable for patients treated with beta-blockers.[3] Still, peak VO_2 exhibits only modest correlation with the degree of left ventricular (LV) dysfunction,[4] due to development of compensatory mechanisms in response to the chronic low output state, reduced peripheral and respiratory muscular perfusion, and/or function.[2] Also, submaximal exercise capacity assessed using 6 min walk test (6MWT) or a fixed-load protocol may be more representative of daily living limitations; they have good prognostic values, but their physiologic determinants remain largely unknown.[1,2]

Right ventricular (RV) dysfunction and/or pulmonary hypertension (PH) are important predictors of outcomes in HF, regardless of LV systolic function.[5–8] As CPET are not broadly available, reliable echocardiographic predictors of exercise intolerance as screening tools for consideration of advanced HF evaluation would be clinically useful. Accordingly, several RV parameters have been proposed, but the quest for the most valuable one(s) is still ongoing.[9,10] The RV-pulmonary artery (PA) coupling, measured as the ratio of longitudinal RV shortening relative to developed pressure [tricuspid annular plane systolic excursion (TAPSE) to estimated pulmonary artery systolic pressure (PASP)[5]; *Figure 1*], has good correlation with PA compliance measured invasively[6] and outcomes in patients with HF and preserved ejection fraction (HFpEF).[7] Unfortunately, this ratio is not always available and neither its relationship nor those of other RV function indices with various CPET have been explored in patients with HF and reduced ejection fraction (HFrEF).[2,5,11,12]

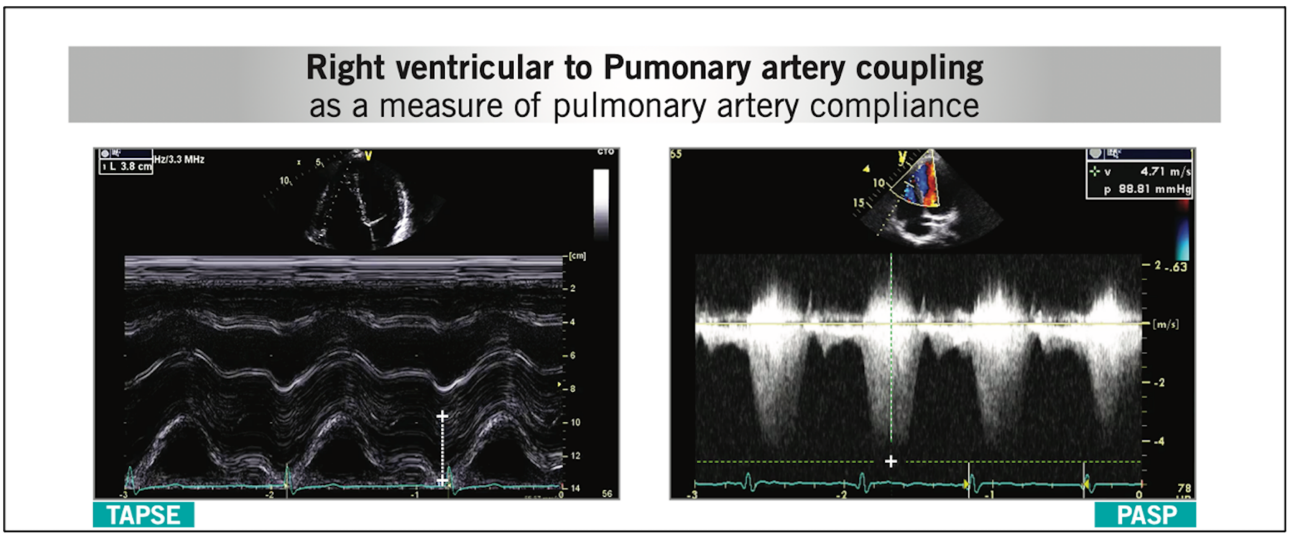
Therefore, we sought to evaluate the effects of various RV function parameters, alone and in association with its coupling to the PA, on several assessments of exercise capacity in ambulatory HFrEF patients.

Materials and methods

Study population

Patients enrolled in Evaluation of Resynchronization Therapy for Heart Failure (EARTH) were divided according to the QRS duration on the surface electrocardiogram: QRS $<$ 120 ms in LESSER-EARTH (LE)[13] and QRS $\geq$ 120 ms in GREATER-EARTH (GE).[14] Their rationale, design, and results have been previously reported. Briefly, EARTH was a randomized-controlled programme performed in 12 Canadian centres comparing the effect of cardiac resynchronization therapy (CRT) on submaximal exercise capacity. LE study was published in 2013 while GE study was published in 2011. Both populations' recruitment started in 2003 and ended in 2011 and 2009, re-

Figure 1 Right ventricular to pulmonary artery coupling as a measure of pulmonary artery compliance. Graphical representation of TAPSE (left) and PASP (right) measurements (top panel). PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.



spectively. Patients with reduced left ventricular ejection fraction (LVEF) (≤35%) on optimal medical therapy and a 6MWT < 400 m were eligible. Patients in chronic atrial fibrillation, those who were limited to exercise by non-cardiac conditions, or who had a recent (<6 weeks) myocardial infarction and/or cardiac intervention were excluded. For the purpose of this analysis, we combined the populations of the two studies, and only data at baseline (pre-randomization, resynchronization-OFF) were analysed.

All local institutional review board approved the protocol, and participants provided written consent.

Echocardiography

A standardized transthoracic echocardiogram protocol was used, and analysis performed by a central core-laboratory.[15] Variables of interests included RV parameters: size (dimensions and end-diastolic area), function [TAPSE, RV fractional area change (RV-FAC, which provides an estimate of the global RV systolic function; it calculates the % of area change within the RV between diastole and systole in the apical four-chamber view. A normal value for the FAC is 35% or higher), and myocardial performance index (RV-MPI) using pulsed wave Doppler], PASP, and tricuspid regurgitation (TR) grade; and LVEF, indexed left atrial volume (LAVi), and mitral regurgitation (MR). All these parameters had to be measured per protocol, as recommended by the American Society of Echocardiography.[16,17] The reproducibility of echocardiographic measurements was excellent, with intraobserver intraclass correlation coefficients (ICCs) ranging from 0.95 to 0.98 for the first ultrasonographer and from 0.98 to 1.00 for the second one. Interobserver ICCs ranged from 0.78 to 0.96.[15]

Maximal and submaximal exercise testing

Two exercise tests were performed at baseline (minimum of 2 h between submaximal and 6MWT and 24 h between the maximal and the others).[14] The maximal cardiopulmonary test consisted of a continuous and incremental exercise performed on a treadmill with an individualized ramp protocol using an automated continuous oxygen uptake determinate on a breath by breath basis,[18] with data recorded at rest, during graded exercise, and throughout a 2 min recovery period; it was ended at either achievement of the primary maximal criteria: respiratory exchange ratio (RER) > 1.01, or with 1 of 2 secondary maximal criteria: (i) inability to maintain exercise and (ii) exhaustion due to fatigue, or cessation due to other clinical symptoms. Peak VO_2 and ventilatory efficiency (VE/VCO_2 slope) are reported here.

The submaximal constant load exercise test was performed on a treadmill using a fixed load protocol at an intensity corresponding to 75% of peak VO_2 measured during the maximal exercise test.[19] After a 2 min warm-up at 30% of the maximal load, the slope and speed observed at 75% of the VO_2 peak was applied. The test was terminated for exhaustion or after 30 min of exercise. The 6MWT was completed as previously published.[20] While 6MWT and submaximal exercise duration (SED) are not per se obtained in the CPET, we have elected to group all the accepted measures of exercise tolerance under the CPET umbrella.

Outcomes

Our primary objective was the relationship between RV function and peak VO_2.

Secondary endpoints included (i) relationship between the TAPSE/PASP ratio and CPET [peak VO_2, VE/VCO_2 slope, SED, and 6 min walk distance (6MWD)] and (ii) relationship between key echocardiographic parameters and clinical characteristics, and all CPET (VE/VCO_2 slope, SED, and 6MWD).

Statistical analyses

Continuous variables are summarized using mean ± standard deviation (SD) unless otherwise specified, while categorical variables are described using frequencies and percentages. No imputation was performed for missing data, as there were few. Statistical analysis was performed using SAS Version 9.4 (SAS Institute, NC), and a two-tailed *P*-value < 0.05 was considered statistically significant. The authors take full responsibility for the integrity of the data.

Baseline characteristics

Differences in baseline characteristics between the TAPSE/PASP subgroup (n = 100) and the remaining subjects (n = 105) were examined using *t*-tests (continuous variables) or χ^2 tests (categorical variables).

Endpoints

Linear regression models were produced to evaluate the relationship between RV function echocardiographic parameters and peak VO_2. Factors selection was based on clinical relevance and univariate association with peak VO_2. All variables with a *P*-value ≤ 0.20 in the univariate model were entered into a multivariate analysis using a stepwise selection procedure. Variables with $P < 0.10$ were kept in the final model to explore potential trends of relationship between factors and endpoints. Secondary endpoints were analysed using the same approach. In the eventuality that a statistically significant relationship is found between TAPSE/PASP and peak VO_2, two receiver operating characteristic (ROC) curves analysis will be performed, the first to define the value predictive of a peak $VO_2 \leq 14$ mL/kg/min, a commonly used cut-off for advanced HF therapies consideration, and the second for

$VO_2 \leq 12$ mL/kg/min, which is more sensitive for outcomes prediction of patients on beta-blockers.

Results

Study population

A total of 205 patients, 120 GE and 85 LE, were enrolled in EARTH (overall population), with 100 having both TAPSE and PASP values available (TAPSE/PASP population). The characteristics of the overall population are shown in *Table 1*, with a majority of male (73.2%), mean age 61.0 ± 9.8 years, New York Heart Association (NYHA) class II–III (87.8%), and severely depressed systolic function (mean LVEF = 26.6 ± 7.7%). Pharmacological treatment was robust for the time, including beta-blockers (97.1%), renin angiotensin system inhibitors (97.6%), loop diuretics (84.9%), and mineralocorticoid receptor antagonists (MRA) (43.4%). Maximal aerobic capacity assessed by peak VO_2 was severely reduced (15.1 ± 4.6 mL/kg/min).[3]

Tricuspid annular plane systolic excursion/pulmonary artery systolic pressure population

Characteristics of the overall and TAPSE/PASP population (n = 100) are summarized in *Table 1*. The latter group exhibited features of more advanced disease, with higher BNP level, wider QRS duration on the electrocardiogram, larger left ventricular end-diastolic volume index (LVEDVi), and more having TR compared with the 105 patients for whom the TAPSE and PASP values were not available (all $P < 0.05$).

Predictors of peak VO_2

Univariate and multivariate analysis of predictors of peak VO_2 for the overall population and the TAPSE/PASP population is shown in *Table 2*.

Predictors of peak VO_2 (overall population)

By multivariate analysis, only RV-FAC (β = 7.5), LAVi ($\beta = -0.1$), and sex (female, $\beta = -1.9$) remained independent predictors of peak VO_2 (all $P < 0.05$).

Predictors of peak VO_2 (tricuspid annular plane systolic excursion/pulmonary artery systolic pressure population)

Only TAPSE/PASP remained associated with peak VO_2 (β = 6.8; $P < 0.01$) by multivariate analysis (*Figure 2*). ROC analysis showed an optimal threshold of TAPSE/PASP ≤ 0.45, for a peak $VO_2 \leq 14$ mL/kg/min, with sensitivity and specificity of 0.63 and 0.62, respectively, and area under the curve (AUC) of 0.66 ($P < 0.01$) (*Figure 3*). Interestingly, increased sensitivity was obtained with a peak $VO_2 \leq 12$ mL/kg/min, a cut-off of 0.39 having a sensitivity of 0.92 and specificity of 0.50 and AUC of 0.74 ($P < 0.01$) (*Figure 4*).

Secondary endpoints

VE/VCO_2 slope

Univariate and multivariate analysis of associations with VE/VCO_2 slope is shown in *Table 3*. By multivariate analysis in the overall population, only sex (female, $\beta = -5.0$; $P < 0.01$) and RV-MPI (β = 21.9; $P < 0.01$) were independently associated with VE/VCO_2. In the TAPSE/PASP population, RV-MPI remained an independent predictor of VE/VCO_2 (β = 18.5; $P < 0.01$), but TAPSE/PASP emerged as another predictor of this endpoint ($\beta = -18.0$; $P < 0.01$).

Six minute walk distance

Results of univariate and multivariate analysis of 6MWD are shown in *Table 4*. For the overall population, only body mass index (BMI) ($\beta = -3.0$; $P < 0.01$) and RV-MPI ($\beta = -69.3$; P = 0.01) were associated with 6MWD. By multivariable analysis in the TAPSE/PASP subgroup, this ratio (β = 72.4; P = 0.04) and BMI ($\beta = -3.7$; $P < 0.01$) were the only predictors of 6MWD.

Submaximal exercise duration

Univariate and multivariate analyses are shown in *Table 5*. In the overall population, only age ($\beta = -0.1$; P = 0.03) and sex (female, $\beta = -0.2$; $P < 0.01$) were independent predictors of SED. In the TAPSE/PASP population, BMI ($\beta = -0.3$; P = 0.02) and TR grade ($\beta = -3.2$; P = 0.03) were associated with SED.

Discussion

We demonstrated that RV but not LV function is associated with exercise capacity in ambulatory HFrEF patients, providing new evidences on the importance of RV function (RV-FAC and RV-MPI) and its coupling to the PA (TAPSE/PASP) on exercise tolerance in HFrEF. Salient findings include (1) overall: (i) RV-FAC, LAVi, and female sex were associated with peak VO_2; (ii) RV-MPI and female sex were the only predictors of VE/VCO_2 slope; (iii) only RV-MPI and BMI were associated with 6MWD; and (iv) age and female sex were predictors of a lower SED; (2) when available, the TAPSE/PASP ratio was the only echocardiographic parameter associated with both maximal and submaximal exercise capacity (peak VO_2 and 6MWD), or in combination with RV-MPI for ventilatory efficiency (VE/VO_2 slope); and (3) a TAPSE/PASP ratio $\leq$ 0.45 mm/mmHg predicts a peak $VO_2 \leq 14$ mL/kg/min.

Right ventricular function and its impact on exercise tolerance

Echocardiography is the main screening tool for assessment of RV function in daily clinical practice, but its interpreta-

Table 1 Baseline characteristics

Baseline characteristics	Overall population (n = 205)	TAPSE/PASP population (n = 100)	Others (n = 105)	P^a
Age, years (n ± SD)	60.97 ± 9.79	61.91 ± 9.04	60.08 ± 10.42	0.182
Male (n, %)	150 (73.17)	70 (70.00)	80 (76.19)	0.317
Caucasian (n, %)	203 (99.51)	99 (100.00)	104 (99.05)	0.330
BMI (kg/m^2)	29.71 ± 6.13	29.08 ± 5.99	30.36 ± 5.99	0.129
NYHA class (n, %)				
1	24 (11.76)	14 (14.00)	10 (9.62)	0.624
2	115 (56.37)	55 (55.00)	60 (57.69)	
3	65 (31.86)	31 (31.00)	34 (32.69)	
4	0 (0)	0 (0)	0 (0)	
Medical history (n, %)				
Aetiology of CMP				
Ischaemic	121 (59.02)	61 (61.00)	60 (57.14)	0.575
Non-ischaemic	84 (40.98)	39 (39.00)	45 (42.86)	
Prior MI	115 (56.10)	57 (57.00)	58 (55.24)	0.799
Prior coronary bypass surgery or PCI	88 (42.93)	44 (44.00)	44 (41.90)	0.762
Prior valvular intervention (surgery or dilatation)	7 (3.41)	5 (5.00)	2 (1.90)	0.223
Stroke/TIA	26 (12.68)	17 (17.00)	9 (8.57)	0.070
Hypertension	102 (49.76)	56 (56.00)	46 (43.81)	0.081
PAD	7 (3.41)	2 (2.00)	5 (4.76)	0.276
Diabetes	71 (34.63)	36 (36.00)	35 (33.33)	0.688
COPD	33 (16.10)	17 (17.00)	16 (15.24)	0.732
Prior ICD implanted	11 (5.37)	6 (6.00)	5 (4.76)	0.694
Prior pacemaker implanted	4 (1.95)	2 (2.00)	2 (1.90)	0.961
History of AF/flutter	35 (17.07)	17 (17.00)	18 (17.14)	0.978
Biochemistry (n ± SD)				
Haemoglobin, g/L	133.53 ± 14.74	130.03 ± 14.98	136.82 ± 13.80	0.001
Creatinine, μmol/L	107.07 ± 31.30	110.13 ± 34.03	104.18 ± 28.36	0.180
GFR, mL/min/1.73 m^2	65.78 ± 19.33	63.30 ± 18.71	68.12 ± 19.69	0.078
Sodium, mmol/L	139.18 ± 2.95	139.32 ± 2.92	139.05 ± 2.99	0.516
BNP, pg/mL (median, lower-upper quartile)	1372 (720–2782)	1710 (907–3533)	1219 (480–2128)	0.005
Resting EKG				
QRS duration, ms (n ± SD)	134.14 ± 31.06	144.18 ± 30.77	124.91 ± 28.45	<0.001
QRS morphology—LBBB (n, %)	82 (40.00)	54 (54.00)	28 (26.67)	<0.001
Clinical parameters (n ± SD)				
Heart rate (b.p.m.)	68.48 ± 11.48	67.82 ± 11.36	69.10 ± 11.60	0.424
Systolic blood pressure (mmHg)	109.00 ± 15.21	109.12 ± 15.68	110.83 ± 14.77	0.423
Diastolic blood pressure (mmHg)	65.94 ± 8.99	64.77 ± 9.19	67.05 ± 8.69	0.070
6MWD (m)	358.73 ± 76.76	362.21 ± 77.07	355.52 ± 76.71	0.539
Peak VO_2 (mL/kg/min)	15.05 ± 4.55	14.81 ± 4.61	15.27 ± 4.50	0.474
Mean RER at peak VO_2	1.10 ± 0.10	1.12 ± 0.12	1.09 ± 0.09	0.015
Exercise duration (min)	9.16 ± 6.19	9.76 ± 6.82	8.60 ± 5.50	0.183
Medications (n, %)				
Beta-blockers	199 (97.07)	96 (96.00)	103 (98.10)	0.374
ACE inhibitor/ARB	200 (97.56)	98 (98.00)	102 (97.14)	0.691
Digoxin	82 (40.00)	44 (44.00)	38 (36.19)	0.254
Diuretics				
MRA	89 (43.41)	48 (48.00)	41 (39.05)	0.196
Loop diuretics	174 (84.88)	87 (87.00)	87 (82.86)	0.408
Left cavity parameters (n ± SD)				
Mean LVEF, %	26.60 ± 7.74	26.50 ± 7.75	26.70 ± 7.77	0.856
Mitral regurgitation grade (n, %)				
0	38 (19.29)	15 (15.31)	23 (23.23)	0.090
1	95 (48.22)	43 (43.88)	52 (52.53)	
2	52 (26.40)	32 (32.65)	20 (20.20)	
3	12 (6.09)	8 (8.16)	4 (4.04)	
4	0 (0)	0 (0)	0 (0)	
LVEDVi, mL	101.34 ± 33.36	106.20 ± 34.22	96.54 ± 31.93	0.042
LVESVi, mL	75.64 ± 30.00	79.29 ± 31.04	72.03 ± 28.64	0.090
LAVi, mL/m^2	33.06 ± 14.24	34.54 ± 14.97	31.59 ± 13.38	0.143

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Right ventricular parameters (n ± SD)				
TAPSE, mm	17.71 ± 5.26	17.18 ± 5.05	19.27 ± 5.63	0.045
PASP, mm Hg	40.85 ± 13.68	41.38 ± 14.47	38.52 ± 9.38	0.246
TAPSE/PASP, mm/mmHg	0.47 ± 0.22	0.47 ± 0.22	-	-
RV dimension, mm	34.52 ± 7.76	35.03 ± 8.11	33.99 ± 7.39	0.347
Tricuspid regurgitation grade (n, %)				
0	49 (25.00)	2 (2.00)	47 (48.96)	<0.001
1	118 (60.20)	73 (73.00)	45 (46.88)	
2	29 (14.80)	25 (25.00)	4 (4.17)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
RV-FAC, %	39.43 ± 11.52	41.15 ± 11.96	37.61 ± 10.81	0.034
RV-MPI	0.47 ± 0.21	0.48 ± 0.21	0.45 ± 0.20	0.246

6MWD, 6 min walk distance; ACE inhibitor, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; GE, GREATER-EARTH; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LAVi, left atrial volume index; LBBB, left bundle branch block; LE, LESSER-EARTH; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA class, New York Heart Association class; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RER, respiratory exchange ratio; RV, right ventricle; RV-FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; VO_2, maximal oxygen uptake.
[a]Comparison between TAPSE–PASP population (n = 100) and others (n = 105).

tion may be confounded by its exquisite sensitivity to increased afterload and challenged by its complex geometry.[17] Consequently, magnetic resonance imaging (MRI) remains the gold standard, but is not as widely available and cannot be used in all patients with an implantable cardioverter defibrillator (ICD). Accordingly, several echocardiographic parameters have been proposed as alternative to assess RV performance, each having its own limitation and none measuring intrinsic RV contractility[6,17]; a reasonable correlation with RV ejection fraction ≤ 45% by MRI has been demonstrated for RV-FAC (r = 0.63) and RV-MPI (r = 0.58).[21] The same parameters were associated with exercise tolerance in our overall population (respectively for peak VO_2; and VE/VCO_2 and 6MWD).

The relationship between RV ejection fraction and peak VO_2 has been previously shown in small radionuclide studies (r = 0.27–0.7),[22–24] but not on other CPET. Also, RV myocardial strain by echocardiography was correlated with peak VO_2 < 14 mL/kg/min (r = 0.70), together with PASP (r = −0.58) and RV-FAC (r = 0.24) but not TAPSE (TAPSE/PASP was not reported) and only after preload augmentation,[12] which is a cumbersome manoeuvre not routinely performed clinically. Furthermore, RV strain is not available in all commercial packages and its reproducibility has been questioned.[17] Lastly, Tajima and colleagues recently showed that the presence of RV dysfunction (binary defined, using at least two criteria among RV-FAC < 35%, TAPSE < 1.6 cm, or S′ < 10 cm/s) reduced the peak VO_2 by 9% in patients with ischaemic heart disease without HF.[25] Unfortunately, many important parameters such as TAPSE/PASP, MR, and/or TR severity were not reported, also their analysis was limited to peak VO_2, and the PASP value in their cohort was within normal range, reflecting the difference in study population.

The relationship between RV function and exercise capacity is not fully understood. First, impaired RV contractility and lower stroke volume lead to reduced LV preload. Also, an enlarged RV could compress the LV, disturbs relaxation, and limits its filling due to ventricular interdependence. In addition, RV dysfunction may be secondary to LV failure as a consequence of elevated pulmonary vascular resistance, reflecting the importance of arterio-ventricular interaction and arterial load on cardiac performance, described in patients with PH.[26] Indeed, higher PASP was present among patients with exercise intolerance in our study. These abnormalities could be present at rest and aggravated during exercise or appear only during exercise, a concept called reactive PH caused by exercise.[27]

The prognostic value of tricuspid annular plane systolic excursion/pulmonary artery systolic pressure

Because the RV is functionally coupled to the pulmonary circulation, the TAPSE/PASP ratio reflects both RV function and the presence/severity of PH, with good correlation with invasive haemodynamics.[7] We found that, when available, TAPSE/PASP is the most powerful and only echocardiographic predictor of peak VO_2 and 6MWD, or in combination with RV-MPI (which encompasses both RV systolic and diastolic functions), for prediction of ventilatory efficiency (VE/VCO_2). A lower TAPSE/PASP was predictive of worse outcome among patients with HFpEF and PH,[7,28] HFrEF,[6,29] or those

Table 2 Primary outcome—peak VO_2 (mL/kg/min)

	Overall population (n = 205)					TAPSE–PASP population (n = 100)				
	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
Study factors	β (95% CI)	P	R^2	β (95% CI)	P	β (95% CI)	P	R^2	β (95% CI)	P
Age	−0.09 (−0.16; −0.03)	0.004	0.040	−0.06 (−0.13; 0.01)	0.064	−0.10 (−0.20; −0.01)	0.044	0.041	-	-
Female	−1.09 (−2.50; 0.32)	0.130	0.011	**−1.86 (−3.28; −0.44)**	**0.011**	−0.47 (−2.48; 1.54)	0.644	0.002	-	-
COPD	−0.50 (−2.21; 1.21)	0.562	0.002	-	-	−1.66 (−4.09; 0.77)	0.178	0.019	-	-
PAD	1.22 (−2.23; 4.68)	0.486	0.002	-	-	1.16 (−5.41; 7.73)	0.727	0.001	-	-
Resting EKG										
QRS duration (mm)	−0.03 (−0.05; −0.01)		0.012	0.031	-	−0.03 (−0.06; 0.01)		0.062	0.035	-
Medication										
Beta-blockers	−2.13 (−5.85; 1.59)		0.259	0.006	-	−4.00 (−8.62; 0.63)		0.090	0.029	-
Right ventricular parameters										
TAPSE (mm)	0.21 (0.07; 0.36)	0.004	0.061	-	-	0.19 (0.01; 0.37)	0.043	0.041	-	-
PASP (mmHg)	−0.09 (−0.15; −0.03)	0.002	0.077	-	-	−0.10 (−0.16; −0.03)	0.002	0.090	-	-
TAPSE/PASP (mm/mmHg)	6.64 (2.70; 10.59)	0.001	0.102	-	-	6.64 (2.70; 10.59)	0.001	0.102	**6.78 (2.89; 10.68)**	**<0.001**
RV dimension (mm)	−0.09 (−0.17; −0.01)	0.039	0.022	-	-	−0.11 (−0.23; −0.01)	0.047	0.040	-	-
Tricuspid regurgitation grade	−1.49 (−2.47; −0.50)	0.003	0.044	-	-	−1.97 (−3.91; −0.04)	0.046	0.040	-	-
RV-FAC (%)	8.85 (3.25; 14.44)	0.002	0.049	**7.50 (1.66; 13.33)**	**0.012**	10.54 (3.12; 17.96)	0.006	0.077	-	-
RV-MPI	−4.81 (−7.79; −1.83)	0.002	0.052	-	-	−3.99 (−8.29; −0.30)	0.068	0.035	-	-
Left cavity parameters										
LVEF mean (%)	0.11 (0.03; 0.20)	0.006	0.037	-	-	0.09 (−0.03; 0.21)	0.144	0.022	-	-
Mitral regurgitation grade	−1.24 (−2.01; −0.46)	0.002	0.048	-	-	−0.88 (−1.98; 0.23)	0.119	0.025	-	-
LVEDVi (mL)	−0.01 (−0.03; 0.01)	0.186	0.009	-	-	−0.01 (−0.04. 0.01)	0.288	0.012	-	-
LVESVi (mL)	−0.02 (−0.04; 0.01)	0.100	0.014	-	-	−0.02 (−0.05; 0.01)	0.247	0.014	-	-
LAVi (mL/m^2)	−0.08 (−0.13; −0.04)	<0.001	0.066	**−0.06 (−0.11; −0.01)**	**0.014**	−0.08 (−0.14; −0.02)	0.012	0.063	-	-

CI, confidence interval; COPD, chronic obstructive pulmonary disease; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; RV, right ventricle; RV-FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; TAPSE, tricuspid annular plane systolic excursion; VO_2, maximal oxygen uptake. Bold highlights the significant P-values by multivariate analysis.

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Figure 2 Relationship between TAPSE/PASP ratio and peak VO_2 in HFrEF population (n = 100). R^2 = 0.10. PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

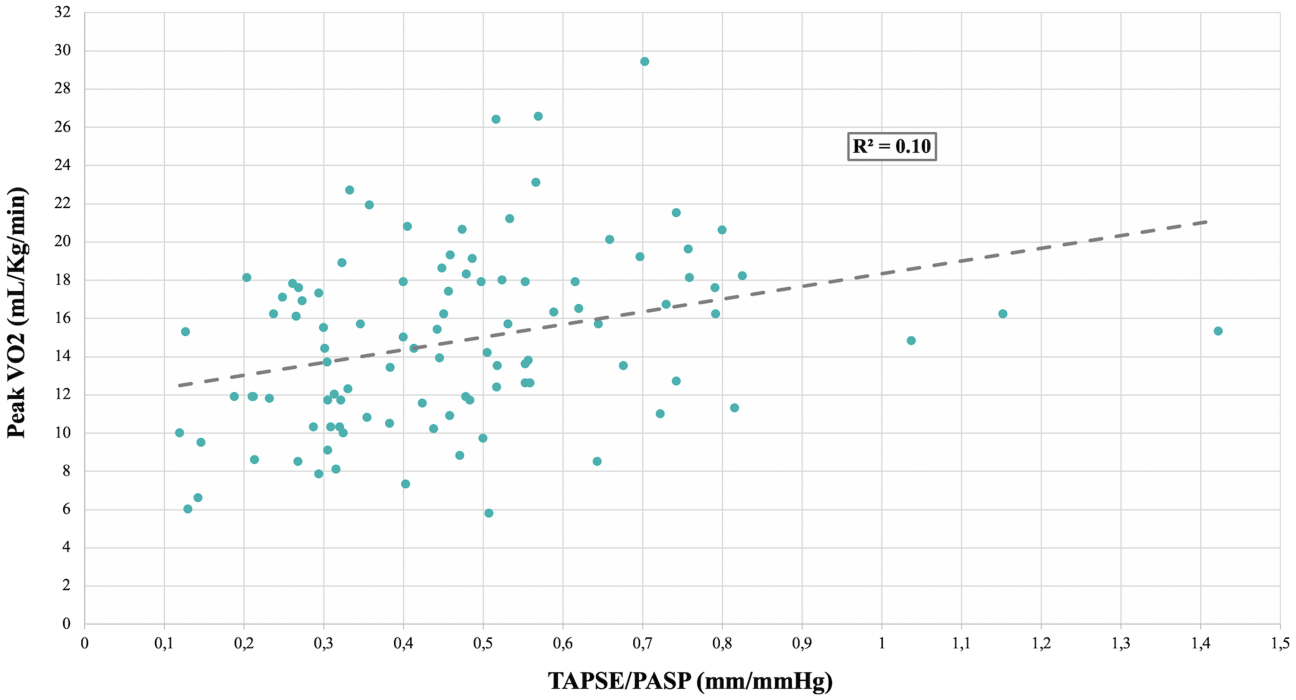

Figure 3 ROC curve depicting the sensitivity and specificity of TAPSE/PASP to predict a peak VO_2 result of ≤14 mL/kg/min. The AUC is 0.66 ($P < 0.01$), and the sensitivity and specificity are 0.63 and 0.62, respectively. The optimal threshold for a peak VO_2 result of ≤14 mL/kg/min is TAPSE/PASP of 0.45. AUC, area under the curve; PASP, pulmonary artery systolic pressure; ROC, receiver operating characteristic; TAPSE, tricuspid annular plane systolic excursion.

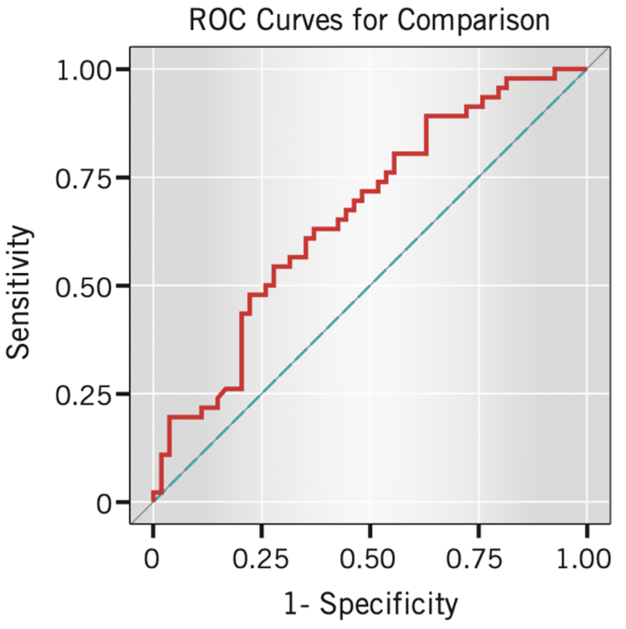

Figure 4 ROC curve depicting the sensitivity and specificity of TAPSE/PASP to predict a peak $VO_2 \leq 12$ mL/kg/min. The AUC is 0.74 ($P < 0.01$), and the sensitivity and specificity are 0.91 and 0.50, respectively. The optimal threshold for a peak $VO_2 \leq 12$ mL/kg/min is TAPSE/PASP of 0.39. AUC, area under the curve; PASP, pulmonary artery systolic pressure; ROC, receiver operating characteristic; TAPSE, tricuspid annular plane systolic excursion.

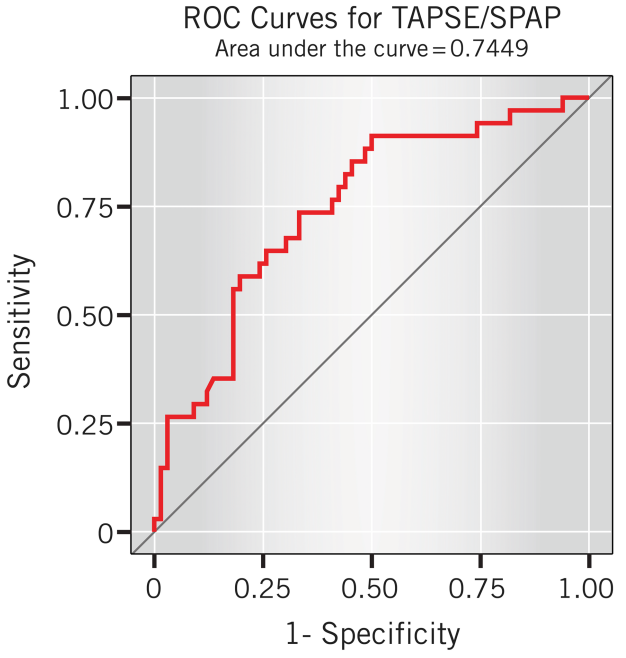

Table 3 Secondary outcome—VE/VCO_2 slope

	Overall population (n = 205)					TAPSE–PASP population (n = 100)				
	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
Study factors	β (95% CI)	P	R^2	β (95% CI)	P	β (95% CI)	P	R^2	β (95% CI)	P
Age	0.24 (0.04; 0.43)	0.019	0.034	-	-	0.13 (−0.20; 0.45)	0.434	0.007	-	-
Female	−5.61 (−9.51; 1.71)	0.005	0.048	**−4.95 (−8.52; −1.39)**	**0.007**	−8.36 (−14.37; −2.35)	0.007	0.083	-	-
BMI (kg/m^2)	−0.22 (−0.52; 0.08)	0.153	0.013	-	-	−0.23 (−0.74; 0.29)	0.380	0.009	-	-
COPD	−0.60 (−5.57; −4.38)	0.813	<0.001	-	-	1.13 (−6.77; 9.02)	0.778	0.001	-	-
PAD	−3.15 (−14.91; 8.61)	0.598	0.002	-	-	1.65 (−25.58; 28.88)	0.905	<0.001	-	-
Resting EKG										
QRS duration (mm)	0.06 (0.01; 0.12)	0.037	0.027	-	-	0.07 (−0.03; 0.17)	0.172	0.022	-	-
Medication										
Beta-blockers	−0.01 (−11.78; 11.76)	0.999	<0.001	-	-	−2.48 (−18.38; 13.43)	0.758	0.001	-	-
Right ventricular parameters										
TAPSE (mm)	−0.89 (−1.33; −0.45)	<0.001	0.124	-	-	−0.97 (−1.52; −0.43)	0.001	0.128	-	-
PASP (mmHg)	0.33 (0.16; 0.49)	<0.001	0.137	-	-	0.36 (0.18; 0.54)	<0.001	0.154	-	-
TAPSE/PASP (mm/mmHg)	−27.29 (−38.82; −15.75)	<0.001	0.207	-	-	−27.29 (−38.82; −15.75)	<0.001	0.207	**−18.03 (−30.13; −5.94)**	**0.004**
RV dimension (mm)	0.33 (0.10; 0.57)	0.006	0.048	-	-	0.53 (0.18; 0.87)	0.003	0.099	-	-
Tricuspid regurgitation grade	5.08 (2.40; 7.76)	<0.001	0.083	-	-	8.65 (2.96; 14.34)	0.003	0.097	-	-
RV-FAC (%)	−25.21 (−40.49; −9.93)	0.001	0.064	-	-	−38.94 (−61.01; −16.87)	0.001	0.127	-	-
RV-MPI	22.06 (13.66; 30.46)	<0.001	0.154	**21.85 (13.73; 29.98)**	**<0.001**	26.16 (13.43; 38.89)	<0.001	0.169	**18.54 (5.48; 31.60)**	**0.006**
Left cavity parameters										
LVEF mean (%)	−0.32 (−0.58; −0.07)	0.013	0.038	-	-	−0.44 (−0.84; −0.05)	0.029	0.055	-	-
Mitral regurgitation grade	1.60 (−0.66; 3.86)	0.163	0.012	-	-	0.60 (−2.86; 4.06)	0.731	0.001	-	-
LVEDVi (mL)	0.07 (0.01; 0.13)	0.016	0.037	-	-	0.08 (−0.01; 0.16)	0.088	0.035	-	-
LVESVi (mL)	0.09 (0.02; 0.15)	0.007	0.047	-	-	0.10 (0.01; 0.20)	0.041	0.049	-	-
LAVi (mL/m^2)	0.19 (0.06; 0.32)	0.004	0.051	-	-	0.21 (0.02; 0.39)	0.033	0.052	-	-

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; RV, right ventricle; RV-FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, minute ventilation/carbon dioxide production slope. Bold highlights the significant P-values by multivariate analysis.

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Table 4 Secondary outcome—6 min walk distance (m)

	Overall population (n = 205)					TAPSE–PASP population (n = 100)				
	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
Study factors	β (95% CI)	P	R^2	β (95% CI)	P	β (95% CI)	P	R^2	β (95% CI)	P
Age	−0.23 (−1.33; 0.87)	0.682	0.001	-	-	−0.07 (−1.83; 1.70)	0.938	<0.001	-	-
Female	−18.30 (−42.47; 5.88)	0.137	0.011	-	-	−27.12 (−61.21; 6.98)	0.118	0.026	-	-
BMI (kg/m^2)	−2.92 (−4.69; −1.16)	0.001	0.052	**−2.99 (−4.80; −1.18)**	**0.001**	−3.26 (−5.74; −0.78)	0.011	0.069	**−3.69 (−6.16; −1.22)**	**0.004**
COPD	−19.82 (−48.59; 8.96)	0.176	0.009	-	-	−8.26 (−49.35; 32.84)	0.691	0.002	-	-
PAD	−49.21 (−111.73; 13.32)	0.122	0.012	−52.21 (−112.20; 7.78)	0.088	−79.03 (−232.82; 74.76)	0.310	0.011	-	-
Resting EKG										
QRS duration (mm)	0.24 (−0.11; 0.58)	0.181	0.009	0.36 (−0.01; 0.72)	0.057	0.24 (−0.28; 0.75)	0.360	0.009	-	-
Medication										
Beta-blockers	−3.08 (−79.73; 73.56)	0.937	<0.001	-	-	−26.85 (−136.64; 82.94)	0.628	0.003	-	-
Right ventricular parameters										
TAPSE (mm)	0.67 (−1.80; 3.15)	0.592	0.002	-	-	0.79 (−2.37; 3.96)	0.620	0.003	-	-
PASP (mmHg)	−0.63 (−1.61; 0.35)	0.205	0.014	-	-	−0.62 (−1.71; 0.47)	0.259	0.014	-	-
TAPSE/PASP (mm/mmHg)	50.94 (−22.23; 124.12)	0.170	0.020	-	-	50.94 (−22.23; 124.12)	0.170	0.020	**72.39 (3.22; 141. 57)**	**0.040**
RV dimension (mm)	−0.40 (−1.81; 1.01)	0.575	0.002	-	-	0.50 (−1.45; 2.45)	0.613	0.003	-	-
Tricuspid regurgitation grade	−8.13 (−25.86; 9.61)	0.367	0.004	-	-	1.12 (−32.48; 34.72)	0.948	<0.001	-	-
RV-FAC (%)	82.18 (−17.00; 181.36)	0.104	0.014	-	-	40.16 (−96.96; 177.28)	0.562	0.004	-	-
RV-MPI	−48.98 (−103.05; 5.09)	0.076	0.017	**−69.29 (−124.63; −13.95)**	**0.014**	−39.41 (−116.49; 37.67)	0.313	0.011	-	-
Left cavity parameters										
LVEF mean (%)	0.75 (−0.67; 2.16)	0.299	0.006	-	-	0.78 (−1.30; 2.86)	0.458	0.006	-	-
Mitral regurgitation grade	4.99 (−8.56; 18.54)	0.469	0.003	-	-	11.83 (−7.44; 31.11)	0.226	0.016	-	-
LVEDVi (mL)	0.13 (−0.19; 0.45)	0.408	0.004	-	-	0.07 (−0.37; 0.52)	0.740	0.001	-	-
LVESVi (mL)	0.09 (−0.27; 0.44)	0.638	0.001	-	-	0.02 (−0.47; 0.51)	0.941	<0.001	-	-
LAVi (mL/m^2)	−0.42 (−1.19; 0.35)	0.283	0.006	-	-	−0.28 (−1.35; 0.79)	0.606	0.003	-	-

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; RV, right ventricle; RV-FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; TAPSE, tricuspid annular plane systolic excursion. Bold highlights the significant P-values by multivariate analysis.

Table 5 Secondary outcome—submaximal (75%) exercise duration (min)

	Overall population (n = 205)					TAPSE–PASP population (n = 100)				
	Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
Study factors	β (95% CI)	P	R^2	β (95% CI)	P	β (95% CI)	P	R^2	β (95% CI)	P
Age	−0.06 (−0.15; 0.03)	0.180	0.009	**−0.10 (−0.19; −0.01)**	**0.033**	−0.04 (−0.19; 0.11)	0.631	0.002	-	-
Female	−1.35 (−3.27; 0.57)	0.167	0.009	**−0.22 (−0.37; −0.07)**	**0.004**	−1.22 (−4.18; 1.74)	0.416	0.007	-	-
BMI (kg/m^2)	−0.20 (−0.34; 0.06)	0.006	0.038	-	-	−0.23 (−0.45; 0.01)	0.051	0.039	**−0.26 (−0.48; −0.04)**	**0.024**
COPD	−0.46 (−2.79; 1.86)	0.697	0.001	-	-	0.37 (−3.26; 3.99)	0.842	<0.001	-	-
PAD	−2.69 (−7.39; 2.00)	0.259	0.006	-	-	−5.28 (−14.94; 4.38)	0.281	0.012	-	-
Resting EKG										
QRS duration (mm)	−0.01 (−0.03; 0.02)	0.841	<0.001	-	-	−0.01 (−0.05; 0.04)	0.672	0.002	-	-
Medication										
Beta-blockers	−0.39 (−5.46; 4.68)	0.880	<0.001	-	-	−0.37 (−7.32; 6.57)	0.915	<0.001	-	-
Right ventricular parameters										
TAPSE (mm)	0.07 (−0.14; 0.28)	0.523	0.003	-	-	−0.01 (−0.28; 0.26)	0.937	<0.001	-	-
PASP (mmHg)	−0.05 (−0.14; 0.04)	0.248	0.011	-	-	−0.07 (−0.16; 0.02)	0.138	0.022	-	-
TAPSE/PASP (mm/mmHg)	3.69 (−2.42; 9.81)	0.234	0.015	-	-	3.69 (−2.42; 9.81)	0.234	0.015	-	-
RV dimension (mm)	0.05 (−0.07; 0.16)	0.408	0.004	-	-	0.03 (−0.14; 0.21)	0.685	0.002	-	-
Tricuspid regurgitation grade	0.06 (−1.35; 1.47)	0.934	<0.001	-	-	−2.78 (−5.64; 0.09)	0.058	0.036	**−3.17 (−6.05; −0.29)**	**0.031**
RV-FAC (%)	3.58 (−4.16; 11.32)	0.363	0.004	-	-	3.41 (−8.14; 14.96)	0.560	0.004	-	-
RV-MPI	−2.09 (−6.48; 2.30)	0.349	0.005	-	-	−1.16 (−7.92; 5.59)	0.733	0.001	-	-
Left cavity parameters										
LVEF mean (%)	−0.02 (−0.14; 0.09)	0.686	0.001	-	-	−0.03 (−0.21; 0.14)	0.700	0.002	-	-
Mitral regurgitation grade	0.33 (−0.74; 1.41)	0.541	0.002	-	-	0.24 (−1.42; 1.89)	0.777	0.001	-	-
LVEDVi (mL)	0.01 (−0.02; 0.04)	0.402	0.004	-	-	0.01 (−0.04; 0.04)	0.958	<0.001	-	-
LVESVi (mL)	0.01 (−0.02; 0.04)	0.443	0.003	-	-	0.01 (−0.04; 0.05)	0.970	<0.001	-	-
LAVi (mL/m^2)	0.04 (−0.03; 0.10)	0.259	0.006	-	-	0.01 (−0.09; 0.09)	0.957	<0.001	-	-

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; PAD, peripheral artery disease; PASP, pulmonary artery systolic pressure; RV, right ventricle; RV-FAC, right ventricular fractional area change; RV-MPI, right ventricular myocardial performance index; TAPSE, tricuspid annular plane systolic excursion. Bold highlights the significant P-values by multivariate analysis.

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with severe RV dysfunction,[30] indicating worse systemic and pulmonary haemodynamics and lack of RV contractile reserve, which correlated with lower exercise capacity, functional class, and ventilatory inefficiency.

In contrast, a small study of 67 patients reported that only sex, RV strain, and S′ were associated with peak VO_2 in NYHA III patients, but not PASP nor TAPSE/PASP[31]; it is uncertain whether these parameters were available for all patients, suggesting that they were potentially underpowered. While we did not measure S′, our study was three times larger and evaluated not only peak VO_2 but also a reliable parameter for ventilatory inefficiency (VE/VCO_2), allowing to expand the predictive value of TAPSE/PASP to a population with milder symptoms and a wider range of RV function.

A good correlation of selected echocardiographic variables, including TAPSE/PASP with peak VO_2 ($r = 0.48$) and VE/VCO_2 ($r = -0.59$) performed on a cycle ergometer, has been shown in 31 patients with wide QRS undergoing CRT.[32] Using conventional treadmill stress testing, we revealed that this relationship was independent of QRS width and emphasized the value of other RV parameters when TAPSE/PASP is not available (>50% of our cohort). Likewise, Teramoto and colleagues showed that a lower RV-FAC/PASP ratio, an unusual surrogate marker of RV-PA coupling, was associated with a worse peak VO_2 and higher VE/VCO_2 slope; furthermore, each 0.1%/mmHg reduction in RV-FAC/PASP increased by 4% of the risk of death, LV assist device implantation, transplantation, or HF hospitalization at 2 years.[8] We chose the TAPSE/PASP ratio because of its well-established good correlation with invasive haemodynamics.[7]

Lastly, Guazzi *et al*. demonstrated the strong predictive value of TAPSE/PASP on cardiac mortality, using a threshold of 0.36 mm/mmHg.[6] We herein expand on their findings by demonstrating that a threshold ≤ 0.45 mm/mmHg predicts a peak $VO_2 \leq 14$ mL/kg/min, a common cut-off for consideration of advanced HF therapies. This threshold could become a trigger for consideration of more specific HF evaluation of advanced HF therapies. Furthermore, a more restrictive cut-off of peak $VO_2 \leq 12$ mL/kg/min[33] was even more sensitive, with a TAPSE/PASP of 0.39 having a sensitivity of 0.92 and specificity of 0.50 and AUC of 0.74 ($P < 0.01$). Therefore, routine reporting of the TAPSE/PASP ratio would be a useful screening tool to help identify HFrEF patients with severely impaired exercise tolerance and triage them to specific CPET as needed.

Impact of tricuspid regurgitation on exercise tolerance

Recent publications showed that the impact of moderate/severe TR on mortality was independent of RV function,[34] even when severe.[30] In EARTH, TR was not associated with CPET results, except in the TAPSE/PASP population for SED, which reflects the level of daily activities. Potential explanations for this apparent discrepancy may be related to differences in study populations. While Padang *et al*. included exclusively patients with severe RV dysfunction,[30] we studied HFrEF patients with a sufficiently good prognosis to undergo ICD implantation, a wide spectrum of RV function, mostly exempt of significant TR (≥2/4, 14.8%). Furthermore, our patients underwent CRT implantation, which has been convincingly shown to positively impact outcomes. Lastly, because EARTH enrolled patients undergoing defibrillator implantation to prevent arrhythmic death, they had to have a good life expectancy otherwise; we may therefore have selected patients with less co-morbidities, including chronic kidney disease; in fact, only a minority of patients had chronic kidney disease, with only 18% of the patients included in our analysis having an estimated glomerular filtration rate below 50%. Accordingly, the 1 year mortality in the cohort studied by Padang *et al*. was 40%, while it was below 10% for death/cardiac transplantation in EARTH.[13,14]

Left-side parameters and exercise tolerance

Left atrial volume index was the only left-side parameters associated with CPET (peak VO_2 in the overall population). The absence of relationship with LVEF has been previously described,[4] but recent reports have suggested the important role of LV diastolic dysfunction[35] and/or MR[36] on exercise capacity. While an association between MR and peak VO_2 was present in our univariate model, MR haemodynamic repercussion and subsequent RV dysfunction and/or PH were stronger predictors of CPET in our cohort. Also, LAVi but not diastolic function grade was associated with lower peak VO_2, but lost significance in presence of TAPSE/PASP. To increase the predictive value of increased filling pressures, LAVi and PASP are now integrated in the evaluation of diastolic function.[37]

Relationship between body mass index and cardio-respiratory capacity

The inverse relationship between BMI and mortality, called the 'obesity paradox', was first observed in 2001.[38] We found a mild but significant negative association between BMI and exercise capacity portrayed by 6MWD and SED. This apparent inconsistency with the obesity paradox has been previously reported by McAuley *et al*., who showed that exercise capacity (per 1 MET) was inversely associated, but BMI was not associated, with all-cause mortality, upholding the presence of an exercise capacity-obesity paradox dichotomy.[39]

Study limitations

This study has some limitations. First, only half of the patients enrolled in EARTH had both TAPSE and/or PASP available at baseline, which has reduced the power of this study. Second, RV strain and S′ were not available to compare their prognostic values with the other RV echocardiographic parameters and TAPSE/PASP ratio. Third, even if the association between TAPSE/PASP and peak VO_2 was statistically significant, its linear correlation coefficient was low ($R^2 = 0.10$). Fourth, our cohort consisted of relatively healthy ambulatory HFrEF patients undergoing ICD implantation, with low incidence of valvular disease (MR and TR) and a wide spectrum of RV function. Therefore, the results cannot be extrapolated to patients with more symptomatic HF patients such as NYHA IV, as patients with inability to perform the exercise treadmill test were excluded. Fifth, TAPSE is preload dependent, so its value and the predictive significance of the ratio cannot be applied in an acute setting. Lastly, as there were few events, we could not relate our findings to clinical outcomes.

Conclusions

In HFrEF patients, the presence of RV dysfunction (assessed using RV-MPI and/or RV-FAC) is closely associated with exercise tolerance tests. When available (<50% of our cohort), the TAPSE/PASP ratio, a surrogate for RV-PA coupling, is strongly associated with all CPET (peak VO_2, VE/VCO_2 slope, and 6MWD) and can help risk-stratify patients. While CPET remains the gold standard to measure functional impairment and prognosis in HFrEF patients, echocardiography is non-invasive, inexpensive, and widely available and can therefore be a helpful screening tool to identify patients with reduced exercise capacity and potentially triage them to formal peak VO_2 and/or evaluation for advanced HF therapies.

Conflict of interest

Valéry Legris, M.D.: None declared.
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