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RESEARCH ARTICLE

Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction

Emil Wolsk[1], David Kaye[2], Barry A. Borlaug[3], Daniel Burkhoff[4], Dalane W. Kitzman[5], Jan Komtebedde[6], Carolyn S.P. Lam[7], Piotr Ponikowski[8], Sanjiv J. Shah[9], and Finn Gustafsson[1]*

[1]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [2]Baker IDI Heart and Diabetes Research Institute, Melbourne, Australia; [3]Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, MN, USA; [4]Cardiovascular Research Foundation, Orangeburg, NY, USA; [5]Department of Internal Medicine, School of Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA; [6]DC Devices, Boston, MA, USA; [7]National Heart Centre Singapore, Singapore, and Duke-National University of Singapore, Singapore; [8]Department of Heart Diseases, Medical University and Centre for Heart Diseases, Military Hospital, Wrocław, Poland; and [9]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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Aims Patients with heart failure and preserved ejection fraction (HFpEF) are characterized by functional impairment and an abnormal haemodynamic response to exercise. The six-minute walk test (6MWT) serves as a standardized test for functional capacity quantification in heart failure patients, and is associated with cardiovascular outcomes. However, as the association between 6MWT and haemodynamic parameters during rest and exercise in HFpEF patients is unknown, we sought to elucidate this relationship.

Methods and results Overall, 64 patients enrolled in the REDUCE LAP-HF trial completed a 6MWT at baseline. Univariate and multivariable linear regression models were used to assess the associations between 6MWT and measured or derived haemodynamic variables at baseline, during light/moderate exercise (20 W), and at peak supine exercise. The average 6MWT distance was 318 ± 106 m. At rest, in a multivariable model, only pulmonary capillary wedge pressure (PCWP) was significantly associated with 6MWT [coefficient: −5.4, 95% confidence interval (CI) −10.4, −0.5, $P = 0.033$]. During light/moderate exercise, mean pulmonary artery pressure was associated with 6MWT in a multivariable model (coefficient: −3.5, 95% CI −6.8, −0.3, $P = 0.033$). During peak exercise, central venous pressure, cardiac index (CI), and PCWP/CI correlated with 6MWT; however, workload corrected PCWP was the only variable independently associated with 6MWT (coefficient: −0.8, 95% CI −1.3, −0.4, $P < 0.001$). The variance in 6MWT was modestly explained by measured or derived haemodynamic variables at rest or at any stage of exercise ($r^2 = 7–17\%$).

Conclusion Workload corrected PCWP correlated best with 6MWT performance in HFpEF patients. Baseline haemodynamic variables were modestly correlated with 6MWT, suggesting that 6MWT performance in HFpEF patients may be significantly influenced by extra-cardiac factors.

Keywords Heart failure with preserved ejection fraction • Six-minute walk test • Haemodynamics • REDUCE LAP-HF • Exercise

*Corresponding author. Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. Tel: +45 61604280, Fax: +45 62604280, Email: finn.gustafsson@regionh.dk

Introduction

Patients with heart failure and preserved ejection fraction (HFpEF) are characterized by an increased filling pressure in the left atrium and ventricles at rest or during exercise.[1−4] These patients experience diminished functional capacity as a key symptom. While it is clear that the background is multifactorial, abnormal haemodynamics are known to play a role.[5] The six-minute walk test (6MWT) serves as a convenient standardized test for assessment of functional performance in heart failure (HF) patients.[1,6] The 6MWT is easy to perform and has the advantage of providing prognostic information on mortality and HF hospitalization in addition to quantification of functional capacity.[7−9] In light of this, the 6MWT has been used as an outcome measure in several trials where various interventions (e.g. angiotensin-converting enzyme inhibitors, aldosterone antagonists, phosphodiesterase-5 inhibitors, cardiac resynchronization therapy) have been tested in patients with HF with both reduced and preserved ejection fraction.[10−12] Indeed, a recent consensus paper resulting from a Food and Drug Administration-facilitated conference of leaders in HF, industry, and regulatory agencies suggested 6MWT as a relevant outcome measure in future HFpEF trials.[13] However, the associations between 6MWT and invasive haemodynamic parameters during rest and exercise are—to our knowledge—unknown in patients with HFpEF.[13] Knowledge of these associations could provide pathophysiological insight into the haemodynamic basis of diminished functional capacity. Furthermore, knowing the strength of association between changes in haemodynamic parameters [e.g. pulmonary capillary wedge pressure (PCWP) and 6MWT] would reveal the magnitude of improvement in 6MWT that could be expected with a given cardiac intervention in HFpEF patients. We investigated the association between baseline invasive haemodynamic measures and 6MWT in patients with HFpEF enrolled in the Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) trial.

Methods

This study used baseline data from the REDUCE LAP-HF trial. The primary findings have previously been published.[14] In summary, 64 patients with elevated PCWP and signs and symptoms of HFpEF were successfully implanted with an InterAtrial Shunt Device (IASD System II, Corvia Medical, Inc., Tewksbury, MA, USA) in a prospective, non-randomized, open-label trial. The primary objective of the trial was to assess the safety and performance of IASD implantation. Key inclusion criteria were: informed consent, ability to perform a 6MWT, New York Heart Association (NYHA) class II–IV, left ventricular ejection fraction (LVEF) ≥40% determined by echocardiography, ≥1 HF hospitalization within the last 12 months prior to screening, age ≥ 40 years, elevated left ventricular filling pressures with a gradient compared to central venous pressure (CVP) documented by ≥1 of the following: PCWP (end-expiratory) or left ventricular end-diastolic pressure (end-expiratory) at rest ≥15 mmHg and greater than CVP, and/or PCWP (end-expiratory) during supine bicycle exercise ≥25 mmHg and CVP <20 mmHg. Key exclusion criteria were: cardiac index (CI) ≤2.0 L/min/m^2 requiring inotropic agents within the last 6 months prior to screening, obstructive or restrictive cardiomyopathy, moderate to severe heart valve disease, or atrial fibrillation with resting heart rate > 100 b.p.m. Additional details on the trial design have been published.[15] The protocol was published on ClinicalTrials.gov (NCT01913613) before enrollment.

Haemodynamic parameters

Haemodynamic variables were measured at rest and during supine ergometer exercise. Ergometer resistance (Lode ergometer, Groningen, The Netherlands) was increased every 3 min with 20 W increments until maximal effort was achieved. A Swan–Ganz catheter was positioned in the pulmonary artery via the internal jugular or brachial vein using fluoroscopy. The catheter was levelled at the mid axillary level, and haemodynamic data obtained were evaluated by an independent haemodynamic core laboratory (PV Loops LLC, New York, NY, USA). For all signals, 10 second segments were recorded, printed and sent to a core laboratory. Signals were quantified by visual estimation of values at end-expiration. At rest, multiple beats (>3) were typically available, but this was not usually the case for signals recorded during exercise with more rapid breathing, especially at peak exercise.

The following haemodynamic data were collected: CVP, mean pulmonary artery pressure (mPAP), PCWP, cardiac output (CO) using thermodilution technique, non-invasive systolic and diastolic blood pressure, and heart rate. In addition, mixed venous oxygen (SvO_2) was sampled from the pulmonary artery at rest and at maximal effort. Delta values were calculated using both absolute and relative values.

Derived haemodynamic variables

Body surface area (BSA) was estimated using the Dubois formula. Systemic vascular resistance (SVR) was calculated as 80 x (mean arterial pressure – mean CVP)/CO. Pulmonary vascular resistance (PVR) in Wood units was calculated as (mPAP – mean PCWP)/CO. Cardiac index was calculated as CO/BSA. Workload corrected PCWP (PCWL) was calculated as PCWP/W achieved during exercise/kg body weight. Cardiac index corrected PCWP was calculated as PCWP/CI.

Baseline data

All subjects underwent a 6MWT as described by Guyatt *et al.*[6] In a long unobstructed corridor, using standardized patient instructions, patients covered as much distance as possible during the allotted 6 min. The total distance covered was measured and recorded. Staff overseeing the 6MWT was unaware of the haemodynamic results.

Each subject underwent transthoracic echocardiography with colour flow Doppler and tissue Doppler, performed according to echocardiographic and core laboratory standards at baseline. Blood samples were collected and analysed according to standards used at each participating site.

Statistical analyses

Baseline characteristics were compared using *t*-tests or rank-sum tests for continuous variables, as appropriate. Numerical values are reported as mean ± standard deviation, median [interquartile range (IQR)], or counts (%). All data were tested for normal distribution. The haemodynamic measures obtained during a conventional right heart catheterization (CVP, mPAP, PCWP, CI) were all included in the linear regression modelling. Furthermore, the composite measure of PCWL was also included, as this measure has been shown to be a strong predictor of mortality in HFpEF patients.[3] Univariate linear regression models using 6MWT as the dependent variable and the following as explanatory variables: CVP, mPAP, PCWP, SVR, PVR, CI, SvO_2, PWCP/CI and PCWL both at rest ($n=64$), 20 W ($n=63$) (only CVP, mPAP, PCWP, PCWL) and maximal exercise ($n=63$). To identify haemodynamic measures that were associated with 6MWT performance below or above the median, logistic regression was used with haemodynamic variables at rest, peak exercise, and absolute changes from rest to peak exercise.

The assumptions of linear regression were formally tested and found to be true, except for co-linearity which was present between CVP and mPAP (rest), and mPAP and PCWP (rest/exercise), as expected. A stepwise forward selection multivariable linear regression model (cut-off: $P<0.1$) was used both at rest and at maximal exercise with 6MWT as the dependent variable and CVP, mPAP, PCWP, CI, and PCWL as the explanatory variables. At 20 W, data on CVP, mPAP, PCWP, and PCWL were recorded and used in the multivariable analyses. Analysis was performed separately with atrial fibrillation, diabetes, chronic obstructive pulmonary disease (COPD), and anaemia, to see if these co-morbidities influenced 6MWT performance. Only COPD influenced 6MWT performance ($r^2=0.10$, $P=0.012$); however, owing to a low number of patients with COPD ($n=6$), estimates were not generated for this population and adjustments for COPD were not applied. Analysis failed to show any significant effect between LVEF and 6MWT performance ($P=0.54$), which excluded further subgroup analysis based on certain LVEF ranges (e.g. mid-range LVEF 40–50%).

To learn if other biomarkers added to the primary haemodynamic variables would independently be associated with 6MWT performance, we included sex, age, body mass index, heart rate, systolic and diastolic blood pressure, NYHA class, estimated glomerular filtration rate, haemoglobin, and LVEF to the base model. Significant variables were identified using multivariable linear regression with bootstrapping and stepwise selection. A *P*-value of 0.05 was considered statistically significant. All analyses were conducted using STATA version 13 (STATA Corp., College Station, TX, USA).

Results

Overall, 64 patients were enrolled and all performed the 6MWT. Patients were elderly, most often female and overweight (*Table 1*), in accord with typical characteristics of HFpEF patients in population-based studies.[16] The average distance in the 6MWT was 318 ± 106 m.

Haemodynamic parameters and six-minute walk test

At rest

Baseline haemodynamics at rest showed preserved CI and elevated PCWP. At rest, only PCWP ($r=-0.27$, $P=0.033$) was significantly associated with 6MWT in a multivariable model. Regression coefficients are summarized in *Table 2*.

At low exercise intensity (20 W)

During exercise at 20 W, univariate associations were significant between 6MWT and CVP ($P=0.042$), mPAP ($P=0.017$), PCWP

Table 1 Baseline characteristics at rest

Patients, *n*	64
Age, years	70 ± 8
Female gender	42 (66)
BMI, kg/m^2	32.7 ± 6.1
NYHA class	
II	18 (28)
III	46 (72)
Medical history	
Atrial fibrillation	23 (36)
Hypertension	52 (81)
Diabetes mellitus	22 (34)
Coronary artery disease	23 (36)
COPD	6 (9)
Anaemia	14 (22)
Obesity (BMI >30 kg/m^2)	40 (63)
Beta-blocker use	58 (91)
ACE-inhibitor/ARB use	59 (92)
Loop diuretic use	42 (66)
Echocardiography	
LVEF, %	47 ± 7
LVEDVi, mL/m^2	68 ± 13
LVMi, g/m^2	119 ± 36
LAVi, mL/m^2	34 ± 17
RVEDVi, mL/m^2	22 ± 9
TAPSE, mm	20 ± 4
E/A ratio	1.3 ± 0.8
E/e' ratio	13.9 ± 5.9
eGFR, mL/min/1.73 m^2	62 ± 21
Haemoglobin, g/L	127 ± 29
NT-proBNP[a], pg/mL	377 [222–925]
Heart rate, b.p.m.	69 ± 14
Systolic blood pressure, mmHg	143 ± 23
Diastolic blood pressure, mmHg	71 ± 13
Haemodynamics – rest	
CVP, mmHg	9 ± 4
mPAP, mmHg	24 ± 7
PCWP, mmHg	17 ± 5
CI, L/min/m^2	2.7 ± 0.6
SVR, dyn x s/cm^5	1343 ± 403
PVR, Wood units	1.2 ± 0.7
PCWL, mmHg/W/kg	89 ± 54
SvO_2, %	69 ± 6
Peak Watts	
20 W	18 (28)
40 W	25 (39)
60 W	16 (25)
80 W	5 (8)
Exercise duration, min	7.3 ± 3.1
6MWT distance, m	318 ± 106

Values are mean ± standard deviation, median [interquartile range], or count (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; mPAP, mean pulmonary artery pressure; 6MWT, six-minute walk test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWL, workload corrected pulmonary capillary wedge pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVEDVi, right ventricular end-diastolic volume index; SvO_2, mixed venous oxygen; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion.
[a]NT-proBNP data available from 54 patients.

Table 2 Association of haemodynamic variables with six-minute walk test at rest ($n = 64$)

	Univariate		Multivariable (r^2=0.07, P = 0.03)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
CVP, mmHg	−5.4 (−12.7, 1.8)	0.14		
mPAP, mmHg	−3.1 (−7.1, 1.0)	0.13		
PCWP, mmHg	−5.4 (−10.4, −0.5)	0.033	−5.4 (−10.4, −0.5)	0.033
CI, L/min/m^2	2.7 (−37.8, 43.2)	0.89		
PVR, Wood units	4.8 (−34.3, 43.9)	0.81		
SVR, dyn x s/cm^5	0.0 (−0.1, 0.1)	0.74		
SvO_2, %	1.0 (−3.6, 5.5)	0.68		
PCWP/CI, mmHg/L/min/m^2	−9.2 (−20.0, 1.7)	0.097		

CI, cardiac index/confidence interval; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen; SVR, systemic vascular resistance.

Table 3 Association of haemodynamic variables with six-minute walk test during light/moderate exercise (20 W) ($n = 63$)

	Univariate		Multivariable (r^2=0.08, P = 0.033)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
CVP, mmHg	−5.3 (−10.5, −0.2)	0.042		
mPAP, mmHg	−3.8 (−6.9, −0.7)	0.017	−3.5 (−6.8, −0.3)	0.033
PCWP, mmHg	−4.0 (−7.2, −0.8)	0.016		
$PCWL_{20}$, mmHg/W/kg	−1.1 (−1.9, −0.2)	0.013		

CI, confidence interval; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PCWL, workload corrected pulmonary capillary wedge pressure (20 W); PCWP, pulmonary capillary wedge pressure.

($P = 0.016$) and $PCWL_{20}$ ($P = 0.013$). After multivariable selection, only mPAP was associated with 6MWT ($P = 0.033$) and explained the variance with an $r^2 = 0.08$. Regression coefficients are summarized in *Table 3*.

At peak exercise

At peak exercise, univariate associations were significant between 6MWT and CVP ($P = 0.020$), CI ($P = 0.044$), PCWP/CI ($P = 0.037$), and PCWL ($P < 0.001$). Only PCWL was associated with 6MWT after multivariable adjustment ($P < 0.001$) and explained the variance with an $r^2 = 0.17$. Regression coefficients are summarized in *Table 4*. The univariate correlation between PCWL and 6MWT was −0.42 ($P = 0.0007$) (*Figure 1*).

Changes in haemodynamic parameters and six-minute walk test (baseline to peak exercise)

When using changes from baseline to peak exercise, univariate associations were significant between 6MWT and ΔCI ($P = 0.019$) and ΔSVR ($P = 0.049$). Only ΔmPAP ($P = 0.081$) and ΔCI ($P = 0.008$) were associated with 6MWT after multivariable adjustment and explained the variance with an $r^2 = 0.13$. Regression coefficients are summarized in *Table 5*.

Associations between baseline characteristics, haemodynamic parameters, and six-minute walk test

Using a base model of baseline characteristics identified significant variables. Adding haemodynamic measures at rest to this base model did not change these variables (base model: $r^2 = 0.24$; base model + haemodynamic variables at rest: $r^2 = 0.24$). Using a base model and adding haemodynamic variables obtained during peak exercise improved the model with regard to the explanatory value of the model (base model: $r^2 = 0.24$; base model + haemodynamic variables at peak exercise: $r^2 = 0.37$). Estimates are provided in the Supplementary material online, *Tables S1* and *S2*.

Sensitivity analysis

The associations between changes in haemodynamic parameters from baseline to peak exercise were comparable between absolute and relative changes (analysis using relative changes is provided in the Supplementary material online, *Table S3*).

Independent significant variables were overall comparable irrespective of whether 6MWT performance was modelled as a categorical (median) or a continuous variable (see Supplementary material online, *Tables S4–S6*).

Table 4 Association of haemodynamic variables with six-minute walk test at peak exercise ($n = 63$)

	Univariate		Multivariable (r^2=0.17, $P = 0.0007$)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
CVP, mmHg	−5.7 (−10.4, −0.9)	0.020		
mPAP, mmHg	−2.8 (−5.7, 0.1)	0.062		
PCWP, mmHg	−2.5 (−6.0, 1.0)	0.16		
CI, L/min/m^2	23.7 (0.7, 46.7)	0.044		
PVR, Wood units	−26.6 (−61.9, 8.6)	0.14		
SVR, dyn x s/cm^5	−0.1 (−0.1, 0.0)	0.23		
SvO_2, %	1.0 (−0.7, 2.8)	0.25		
PCWP/CI, mmHg/L/min/m^2	−9.6 (−18.5, −0.6)	0.037		
PCWL, mmHg/W/kg	−0.8 (−1.3, −0.4)	<0.001	−0.8 (−1.3, −0.4)	<0.001

CI, cardiac index/confidence interval; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PCWL, workload corrected pulmonary capillary wedge pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen; SVR, systemic vascular resistance.

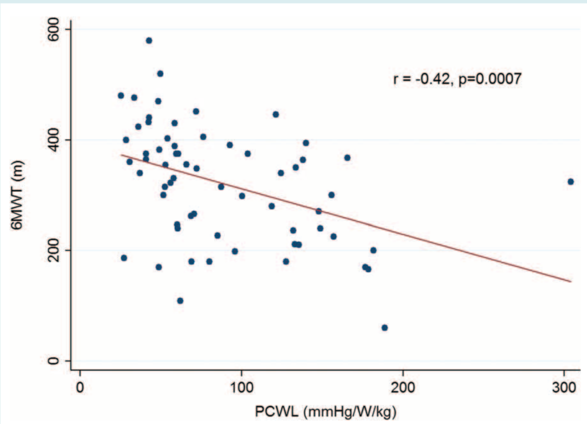

Figure 1 Scatterplot of six-minute walk test (6MWT) and workload corrected pulmonary capillary wedge pressure (PCWL) during peak exercise.

Discussion

The main findings of the present study were that invasive haemodynamics measured at supine rest did not correlate well with 6MWT distance, whereas stronger associations were observed during light to moderate (20 W) and peak exercise between 6MWT and indices of left ventricular filling pressure and CO. The strongest correlation with 6MWT was PCWL. Overall, rest and exercise invasive haemodynamics explained only a relatively modest proportion of the variance in 6MWT distance.

Hemodynamic measures and six-minute walk test

At rest

In this study, haemodynamic measures at rest were relatively poor predictors of 6MWT performance. Invasive haemodynamic measures obtained during rest are not predictive of haemodynamic changes during exercise, neither in healthy people[17,18] nor in HFpEF patients.[2,3,19] Hence, it is not surprising that unless haemodynamics are severely deranged at rest—which is uncommon in outpatients—exercise haemodynamics should be superior to resting haemodynamics in explaining the cardiac component of exercise intolerance in HF.[2,18–20] This is further supported by an enhanced prediction of morbidity and mortality in HFpEF when invasive haemodynamic testing during exercise is used.[2,3]

During exercise

The associations between 6MWT and haemodynamic measures were stronger during exercise compared to rest. The strongest associations were observed during peak exercise and when changes from baseline to peak exercise were analysed.

The haemodynamic measures most strongly associated with 6MWT after multivariable adjustment were mPAP, CI and PCWL. Maeder *et al.*[19] showed how PCWL was a sensitive measure of abnormal haemodynamics in HFpEF patients, and recently Dorfs and co-workers[3] elegantly showed how PCWL added incremental prognostic value with respect to morbidity and mortality when used with PCWP in HFpEF patients. In this study, PCWL was the strongest variable associated with 6MWT during exercise. These data examining determinants of submaximal exercise capacity are in agreement with a recent study showing that elevated PCWP during exercise is associated with poorer maximal exercise capacity, as assessed by peak oxygen consumption.[4] Importantly, the present study demonstrates an independent effect: after correction for multiple haemodynamic confounding variables, the correlation between PCWL and 6MWT remained significant ($r = -0.42$, $P = 0.0007$), highlighting the importance of elevated filling pressures relative to workload as a credible therapeutic target. Adding haemodynamic measures at rest to baseline characteristics did not improve the explanatory value of the model, whereas adding haemodynamic measures obtained during exercise significantly improved the model. This reiterates the value of obtaining measurements during exercise to assess

Table 5 Association of absolute changes (Δ) in haemodynamic variables from baseline to peak exercise with six-minute walk test

	Univariate		Multivariable ($r^2 = 0.13$, $P = 0.01$)	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Δ CVP, mmHg	−4.6 (−10.2, 1.1)	0.11		
Δ mPAP, mmHg	−2.4 (−6.2, 1.4)	0.22	−3.2 (−6.9, 0.4)	0.081
Δ PCWP, mmHg	−0.2 (−4.1, 3.8)	0.93		
Δ CI, L/min/m^2	33.9 (5.8, 61.9)	0.019	38.2 (10.2, 66.2)	0.008
Δ PVR, Wood units	−33 (−68, 1)	0.058		
Δ SVR, dyn x s/cm^5	−0.1 (−0.2, −0.0)	0.049		
Δ SvO_2, %	1.5 (−0.3, 3.3)	0.11		
Δ PCWP/CI, mmHg/L/min/m^2	−5.3 (−16.9, 6.2)	0.36		

CI, cardiac index/confidence interval; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen; SVR, systemic vascular resistance.

functional capacity, as well as the importance of factors beyond haemodynamics.

Implications for the six-minute walk test as an outcome measure in clinical trials

Although measures of filling pressure, CO and PCWL have been shown to be associated with maximal exercise capacity in HFpEF patients, as assessed by maximal oxygen uptake,[3,4,19,21] the associations with an easily obtainable measure of daily physical activity such as the 6MWT have not been previously explored. We believe it is important to investigate this relationship as 6MWT is widely used, is suggested as an outcome measure in HFpEF trials, and is likely better at quantifying the capacity to perform daily activities than maximal oxygen uptake during a cardiopulmonary exercise test.[13,22,23] Furthermore, it is known that the correlation between changes in maximal oxygen uptake and 6MWT is poor in HFpEF patients,[24,25] suggesting that 6MWT performance is not only based on cardiopulmonary conditions.[23] Apart from the cardiopulmonary limitations that restrict functional capacity in patients with HFpEF, peripheral factors (reduced skeletal muscle mass and function, increased skeletal muscle adipose tissue infiltration, and potentially muscle perfusion) and co-morbidities also influence functional capacity.[26–28] Patients with HFpEF are burdened with numerous co-morbidities,[29,30] which have been attributed to impact cardiovascular morbidity and mortality.[30–33] It is conceivable that since 6MWT performance is predictive of cardiovascular outcomes,[8,9] 6MWT performance reflects more than the haemodynamic severity of HF. In addition to peripheral factors, 6MWT performance is likely influenced by factors such as obesity, anaemia, sarcopenia, diabetes, frailty, orthopaedic problems, and other frequent co-morbidities of HFpEF.[26,34] Hence, the 6MWT might be a global indicator of multiple risk factors as well as abnormal exercise haemodynamics present in HFpEF patients.

The modest invasive haemodynamic associations with 6MWT may potentially help explain the heterogeneous results of intervention trials that have tested preload and afterload modifying therapies for improving 6MWT performance. In HFpEF studies with 6MWT as an outcome and cardiovascular modifying drugs as the intervention (e.g. angiotensin-converting enzyme inhibitors, beta-blockers, phosphodiesterase-5 inhibitors, or aldosterone receptor blockers), 6MWT did not change with the active comparators.[10,26,35] Although most interventional studies were small, larger interventional studies performed in patients with HF and reduced ejection fraction have also shown a poor association between changes in 6MWT and cardiovascular effects.[11] This may indicate that the 6MWT serves as a global measure of cardiovascular function, extra-cardiac factors (arterial and skeletal muscle function) that determine exercise capacity, as well as the overall burden of co-morbidities which can strongly impact these. A significant contribution of extra-cardiac factors to 6MWT is supported by reports showing that peak exercise oxygen consumption in HFpEF is determined at least 50% by extra-cardiac factors.[36] In addition, exercise training, which has been shown to improve peak exercise oxygen consumption (and 6MWT) appears to do so primarily by influencing extra-cardiac factors.[37] These aspects are important when evaluating new therapeutic interventions in HFpEF. While the intervention may be effective in treating the core of cardiac disease and lowering filling pressures at rest or during exercise such as sodium nitrite treatment,[38] this may not necessarily translate into an effect on 6MWT performance in individual patients.

Limitations

This study included stable ambulatory HFpEF patients; thus our findings may not apply to patients with acute decompensation. Furthermore, our patients were older than typically reported in most HFpEF studies.[39] This might have amplified the potential contributions of extra-cardiac factors in influencing 6MWT performance.

The inclusion criteria were in part based on LVEF ≥40%, which may have included patients with HF and mid-range ejection fraction as defined in the recent European Society of Cardiology HF guidelines;[1] however, we did not find indication that LVEF was associated with 6MWT performance.

Importantly, haemodynamics were assessed during supine exercise, whereas the 6MWT was performed in the upright position. Furthermore, as the haemodynamic assessment and 6MWT were not performed simultaneously, this could have weakened the associations observed. Repeated 6MWT bouts were not performed, which could have also contributed to the modest associations between haemodynamic variables and 6MWT.

Patients were enrolled in the REDUCE LAP-HF study with pre-specified inclusion and exclusion criteria, which may reduce generalizability to HFpEF patients who do not meet these criteria. Furthermore, due to the heterogeneous phenotypes of HFpEF patients in general, these results may not be applicable to other HFpEF populations.

Conclusion

The haemodynamic parameters most closely associated with 6MWT performance were measures of filling pressure and/or CI recorded during exercise. Workload corrected PCWP was the best—although only a modest—predictor of 6MWT performance. Functional capacity in HFpEF patients—as quantified by 6MWT—is only in part determined by invasive haemodynamic factors.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Independent measures associated with 6MWT using multiple linear regression with stepwise selection using base model.

Table S2. Independent measures (peak exercise) associated with 6MWT using multiple linear regression with stepwise selection using base model + haemodynamic measures during peak exercise.

Table S3. The association of relative changes in haemodynamic variables (Δ) from baseline to peak exercise and 6MWT.

Table S4. Independent haemodynamic measures during rest associated with median 6MWT performance using logistic regression with stepwise selection.

Table S5. Independent haemodynamic measures during peak exercise associated with median 6MWT performance using logistic regression with stepwise selection.

Table S6. Independent derived haemodynamic measures of absolute changes from rest to peak exercise associated with median 6MWT performance using logistic regression with stepwise selection.

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