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ORIGINAL ARTICLE

Resting and exercise haemodynamic characteristics of patients with advanced heart failure and preserved ejection fraction

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Abstract

Aims This study aimed to describe haemodynamic features of patients with advanced heart failure with preserved ejection fraction (HFpEF) as defined by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).

Methods and results We used pooled data from two dedicated HFpEF studies with invasive exercise haemodynamic protocols, the REDUCE LAP-HF (Reduce Elevated Left Atrial Pressure in Patients with Heart Failure) trial and the REDUCE LAP-HF I trial, and categorized patients according to advanced heart failure (AdHF) criteria. The well-characterized HFpEF patients were considered advanced if they had persistent New York Heart Association classification of III–IV and heart failure (HF) hospitalization $<$ 12 months and a 6 min walk test distance $<$ 300 m. Twenty-four (22%) out of 108 patients met the AdHF criteria. On evaluation, clinical characteristics and resting haemodynamics were not different in the two groups. Patients with AdHF had lower work capacity compared with non-advanced patients (35 ± 16 vs. 45 ± 18 W, P = 0.021). Workload-corrected pulmonary capillary wedge pressure normalized to body weight (PCWL) was higher in AdHF patients compared with non-advanced (112 ± 55 vs. 86 ± 49 mmHg/W/kg, P = 0.04). Further, AdHF patients had a smaller increase in cardiac index during exercise (1.1 ± 0.7 vs. 1.6 ± 0.9 L/min/m^2, P = 0.028).

Conclusions A significantly higher PCWL and lower cardiac index reserve during exercise were observed in AdHF patients compared with non-advanced. These differences were not apparent at rest. Therapies targeting the haemodynamic compromise associated with advanced HFpEF are needed.

Keywords Advanced heart failure; Heart failure with preserved ejection fraction; Haemodynamics; Invasive exercise testing

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Introduction

Advanced heart failure (AdHF) develops in approximately 5–10% of patients with left ventricular systolic dysfunction and is associated with a poor prognosis if not treated with mechanical circulatory support or heart transplantation.[1] AdHF in patients with reduced ejection fraction (HFrEF) is generally associated with high ventricular filling pressures and low cardiac output (CO).[2] For patients with heart failure with preserved ejection fraction (HFpEF), which accounts for approximately half of all heart failure (HF) cases in the western world,[3] the correlation between haemodynamics and advanced symptoms is less well characterized.

Recently, increased focus on AdHF in patients with HFpEF was placed in the consensus statement published by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC),[4] and herein, it is recognized that not just patients with HFrEF develop AdHF. HFA-ESC criteria to identify AdHF are presented in *Table 1*.

Many HFpEF patients are severely limited in terms of functional capacity and quality of life.[5] Moreover, patients with HFpEF derive limited benefit from neurohumoral blockade, and relief of symptoms with diuretics is currently the therapeutic strategy recommended in guidelines for HFpEF.[6] As advanced therapies, such as heart transplantation, mechanical circulatory support, and total artificial heart implantation, are evolving to treat advanced HFpEF in selected cases, it is important to understand the haemodynamic and clinical characteristics of AdHF in HFpEF. A hallmark of HFpEF is impaired exercise capacity, and as the advanced symptoms in many HFpEF patients are present mainly during exertion, it is important to acquire information about the haemodynamic state in advanced HFpEF, not just at rest but also during exercise. Using data from two dedicated HFpEF studies incorporating invasive haemodynamic exercise testing, the aim of this study was to characterize the haemodynamic profile of patients with AdHF as defined by the HFA and to test the hypothesis that patients with advanced disease present with a haemodynamic profile distinctly different from that of patients with non-advanced HF.

Methods

Patients and study design

The study is based on pooled data from the two clinical trials, the REDUCE LAP-HF (Reduce Elevated Left Atrial Pressure in Patients with Heart Failure) trial and the REDUCE LAP-HF I trial, that investigated well-defined HFpEF patients. Detailed trial design descriptions have previously been published.[7,8] In brief, patients with signs and symptoms of HF and elevated pulmonary capillary wedge pressure (PCWP) either at rest or during exercise were included in the two studies evaluating the safety and performance of an interatrial shunt device (IASD). REDUCE LAP-HF had a non-randomized, open-label design, whereas REDUCE LAP-HF I had a sham controlled randomized, double-blinded design. We only used data from the baseline investigation. Key inclusion criteria into the studies were age $\geq$ 40 years, New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction (LVEF) $\geq$ 40%, and elevated left-sided filling pressures. Key exclusion criteria included substantial right ventricular (RV) dysfunction [defined as more than mild RV dysfunction as estimated by transthoracic echocardiography (TTE) or tricuspid annular plane systolic excursion $<$ 14 mm or RV size $>$ LV size], central venous pressure (CVP) $>$ 14 mmHg, cardiac index (CI) $<$ 2 L/min/m^2, evidence of pulmonary hypertension with PVR $>$ 4 Wood units, moderate to severe heart valve disease, infiltrative or hypertrophic cardiomyopathy, atrial fibrillation with resting heart rate (HR) $>$ 100 b.p.m., and dialysis or estimated glomerular filtration rate (eGFR) $<$ 25 mL/min/1.73 m^2.

All patients had echocardiographic and invasive haemodynamic evidence for HFpEF. For the purpose of this study, the HFpEF patients were grouped according to whether or not they fulfilled the 2018 HFA-ESC criteria for AdHF; that is, severe and persistent HF symptoms equal to NYHA III or IV *and* HF hospitalization within the last 12 months *and* severe impairment of exercise capacity with a 6 min walk test distance (6MWD) less than 300 m. The studies were approved by relevant ethics committees and in accordance with the Declaration of Helsinki with informed consent obtained from patients before enrolment.

Haemodynamic evaluation

All patients underwent right heart catheterization with exercise haemodynamic assessment. The two studies had similar invasive protocol, and all measurements were obtained before IASD implantation or sham procedure (femoral venous access and intracardiac echocardiography). A Swan-Ganz catheter was inserted through the internal jugular or the

Table 1 HFA-ESC 2018 criteria defining advanced heart failure[4]

(1) Severe and persistent HF symptoms of heart failure [NYHA class III (advanced) or IV]
(2) Severe cardiac dysfunction defined by a reduced LVEF $\leq$ 30%, isolated RV failure (e.g. ARVC), or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF[6]
(3) Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing $>$1 unplanned visit or hospitalization in the last 12 months
(4) Severe impairment of exercise capacity with inability to exercise or low 6MWD less or equal to 300 m or pVO_2 ($<$12–14 mL/kg/min), estimated to be of cardiac origin
All of the criteria must be present

6MWD, 6 min walk test distance; ESC, European Society of Cardiology; HF, heart failure; HFA, Heart Failure Association; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.

brachial vein, and the correct placement was evaluated by visualization of pressure curves with fluoroscopic confirmation when needed. Patients underwent haemodynamic evaluation during rest and during supine ergometer exercise. Ergometer resistance was increased with 20 W every 3 to 4 min until maximal effort was achieved. Maximal effort was determined by patients and physicians when patients were not able to maintain 60 revolutions/min on the ergometer at a given workload.

The invasive haemodynamic measurements collected included PCWP, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), CVP, and CO estimated by the thermodilution technique. Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were reported. All invasive haemodynamic pressures were measured at end-expiration by an independent haemodynamic core laboratory, blinded to all other data. More specifically for PCWP measurements, investigators were instructed to measure PCWP during end-expiration and print pressure tracing during measurements. These prints were sent to the core laboratory for analysis.

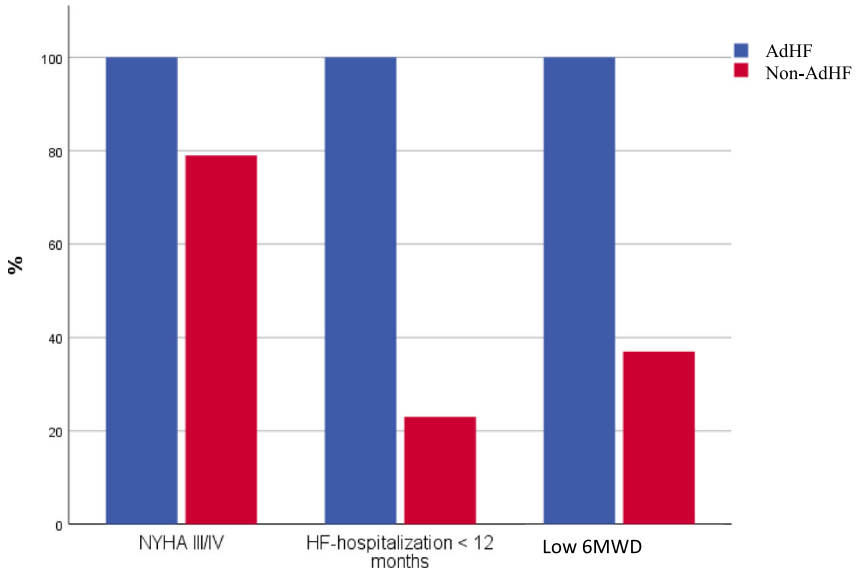
Mean arterial pressure (MAP) was calculated using the formula ([2 × DBP] + SBP)/3. Systemic vascular resistance (SVR) was calculated as 80 × (MAP − CVP)/CO. Body surface area (BSA) was calculated using DuBois formula and reported in m^2. CI was calculated as CO/BSA. Pulmonary vascular resistance (PVR) was calculated as (mPAP − PCWP)/CO and reported in Wood units. Stroke volume (SV) was calculated as CO/HR × 1000, and stroke volume index (SVi) as CI/HR × 1000. Pulmonary artery compliance (PAC) was calculated as SV/(sPAP – dPAP). Workload-corrected pulmonary capillary wedge pressure normalized to body weight (PCWL) was estimated by normalizing peak PCWP to number of Watts at peak exercise relative to body weight, where PCWL can be understood as the filling pressure required by the LV for the generation of 1 W for every kilogram the patient weighs. We calculated PCWP using the formula PCWP/(body weight × Watts).

Ejection fraction (EF) was determined by an independent echocardiographic core laboratory, blinded to all other clinical data.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD), and categorical variables as numbers (*n*) and percentages (%) unless indicated otherwise. To test for differences between groups, Student's *t*-test was applied to continuous data whereas a χ^2 test was used for categorical data. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was log transformed for analyses because it was not normally distributed and reported as median and interquartile range. Univariable logistic regression analysis was constructed to analyse the association between advanced HFpEF and selected resting haemodynamic parameters. Haemodynamic changes from baseline to maximum workload are reported as absolute delta (Δ)-values. Two-sided *P*-values were used, and a *P*-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (Version 27, IBM Corp.).

Figure 1 Proportion of HFpEF patients reaching the individual AdHF criteria. 6MWD, 6 min walk test distance; AdHF, advanced heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.



Results

The studied population consisted of a total of 108 well-characterized HFpEF patients from the REDUCE LAP-HF trial (n = 64) and the REDUCE LAP-HF I trial (n = 44). Twenty-four patients (22%) met AdHF criteria, whereas 84 (78%) did not. Of the 84 patients not meeting the AdHF criteria, 65 (77%) had not been hospitalized for HF within the last year, 57 (68%) walked 300 m or more during 6MWD, and 18 (21%) were in NYHA class II. A non-advanced HFpEF patient could have more than one AdHF criterion they did not meet. The proportions of patients satisfying the individual AdHF criteria are presented in *Figure 1*.

We further separated patients according to fulfilment of only prior HF hospitalization criteria and low 6MWD criteria. These data are presented in Supporting Information, *Table S1*.

Clinical characteristics

Clinical features are summarized in *Table 2*. The studied population was elderly, with a majority of female and obese patients, without significant divergences between the two groups in age, sex, or body mass index.

In our total cohort, 48 patients had an LVEF lower than 50% whereas 60 patients had an LVEF of more or equal to 50%. Comparing the two groups, we found that patients with AdHF had a higher mean LVEF (56 ± 10% vs. 51 ± 9%, P = 0.018) than patients without AdHF. There were no statistical differences in all other echocardiographic measurements. We further found that AdHF patients had lower haemoglobin levels (12.0 ± 2.1 vs. 12.9 ± 1.8 g/dL, P = 0.039) compared with patients who did not have AdHF. As expected, higher NYHA class was more prevalent in AdHF, because high NYHA class (III–IV) is one of the criteria for AdHF. The two groups did not differ with respect to any other clinical variables nor with respect to NT-proBNP levels. The burden of comorbidities was similar, although patients with AdHF had numerically (but not statistically significant) higher prevalence of chronic obstructive pulmonary disease. There were no significant differences between groups in medical treatment with loop diuretics, ACE-inhibitors, and angiotensin receptor antagonist.

Table 2 Clinical characteristics of the heart failure with preserved ejection fraction cohort

	Total		Non-AdHF	AdHF	*P*-
	N	(n = 108)	(n = 84)	(n = 24)	value
Age	*108*	70 ± 8	69 ± 9	72 ± 7	*0.067**
Sex (female)	*108*	64 (59%)	51 (61%)	13 (54%)	*0.565**
Weight (kg)	*108*	94 ± 22	92 ± 19	99 ± 31	*0.312**
BMI (kg/m^2)	*108*	33.7 ± 6.9	33.5 ± 6.1	34.3 ± 9.2	*0.640**
BSA (m^2)	*108*	2.0 ± 0.3	2.0 ± 0.2	2.1 ± 0.3	*0.263**
Comorbidities					
Atrial fibrillation	*108*	45 (42%)	34 (41%)	11 (46%)	*0.639**
COPD	*108*	16 (15%)	10 (12%)	6 (25%)	*0.111**
Diabetes	*108*	46 (43%)	36 (43%)	10 (42%)	*0.917**
Hypertension	97	91 (94%)	69 (95%)	22 (92%)	*0.615**
NYHA functional class					**0.009**
II	*108*	18 (17%)	18 (21%)	0	
III	*108*	89 (82%)	66 (79%)	23 (96%)	
IV	*108*	1 (1%)	0	1 (4%)	
Laboratory analysis					
eGFR (mL/min/1.73 m^2)	*107*	57 ± 21	59 ± 21	52 ± 17	*0.141**
Haemoglobin (g/dL)	*108*	12.7 ± 1.9	12.9 ± 1.9	12.0 ± 2.1	**0.039**
NT-proBNP (pg/mL), median (IQR)	*73*	390 (216–996)	354 (199–1076)	442 (243–930)	*0.663**
Echocardiography					
LVEF (%)	*108*	52 ± 10	51 ± 9	56 ± 10	**0.018**
LVEDVi (mL/m^2)	*107*	69 ± 21	69 ± 18	67 ± 30	*0.782**
LAi (mL/m^2)	*105*	39 ± 22	38 ± 17	43 ± 35	*0.341**
E/A ratio	*86*	1.5 ± 1.2	1.6 ± 1.3	1.2 ± 0.7	*0.235**
E/e′ ratio	*92*	15 ± 6	15 ± 6	15 ± 7	*0.924**
TAPSE (cm)	*96*	2.0 ± 0.3	2.0 ± 0.5	2.0 ± 0.5	*0.889**
Medications					
ACE-inhibitors	*90*	68 (76%)	56 (78%)	12 (67%)	*0.327**
Angiotensin receptor antagonist	*64*	48 (75%)	44 (79%)	4 (50%)	*0.081**
Beta-blockers	*97*	81 (84%)	66 (87%)	15 (71%)	*0.092**
Loop diuretics	*82*	53 (65%)	41 (67%)	12 (57%)	*0.405**

ACE, angiotensin-converting enzyme; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAi, indexed left atrium; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.

N defines the number of patients with obtained information in the category. Values are given as numbers and valid per cent [*n* (%)], as means with standard deviations (SDs), or as median or interquartile range (IQR).

*Not significant.

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Table 3 Haemodynamic features at rest and at exercise at maximum workload

	Non-AdHF	AdHF	*P*-value
Maximum workload (W)	45 ± 18	35 ± 16*	**0.021**
Exercise duration (min)	7.8 ± 3.2	7.0 ± 3.7	*0.315**
HR (b.p.m.)			
Rest	69 ± 13	73 ± 15	*0.251**
Exercise at maximum workload	99 ± 20	98 ± 19	*0.769**
ΔHR	30 ± 19	25 ± 19	*0.276**
SBP (mmHg)			
Rest	138 ± 24	138 ± 17	*0.947**
Exercise at maximum workload	162 ± 37	169 ± 31	*0.411**
ΔSBP	24 ± 37	31 ± 22	*0.253**
DBP (mmHg)			
Rest	71 ± 13	70 ± 11	*0.516**
Exercise at maximum workload	85 ± 22	83 ± 22	*0.671**
ΔDBP	14 ± 23	14 ± 17	*0.943**
MAP (mmHg)			
Rest	94 ± 15	92 ± 11	*0.723**
Exercise at maximum workload	111 ± 24	112 ± 22	*0.874**
ΔMAP	17 ± 25	20 ± 15	*0.626**
PCWP (mmHg)			
Rest	18.2 ± 6.4	20.0 ± 6.4	*0.229**
Exercise at maximum workload	35.3 ± 7.5	34.9 ± 6.9	*0.845**
ΔPCWP	17.3 ± 6.9	13.7 ± 7.6	**0.045**
mPAP (mmHg)			
Rest	25.2 ± 7.7	29.0 ± 8.9	**0.044**
Exercise at maximum workload	45.1 ± 10.4	48.0 ± 11.2	*0.239**
ΔmPAP	20.1 ± 7.7	18.8 ± 9.8	*0.497**
CVP (mmHg)			
Rest	9.0 ± 3.4	10.3 ± 3.3	*0.097**
Exercise at maximum workload	18.7 ± 5.9	19.0 ± 3.7	*0.701**
ΔCVP	9.7 ± 5.1	8.8 ± 3.4	*0.381**
CO (L/min)			
Rest	5.5 ± 1.7	6.0 ± 2.7	*0.225**
Exercise at maximum workload	8.8 ± 2.9	8.5 ± 3.7	*0.774**
ΔCO	3.2 ± 1.9	2.5 ± 1.8	*0.110**
CI (L/min/m^2)			
Rest	2.8 ± 0.7	2.9 ± 1.0	*0.540**
Exercise at maximum workload	4.4 ± 1.2	4.0 ± 1.1	*0.167**
ΔCI	1.6 ± 0.9	1.1 ± 0.7	**0.028**
SV (mL)			
Rest	81.1 ± 25.8	85.4 ± 41.1	*0.535**
Exercise at maximum workload	90.0 ± 28.4	88.8 ± 32.9	*0.887**
ΔSV	8.3 ± 21.2	4.8 ± 18.9	*0.486**
SVi (mL/m^2)			
Rest	40.7 ± 11.5	40.8 ± 16.9	0.983*
Exercise at maximum workload	45.0 ± 12.1	42.1 ± 12.1	*0.329**
ΔSVi	4.0 ± 10.6	2.3 ± 9.4	*0.513**
SVR (dynes × s/cm^5)			
Rest	1345 ± 416	1272 ± 412	*0.447**
Exercise at maximum workload	920 ± 342	1016 ± 395	*0.256**
ΔSVR	405 ± 368	238 ± 328	*0.053**
PVR (Wood units)			
Rest	1.4 ± 0.8	1.7 ± 1.1	*0.251**
Exercise at maximum workload	1.3 ± 1.2	2.0 ± 1.3	**0.013**
ΔPVR	0.1 ± 1.0	0.3 ± 1.1	*0.096**
PAC (mL/mmHg)			
Rest	4.0 ± 1.9	3.8 ± 2.2	*0.854**
Exercise at maximum workload	2.8 ± 2.1	3.0 ± 2.0	*0.735**
ΔPAC	1.3 ± 2.8	1.2 ± 1.5	*0.945**
PCWL (mmHg/W/kg)	85.9 ± 48.9	112.0 ± 55.1	**0.040**

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PCWL, workload-corrected PCWP normalized to body weight; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SV, stroke volume; SVi, indexed stroke volume; SVR, systemic vascular resistance.

Values are mean ± standard deviation. One non-advanced heart failure with preserved ejection fraction patient was not able to exercise, and the patient's data were not included in the workload analysis.

*Not significant.

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Resting haemodynamics

Haemodynamic resting and exercise features are presented in *Table 3*. There were no significant differences between groups in mean resting HR, SBP, DBP, and MAP, and these parameters were all within normal range; however, on average, patients in both subgroups were borderline hypertensive. Patients presented with elevated mean CVP, SVR, and PCWP but with no statistical differences between the AdHF and non-advanced groups.

Mean CI, SV, SVi, and PVR were within normal range, and neither of these values differed in group comparisons, although mPAP was higher in patients with AdHF. Patients included in the two studies were required to have elevated left-sided filling pressures either at rest (PCWP $\geq$ 15 mmHg) or during exercise (PCWP $\geq$ 25 mmHg). Thirty-three patients (31%) had normal left-sided filling pressures at rest (and high filling pressures during exercise), while 75 (69%) had elevated filling pressures at rest. There was a trend towards higher left-sided filling pressures at rest in the AdHF group where only 4 (17%) patients had normal resting filling pressures in contrast to the non-advanced group where 29 (35%) patients had normal resting pressures (P = 0.09).

We further analysed resting PCWP only in regard to increasing NYHA classification and found that patients in NYHA III–IV had a significant higher resting PCWP compared patients in NYHA II (19.1 ± 6.4 vs. 15.7 ± 6.1, P = 0.040).

In univariable logistic regression analysis, the association between advanced HFpEF and resting as well as peak CVP, CI, and PCWP was non-significant (Supporting Information, *Table S2*).

Exercise haemodynamics

Exercise duration for advanced HFpEF patients using the standard supine bicycle exercise protocol was 7.0 ± 3.7 min and for patients without AdHF 7.8 ± 3.2 min with no statistical difference between groups. The average number of step increasements performed was 1.8 ± 0.8 for AdHF and 2.2 ± 0.8 for non-AdHF (P = 0.13). Advanced HFpEF patients achieved a significantly lower maximum workload compared with non-advanced patients (35 ± 16 vs. 45 ± 18 W, P = 0.021). As the two groups achieved different workloads, we reported workload-corrected pulmonary capillary wedge pressure normalized to body weight (PCWL). Both patients with and without advanced HFpEF had an elevated PCWL compared with non-HF patients described by Maeder *et al.*,[9] but PCWL was significantly more abnormal in patients with advanced HFpEF (112 ± 55.1 vs. 85.9 ± 48.9 mmHg/W/kg, P = 0.04) (*Figure 2*). At maximum workload, PVR was significantly higher in advanced HFpEF patients compared with patients without advanced HFpEF (2.0 ± 1.3 vs. 1.3 ± 1.2 Wood units, P = 0.013). Patients with advanced HFpEF did not differ from non-advanced HFpEF patients with respect to peak exercise HR, SBP, DBP, MAP, mPAP, CVP, CI, PCWP, SV, SVi, and SVR.

Advanced HFpEF patients experienced a significant smaller increase in PCWP during exercise (P = 0.045). In contrast, a large difference in the increase in CI was demonstrated, with a 45% greater increase in non-advanced HFpEF patients compared with in advanced HFpEF patients (ΔCI 1.6 ± 0.9 L/min/m^2 vs. 1.1 ± 0.7, P = 0.028) (*Figure 3*).

Figure 2 PCWL in patients with AdHF compared with non-AdHF. PCWL, workload-corrected pulmonary capillary wedge pressure normalized to body weight.

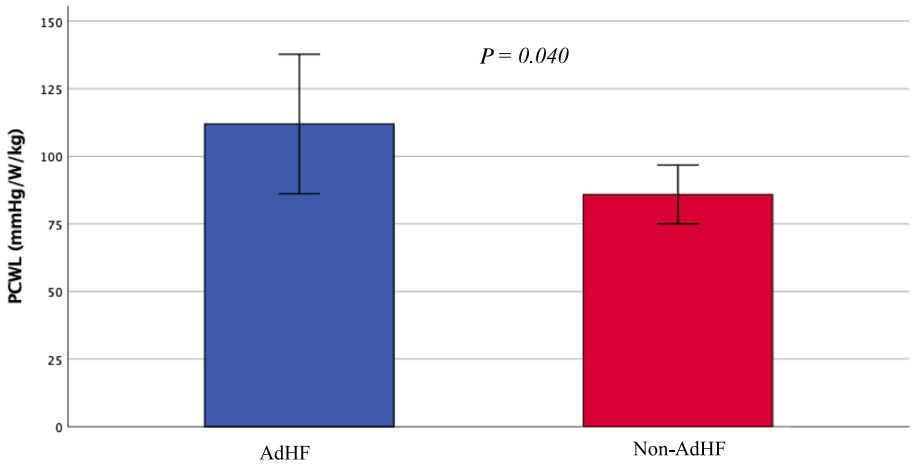
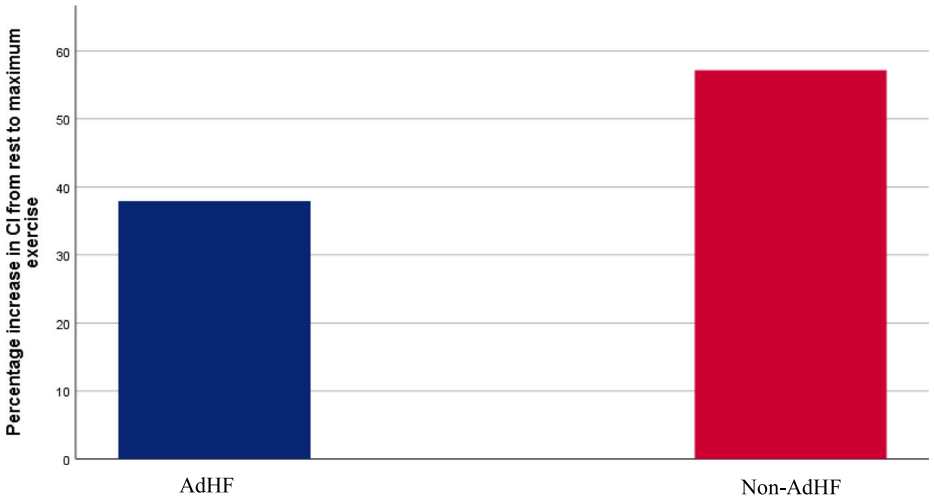


Figure 3 Percentage increase in CI from baseline to exercise at maximum workloads in patients with AdHF compared with non-AdHF. CI, cardiac index.



Discussion

This study is to our knowledge the first to describe haemodynamic features of patients with advanced HFpEF according to the recently established criteria by the HFA of ESC.

The main finding of the study is that HFpEF patients with AdHF have an altered haemodynamic exercise phenotype that was not evident at rest. First, peak exercise PCWP corrected for workload and weight (PCWL) was higher amongst patients with advanced HFpEF. Second, we observed a significantly more impaired ability for AdHF patients to increase CI during exercise compared with patients without AdHF. Hence, compared to patients without AdHF, patients with advanced HFpEF are not able to increase CO as much despite exposure of the LV to a higher filling pressure for the actual work required by the body.

This study reinforces the importance of invasive haemodynamic exercise testing, as there was no resting haemodynamic profile that could distinguish AdHF patients from patients without AdHF, nor a distinct clinical presentation of AdHF patients, except that they were, by the definition, more burdened by dyspnoea and prior HF hospitalization. A typical haemodynamic response in HFpEF is an excessive increase in cardiac filling pressures during exercise where resting filling pressures can be elevated or normal.[10] Prior studies have established a relationship between elevated exercise cardiac filling pressures and reduced exercise capacity, and the severity of exercise-induced dyspnoea in HFpEF is in line with the findings of the current investigation.[11,12] While resting CI is generally preserved in HFpEF, decreased CI reserve during exercise is well described and has been attributed to chronotropic incompetence and impaired SV reserve.[9,13,14] In the current study, we demonstrated a significantly lower rise in CI during exercise in patients with AdHF, but we could not determine whether inadequate SV, chronotropic incompetence, or both were responsible nor if it was due comorbidity resulting in lower workload achievement. We found that the point estimate for the increase in SVi in advanced HFpEF patients was almost two-fold lower during exercise compared with patients without advanced HFpEF, but the difference was not statistically significant likely owing to the variability in this measure. Larger studies are ongoing to assess this further.

Our HFpEF population had increased resting and peak PCWP with no statistically significant differences noted between groups. Analysing the haemodynamic changes from rest to maximum workload, AdHF patients experienced a significantly smaller increase in PCWP during exercise; however, this should be viewed in the context that AdHF patients had a numerically higher resting PCWP.

The exercise-induced altered haemodynamic response was not attributed to more pronounced systolic dysfunction in advanced HFpEF; that is, the AdHF group was not dominated by HF with mid-range ejection fraction (HFmrEF). On the contrary, we observed a significantly higher LVEF in this group. LVEF correlates poorly to patient symptoms, and while decreasing LVEF in HFrEF is a prognostic indicator for adverse cardiovascular outcome, this does not necessarily apply to HFpEF.[15] There were no significant differences between groups in all other echocardiographic parameters, even though the left atrium of the AdHF patients was numerically larger than that of patients without AdHF; it did not reach statistical significance. Larger studies may be able to detect a difference in atrial remodelling in advanced HFpEF, which would be consistent with greater haemodynamic impairment in these patients. NT-proBNP was numerically higher for advanced HFpEF patients however did not differ significantly, possibly explained by lack of power.

In a large study of patients with unexplained dyspnoea, Dorfs *et al*.[16] reported elevated cardiac filling pressures during exercise to be strongly associated with poor survival, even when resting pressures were normal. Moreover, they reported a significant increase in mortality risk with increasing PCWL. It should be noted, however, that the study by Dorfs *et al*. included patients with less deranged haemodynamics than those observed in our study and studies documenting that patients with advanced HFpEF per HFA-ESC criteria have a worse prognosis because of an impaired haemodynamic state are needed.

Obesity is frequent in HFpEF and known to correlate to exercise impairment.[17,18] Our cohort was burdened by obesity, but we did not find that AdHF patients tended to be more obese than non-AdHF.

Although there was no statistical difference between groups in medical treatment, there was a trend towards a lower medical use amongst patients with AdHF. This could suggest that advanced HFpEF patients have a lower tolerance to medical therapies; but this is speculative and should be explored further.

Heart failure with preserved ejection fraction is a complex disorder with a heterogeneous patient population, and identifying patients at increased risk of adverse outcome is challenging. No pharmacological intervention has proven effective in reducing mortality in HFpEF patients, but diuretics are recommended for relieving symptoms due to volume overload. Our study demonstrated altered haemodynamics during exercise with an increasing PCWL and a more impaired ability to increase CI as the symptom severity progressed to AdHF. Interventions should be focused not only on reducing high filling pressures but also on improving CI reserve. Milrinone, a phosphodiesterase type III inhibitor with vasodilatory and positive inotropic effects, could have a potential role in HFpEF treatment. Kaye *et al*.[19] showed that milrinone had favourable haemodynamic effects on PCWP and CI; however, larger and longer-term trials are needed to test the clinical efficacy. The finding that patients with AdHF have greater haemodynamic impairment both with respect to filling pressures and CI is also important when potentially considering advanced therapies for these patients such as mechanical circulatory support, cardiac transplantation, or total heart implantation, which will improve haemodynamics.[20,21]

Development of new, less invasive device-based treatments, including atrial shunts and circulatory support systems dedicated to HFpEF patients will require a better understanding of the haemodynamic response to exercise in patients with advanced symptoms in order to facilitate appropriate and rational patient selection. The current study provides the first attempt at this and highlights future directions of research, in particular that haemodynamic stress using exercise may be necessary in this patient population unlike the HFrEF population where resting haemodynamic evaluation is often sufficient. Defining AdHF in HFpEF is still in its infancy, and future studies are needed to test whether the HFA criteria mainly derived from studies of HFrEF patients will be applicable in clinical practice to HFpEF and HFmrEF patients. Possibly more objective criteria (especially pVO_2) for functional limitation and diastolic function will be helpful to better characterize this population. This study, as a start, demonstrated that invasive exercise haemodynamics were distinct in the group with AdHFpEF.

Limitations

The main limitations of the current study are limited sample size, especially of the advanced HFpEF population, and selection bias. Inclusion in the two studies depended on invasive evaluation with elevated PCWP at rest and/or during exercise. Invasive measurement is currently not mandatory in HFpEF diagnostics, and surrogate markers for increased left-sided filling pressure are used according to current ESC[6] and ACC/AHA guidelines.[22] The current study population is haemodynamically phenotyped and therefore likely has more abnormal haemodynamics and—given the inclusion criteria for the REDUCE LAP-HF studies—less right HF compared with an unselected cohort of HFpEF patients. This may limit the generalizability of our findings. Furthermore, an exclusion criterion was CI below 2 L/min/m^2, excluding patients with most advanced HF. The use of diuretics was remarkably low in the study population. Significant RV failure was an exclusion criterion for the trials, and consequently, patients with less tendency to fluid overload may have been selected as evidenced by the relatively low CVPs. This implies that the results of the study may not be applicable to HFpEF phenotypes dominated by significant fluid retention. Haemoglobin levels were significantly lower in the advanced group, and we cannot exclude that it could have had a small impact on the patients' exercise capacity.

Given the fact that exercise was supine and protocols were similar for, for example, large and small individuals, the reported maximal exercise capacity is likely not similar to that which could have been obtained during an upright bicycle test with an individualized ramp protocol. However, the protocol used ensured standardization of the load and the haemodynamic measurements during exercise. Caution should be made to extrapolate the exercise test findings from the current study (power) to exercise studies in HFpEF using different protocols.

The study was descriptive and exploratory, and no formal power calculations were performed. Further, multiple testing was undertaken without correction. We acknowledge that the findings of our study require confirmation in larger studies including more symptomatic HF (this is also supported by the fact that patients in higher NYHA class had significantly higher left-sided filling pressure).

Conclusions

Patients with advanced HFpEF according to the ESC-HFA criteria presented with higher workload-corrected filling pressures and a lower CI reserve than non-advanced HFpEF patients. The HFA criteria for AdHF appear to identify HFpEF patients with greater haemodynamic impairment. Current and future interventions to improve symptoms and outcome of the advanced HFpEF population need to target these specific haemodynamic perturbations.

Conflict of interest

F.G. has received research grants from the Novo Nordisk Foundation (NNF 20OC0060561) and honoraria from Abbott, Pfizer, Amgen, Bayer, Boehringer-Ingelheim, Pharmacosmos, Alnylam, Novartis, Astra-Zeneca, and Orion Pharma. J.K. is an employee of Corvia. S.J.S. has received research grants from Actelion, AstraZeneca, Corvia, Novartis, and Pfizer and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Axon Therapies, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiora, CVRx, Cytokinetics, Eidos, Eisai, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Sanofi, Shifamed, Tenax, and United Therapeutics.

Supporting information

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

Table S1. Supporting Information.
Table S2. Univariable logistic regression model for the association between advanced HFpEF and hemodynamic parameters.

References

1. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015; **175**: 996.
2. Vishram-Nielsen JKK, Deis T, Rossing K, Wolsk E, Alba AC, Gustafsson F. Clinical presentation and outcomes in women and men with advanced heart failure. *Scand Cardiovasc J* Taylor and Francis Ltd 2020; **54**: 1–8.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* Massachusetts Medical Society 2006; **355**: 251–259.
4. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, de Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, Mcdonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* Wiley 2018; **20**: 1505–1535.
5. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, Abouezzedine OF, Dunlay S, Mcnulty S, Chakraborty H, Stevenson LW, Redfield MM, Borlaug BA. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* Wiley 2020; **22**: 1009–1018.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Van der Meer P; ESC Scientific Document Group. 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 Heart J* 2016; 14;**37**(27): 2129–2200.
7. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, van der Heyden J, Lang I, Petrie MC, Cleland JGF, Leon M, Kaye DM. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* Elsevier BV 2016; **387**: 1298–1304.
8. Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der HP, Penicka M, Fail PS, Kaye DM, Petrie MC, Basuray A, Hummel SL, Forde-Mclean R, Nielsen CD, Lilly S, Massaro JM, Burkhoff D, Shah SJ. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients with Heart Failure]). *Circulation* Ovid Technologies (Wolters Kluwer Health) 2018; **137**:364–375.
9. Maeder MT, Thompson BR, Brunner-La Rocca H-P, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* Elsevier BV 2010; **56**: 855–863.
10. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* Springer Science and Business Media LLC 2014; **11**: 507–515.
11. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J* Oxford University Press (OUP) 2018; **39**: 2810–2821.
12. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Hear Fail* Elsevier BV 2018; **6**: 665–675.
13. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J* Oxford University Press (OUP) 2016; **37**: 3293.2–3293.3302.

14. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail* Wiley 2013; **15**: 776–785.
15. Solomon SD, Anavekar N, Skali H, Mcmurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* Ovid Technologies (Wolters Kluwer Health) 2005; **112**: 3738–3744.
16. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle R-P, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* Oxford University Press (OUP) 2014; **35**: 3103–3112.
17. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, Bonderman D. Functional status, pulmonary artery pressure, and clinical outcomes in heart failure with preserved ejection fraction. *J Am Coll Cardiol* Elsevier 2016; **68**: 189–199.
18. Edelmann F, Gelbrich G, Duvinage A, Stahrenberg R, Behrens A, Prettin C, Kraigher-Krainer E, Schmidt AG, Düngen HD, Kamke W, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Wachter R, Pieske B. Differential interaction of clinical characteristics with key functional parameters in heart failure with preserved ejection fraction—results of the Aldo-DHF trial. *Int J Cardiol* Elsevier 2013; **169**: 408–417.
19. Kaye DM, Nanayakkara S, Vizi D, Byrne M, Mariani JA. Effects of milrinone on rest and exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2016; **67**: 2554–2556.
20. Burkhoff D, Maurer MS, Joseph SM, Rogers JG, Birati EY, Rame JE, Shah SJ. Left atrial decompression pump for severe heart failure with preserved ejection fraction. *JACC Hear Fail* Elsevier BV 2015; **3**: 275–282.
21. Netuka I, Pya Y, Bekbossynova M, Ivak P, Konarik M, Gustafsson F, Smadja DM, Jansen P, Latrémouille C. Initial bridge to transplant experience with a bioprosthetic autoregulated artificial heart. *J Heart Lung Transplant*. Elsevier USA 2020; **39**: 1491–1493.
22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. *J Am Coll Cardiol* 2017; **70**: 776–803.