Determinants and consequences of heart rate and stroke volume response to exercise in patients with heart failure and preserved ejection fraction

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Abstract

Aims

A hallmark of heart failure with preserved ejection fraction (HFpEF) is impaired exercise capacity of varying severity. The main determinant of exercise capacity is cardiac output (CO), however little information is available about the relation between the constituents of CO - heart rate and stroke volume and exercise capacity in HFpEF. We sought to determine if a heterogeneity in heart rate and stroke volume response to exercise exists in patients with HFpEF and describe possible clinical phenotypes associated with differences in these responses.

Methods and Results

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Data from two prospective trials of HFpEF (n=108) and a study of healthy participants (n=42) with invasive hemodynamic measurements during exercise were utilized. Differences in central hemodynamic responses were analyzed with regression models.

Chronotropic incompetence was present in 39-56% of patients with HFpEF and 3-56% of healthy participants depending on the definition used, but some (n=47, 44%) had an increase in heart rate similar to that of healthy controls. Patients with HFpEF had a smaller increase in their stroke volume index (SVI) [HFpEF: +4±10 ml/m^2, healthy participants: +24±12 ml/m^2, p<0.0001], indeed, SVI fell in 28% of patients at peak exercise. Higher BMI and lower SVI at rest were associated with smaller increases in heart rate during exercise, whereas higher resting heart rate, and ACE-inhibitor/angiotensin II receptor blocker use were associated with a greater increase in SVI in patients with HFpEF.

Conclusion

The hemodynamic response to exercise was very heterogenous among patients with HFpEF, with chronotropic incompetence observed in up to 56% and 28% had impaired increase in SVI. This suggests that hemodynamic exercise testing may be useful to identify which HFpEF patients may benefit from interventions targeting stroke volume and chronotropic response.

Clinical Trial Registration

Clincaltrial.gov (NCT01913613, NCT02600234, NCT01974557)

Introduction

Patients with heart failure with preserved ejection fraction (HFpEF) have a reduced exercise capacity compared to healthy people[1,2]. A major determinant of the reduced exercise capacity in HFpEF is an impaired ability to increase cardiac output in response to peripheral demands during physical activity[3,4]. As cardiac output is the product of heart rate and stroke volume, both chronotropic incompetence and restrictive left ventricular filling are plausibly implicated[2,5]. Whether differences in these responses are present within the HFpEF population have not been fully explored. Hemodynamic studies in healthy people show that there is a substantial interplay between

heart rate and stroke volume during exercise; stroke volume increase initially during exercise but becomes blunted as high heart rates are attained towards the end of exercise[6,7]. However, despite the importance of reduced exercise capacity in HFpEF, relatively scarce information is available regarding the interplay between heart rate and stroke volume reserves and their impact on impaired exercise capacity in HFpEF. This may be due to the difficulty in measuring stroke volume accurately during exercise. Prior reports suggest a relatively high prevalence of impaired chronotropic response in patients with HFpEF[4,8–10]. However, little information is available regarding resting factors associated with impaired chronotropic response in HFpEF, or whether there are specific phenotypes or hemodynamic subsets within the HFpEF population. This information could improve our understanding of how to personalize therapy for an individual patient within the heterogeneous population with HFpEF[1,5,8,11,12]. Using invasive, exercise hemodynamic examination, the current study tested the hypothesis that clinical HFpEF phenotypes are different in patients with a reduced stroke volume reserve compared to patients who mainly suffer from chronotropic incompetence.

Methods

This study used baseline data from 2 clinical trials and one population study with invasive hemodynamic measurements during rest and exercise; Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF) trial, REDUCE LAP-HF I trial, and The Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans (HemReX) study[1,13,14]. Patients (n=108) and healthy participants (n=42) were recruited between 2013-2016. All

participants provided oral and written informed consent prior to enrollment. All studies were approved by relevant ethical committees and respected the Helsinki Declaration. The primary findings of the studies have been published[1,13,14]. All measurements from HFpEF patients in the 2 clinical trials were obtained prior to interatrial septum device (IASD) implantation.

HFpEF population

Patients with elevated pulmonary capillary wedge pressure (PCWP) either at rest or during exercise, and signs and symptoms of HF were included in two studies evaluating an IASD (IASD® system II, Corvia Medical, Inc. [Tewksbury, MA, USA]) (REDUCE LAP-HF: nonrandomized, open-label design. REDUCE LAP-HF I: randomized, sham controlled, double-blinded design). The primary objective of the trials was to assess the safety, hemodynamic effects, and efficacy of IASD implantation. Key inclusion criteria were: informed consent, New York Heart Association (NYHA) class II-IV, left ventricular ejection fraction (LVEF)≥40% determined by echocardiography, ≥ 1 HF hospitalization within last 12 months prior to screening and/or elevated natriuretic peptides, age ≥ 40 years, elevated left ventricular filling pressures with a gradient compared to central venous pressure (CVP) documented by ≥1 of the following: [end-expiratory PCWP or LV end-diastolic pressure (LVEDP) at rest ≥15 mmHg and greater than CVP] and/or PCWP during supine bike exercise ≥25 mmHg. Key exclusion criteria were: cardiac index ≤2.0 l/min/m^2, obstructive or restrictive cardiomyopathy, tricuspid annular plane systolic excursion (TAPSE) < 1.4 cm, moderate-severe heart valve disease, atrial fibrillation with resting heart rate >100 beats/min and dialysis or estimated glomerular filtration rate (eGFR) <25 ml/min/1.73m^2. As the inclusion criteria and the invasive protocol were similar, data was pooled from the two studies. Additional details on the trial designs have been published[15,16].

Healthy population

Sixty-two healthy subjects aged 20-80 years were enrolled in the original prospective study; however, only patients aged ≥40 years were included in the present study (n=42), as this was the age inclusion criteria for the REDUCE LAP-HF studies. Healthy subjects were deemed eligible if they fulfilled inclusion criteria; free from history of any acute or chronic cardiac or pulmonary disease; echocardiography without structural cardiac changes, depressed LVEF or significant valvular disease; normal spirometry for their age; routine blood chemistry test with normal values (including NT-proBNP); body mass index (BMI) 20-30 kg/m^2; and an exercise test with electrocardiogram (ECG) without any pathological findings. Additional details on study design have been published[1].

The protocols of all 3 studies were published on clinicaltrials.gov (NCT01913613, NCT02600234, NCT01974557) before subject enrollment.

Baseline data

Each subject underwent transthoracic echocardiography (TTE) at rest performed according to echocardiographic core laboratory standards at baseline. Blood samples were collected and analyzed according to standards used at each participating site.

Hemodynamic variables

Hemodynamic variables were measured at rest and during supine ergometer exercise in both HFpEF patients and healthy participants. Ergometer resistance was increased every 3-4 minutes with increments of either 20 watt (HFpEF) or 25 watt (controls) until maximal effort was achieved. In HFpEF patients, maximal effort/peak exercise was judged by patients and physicians when patients were not able to maintain 60 revolutions per minute on the ergometer at a given workload. In healthy participants, maximal effort was defined as 4 minutes of exercise with lactate buildup and objective signs of severe exertion at a workload corresponding to 75% of VO_2-max identified during a previous test on an upright ergometer, in accordance with the lower VO_2-max achievable

in a supine compared to an upright position[11]. Prior to invasive measurements, all healthy participants and a subset of patients (n=21, 19%) performed cardio-pulmonary exercise test until maximal exertion. A Swan-Ganz catheter was positioned in the pulmonary artery via the internal jugular or brachial vein. For all signals, 10 second segments were recorded. Signals were quantified by visual estimation of values at end-expiration. At rest, multiple beats (>3) were typically available, but often this was not the case during exercise with higher ventilatory frequency.

The following hemodynamic data were collected; CVP, mean pulmonary artery pressure (mPAP), PCWP, cardiac output using thermodilution technique (CO), non-invasive systolic blood pressure (SBP), non-invasive diastolic blood pressure (DBP), non-invasive peripheral oxygen saturation (SaO_2), and heart rate (HR). In addition, mixed venous oxygen (SvO_2) was sampled from the pulmonary artery.

Derived variables

Body surface area (BSA) was estimated using the Dubois formula. Cardiac index (CI) was calculated as CO/body surface area (BSA). Stroke volume indexed was calculated as CI/heart rate (HR). Heart rate reserve (HRR) was calculated as the difference between heart rate at peak exercise – heart rate at baseline. Workload-corrected PCWP (PCWL) was calculated as PCWP/(peak workload/body weight).

The maximal age-predicted peak heart rate during exercise was calculated using 2 different assumptions as suggested by Brawner et al.[17] [164 - (0.7 x age)] and Astrand et al.[18] [220 – age]. Chronotropic incompetence was either defined as a peak heart rate <80% of predicted using the Brawner equation, or according to the Astrand equation; <80% of predicted heart rate, or <62% if patients used betablockers[19].

Stroke volume reserve impairment was defined as changes in stroke volume from rest to peak exercise below the observed mean - 2SD in healthy participants.

Statistics

Data were summarized using mean SD, except NT-proBNP which was summarized as median [IQR]. Student's t-test and Wilcoxon rank-sum test was used to test for differences between groups. Univariable and multivariable linear regression models were used to analyze variables at rest associated with increases in cardiac index and heart rate (changes from rest to peak exercise) for the HFpEF group. Significant independent variables were identified using stepwise selection ($p<0.10$), adjusted for peak workload. Echocardiographic variables were not included in the primary multivariable analyses due to missing data, however a sensitivity analyses including patients with echocardiographic data was performed. To minimize collinearity issues no derived variables or indexed variables were included in the models apart from BMI. Mean pulmonary artery pressure and PCWP were collinear; therefore, only PCWP was used in the statistical models. The distribution of PCWL was right-skewed, and was log transformed prior to regression analysis. Included baseline variables were chosen based on their reported associations with stroke volume and/or heart rate.

HFpEF patients were divided into four groups depending on whether patients responded to exercise with a change in heart rate and stroke volume above or below the median. To identify independent variables that were significantly associated with each subgroup among HFpEF patients, logistic regression with stepwise selection ($p<0.10$) was used for each subgroup versus the rest of the HFpEF group. Estimates were reported as odds ratio (95% confidence intervals).

A p value of 0.05 was considered statistically significant. All analyses were conducted using STATA version 14 (College Station, TX).

Results

The examined group of patients with HFpEF were aged (70±8 years old), obese (BMI: 34±7 kg/m^2) and had a high comorbidity burden. A large proportion of patients were taking beta blockers (84%) and ACE inhibitors or angiotensin II receptor blockers (76%). Patients had high filling pressures and pulmonary arterial pressures at rest. These characteristics were significantly different than those of healthy participants as shown in Tables 1 and 2. The maximal watts achieved by HFpEF patients was significantly lower compared to healthy participants (HFpEF: 43±18 W, Healthy: 137±35 W, $p<0.001$).

Changes in heart rate and stroke volume in response to exercise

In *healthy* participants, the association between changes in heart rate (HRR) and stroke volume index between rest and peak exercise was linear and negative. A similar inverse association was observed in patients with HFpEF, but the intercept was lower compared to healthy participants (Figure 1). The change in stroke volume index in healthy participants was (mean±SD) +24±12 ml/m^2, compared to +4±10 ml/m^2 in HFpEF ($p<0.0001$). An impaired stroke volume reserve was observed in 28% HFpEF patients (stroke volume reserve < mean – 2SD of healthy participants [= 0 ml/m]). Seven patients (7%) had both a HRR and a stroke volume reserve below any of the healthy participants. In a sensitivity analysis, the association between changes in HRR and stroke volume index between rest and peak exercise was not different in patients with LVEF above or below 49% (Figure S1, supplemental data). This was also true, when healthy participants were age-matched with HFpEF patients including only healthy >60 years (n=20: mean age [95% CI]: Healthy 69 [67 – 72] years vs. HFpEF 72 [71 – 73] years, p=0.052), figure S2, supplemental data.

Chronotropic incompetence was present in 56% of HFpEF patients and 56% in healthy participants (p=0.94) when using the Astrand approximation. Using the Brawner equation, 39% (n=41) of HFpEF patients were chronotropic incompetent compared to 3% (n=1) of healthy participants (p<0.0001). There was no significant difference in the incidence of chronotropic incompetence depending on LVEF above (n=59, 55%) or below 49% (n=48, 45%) in HFpEF (data not shown). Some HFpEF patients (n=47, 44%) were able to increase their heart rate to the extent of healthy participants in response to peak exercise, but at the expense of a lower increase in their stroke volume index compared to healthy participants. Hence, 56% did not increase their heart rate to a level of healthy participants in response to peak exercise. A decrease in stroke volume was observed in 28% of HFpEF patients in response to exercise (Figure 1).

Patients with lower heart rate response, had higher workload-corrected PCWP [PCWL] (p<0.001), as depicted in Figure 2. Most HFpEF patients (99%) had a PCWL >25.5 mmHg/(watt/kg), compared to 5% of healthy participants. When grouped into tertiles of HRR, patients with lower HRR had higher RAP (p=0.05) and lower CI (p<0.05) and workload capacity (p=0.005) compared to patients with higher HRR (Table S3).

In linear regression analysis, each 1 beat increase in heart rate augmented cardiac output to the same extent as each 1 ml increase in stroke volume (ΔCI: 40 ml/min/m^2 per HR beat/SV ml change), which was observed for both healthy participants and HFpEF patients. Consequently, there were stepwise changes in cardiac index, depending on whether patients responded to exercise with a change in heart rate and stroke volume above or below the median. An additive effect of having the highest increases in both heart rate and stroke volume in response to exercise was observed (Figure 3).

Baseline characteristics associated with changes in heart rate during peak exercise

The univariable association of selected baseline characteristics with the heart rate response to peak exercise showed that higher resting heart rate, lower LVEDV, and beta blocker use were negatively associated with HRR. In a multivariable analysis, beta blocker use (p=0.06), higher age (p=0.06) and BMI, being male (p=0.07), and lower stroke volume also emerged as independent variables negatively associated with HRR (Table 3). In a sensitivity analysis only including patients with LVEF >49%, BMI, being male, and lower stroke volume emerged as independent variables (Table S5, supplemental data)

Baseline characteristics associated with changes in stroke volume during peak exercise

The univariable association of selected baseline characteristics with changes in stroke volume in response to exercise showed that resting heart rate and ACE inhibitor/angiotensin II receptor blocker use, E/A ratio, and LVEDV were positively associated with stroke volume reserve. In contrast, a higher stroke volume at rest was negatively associated with changes in stroke volume during exercise. In a multivariable model, ACE inhibitor/angiotensin II receptor blocker use, higher resting heart rate and right atrial pressure (p=0.09), and lower PCWP (p=0.07) emerged as independent variables positively associated with stroke volume reserve (Table 4). In a sensitivity analysis only including patients with LVEF >49%, ACE inhibitor/angiotensin II receptor blocker use and higher resting heart rate emerged as independent variables (Table S6, supplemental data) In an analysis including patients with echocardiographic variables present, a larger LVEDV and smaller TAPSE emerged as being negatively associated with stroke volume changes during exercise (Table S2). Patients using ACE inhibitor/angiotensin II receptor blockers had a larger increase in stroke volume index in response to exercise (+5.3±9.0 vs. +0.3±11.9 ml/m2, p=0.02) compared to patients not using. This was accompanied by a trend towards lower heart rate increases (26±18 vs. 33±22 bpm, p=0.09). No differences in BMI, workload or cardiac output at peak exercise were

observed between groups, whereas betablocker use was more prevalent in patients also using ACE inhibitor/angiotensin II receptor blockers (Table S4).

Baseline characteristics associated with changes in stroke volume and heart rate during peak exercise

Patients were grouped into 4 subgroups based on their hemodynamic response to exercise (ie. change in heart rate and stroke volume above or below the median.). This revealed that the following variables alone or in combination, were uniquely associated with specific hemodynamic profiles; resting heart rate, eGFR, ACE-inhibitor/angiotensin II receptor blocker use, beta blocker use, and age (Figure 4 and Table 5).

Discussion

We sought to determine if a heterogeneity in heart rate and stroke volume response to exercise exists in patients with HFpEF, compared with healthy controls. We observed that HFpEF patients – and healthy participants depending on the method used - were frequently chronotropic incompetent in response to exercise. Conversely, many HFpEF patients with a retained ability to increase their heart rate in response to exercise did so at the expense of impaired stroke volume responses.

Furthermore, we sought to identify whether principal differences in baseline characteristics of HFpEF patients exists between different hemodynamic profiles in response to exercise. When patients were grouped according to both their heart rate and stroke volume changes in response to exercise, different phenotypes emerged, suggesting that HFpEF patients differ with respect to their ability to increase stroke volume or cardiac output during exercise and that these phenotypes are identifiable at rest. This could potentially impact how we manage HFpEF patients. We examined

the interplay between chronotropic and stroke volume response to exercise adding knowledge of factors that limit functional capacity in this population. However, many other factors have also been found to affect functional capacity (e.g. BMI[20,21], left atrial function[22,23], PCWP[21,24,25], skeletal muscle dysfunction[26] etc.)

Chronotropic incompetence

A substantial proportion of patients were chronotropic incompetent. The Astrand approximation classified equally many HFpEF and healthy participants as being chronotropic incompetent, whereas the Brawner formula classified only one healthy as being chronotropic incompetent (n=1, 3%). The methods used to classify chronotropic incompetence differed in results, mostly with respect to healthy participants. Perhaps the models perform best in populations where chronotropic competency is impaired, rather than in healthy persons. However, as our data show, the chronotropic response to exercise was distributed over a wide spectrum of changes in heart rate, making absolute cutoffs (e.g. <80% of predicted maximal heart rate) less informative. Of note, LVEF did not affect estimates of chronotropic incompetence in HFpEF.

As heart rate increase is a physiological mechanism to augment cardiac output - and in turn increase exercise capability - an inability to produce a necessary chronotropic response would be expected to affect functional capacity. However, prior reported data are disparate with regard to the importance of chronotropic incompetence in HFpEF[2,4,5,8,21]. Non-cardiac factors such as BMI, peripheral oxygen uptake, intramuscular lipid content, and renal function have all been independently associated with exercise capacity[21,26–28]. Depending on the comorbid burden of various HFpEF populations examined, differences in the importance of central determinants such as heart rate have been observed. Most factors that were associated with chronotropic response (ie. age, stroke volume, beta blocker use) have previously been associated with functional capacity[1,28,29].

As our data show, there was a range amongst HFpEF patients with regard to the contribution of heart rate and stroke volume changes to increases in cardiac output. This emphasizes that there is heterogeneity in the central hemodynamic response to exercise in HFpEF patients. Obviously, having higher chronotropic and stroke volume responses yielded a higher cardiac output, but the question of the optimal interplay between these two factors in a given patient was not discernable in this study. Whether a lowering (ie. beta blocker use) or increase (ie. atrial pacing) in heart rate during exercise would provide a higher cardiac output remains to be determined. Our data suggests that the heterogeneity in observed hemodynamic response to exercise would mandate tailored approaches to chronotropic guided therapy. Trials examining effects of beta blockers [29] and ivabradine[30,31] on exercise capacity in HFpEF showed both increases and decreases in exercise capacity following intervention supporting our findings.

When the heart rate response at peak exercise was plotted against PCWL, a strong predictor of death in HFpEF[32], patients with lower HRR had higher PCWL. A high PCWL (i.e. >25.5) has been described as a poor prognostic marker[32] and was observed in 99% of patients compared to 5% of healthy participants.

Stroke volume

Restrictive left ventricular physiology was apparent in our HFpEF patients compared to the healthy participants, as left ventricular filling pressures were higher (which was expected since this was an inclusion criterion), and the ability to increase stroke volume during peak exercise was attenuated. Notably, changes in stroke volume also differed greatly between HFpEF patients and healthy participants and was tightly associated with heart rate response. But where stroke volume in healthy participants remained either stable or increased, stroke volume *decreased* during peak exercise in 28% of HFpEF patients, displaying an impaired stroke volume reserve.

Patients with the largest left ventricular end-diastolic volumes at rest displayed the smallest increases – often negative – in response to exercise. Perhaps the observed eccentric ventricular remodeling is a more advanced stage of HFpEF.

The large spectrum of differences in the relationship between changes in heart rate and stroke volume during peak exercise indicates that HFpEF patients may compensate for either chronotropic incompetence or impaired stroke volume reserve by augmenting one or the other in order to maintain an adequate cardiac output. Prior studies have eluded to this mechanism in healthy humans showing that the relationship between stroke volume and heart rate is dynamic during incremental exercise[6,33], and that experimentally controlled heart rate leads to inverse changes in stroke volume resulting in fixed cardiac outputs[34,35].

There was a significant higher increase in stroke volume in response to exercise in patients using ACE-inhibitor/Angiotensin II receptor blocker, whilst the increase in heart rate response tended to be lower. Of note, no differences in exercise capacity or cardiac output was found between users and non-users of ACE-inhibitor/Angiotensin II receptor blockers in line with larger interventional studies[36,37]. This complies with the notion of a dynamic shift between heart rate and stroke volume responses in order to maintain cardiac output.

Hemodynamic phenotypes

HFpEF patients were grouped according to their heart rate and stroke volume response during exercise, as observations suggested differences in the central hemodynamic responses to exercise. We sought to identify baseline characteristics known to affect exercise capacity that were independently associated with each subgroup. The following were identified: resting heart rate, age, renal function (eGFR) and use of beta blockers and ACE-inhibitor/angiotensin II receptor blockers. All these factors – except ACE-inhibitor/angiotensin II receptor blockers - have been implicated

previously in determining exercise capacity in various studies[1,9,29,30]. The size of our examined HFpEF group made it possible to confirm the associations of these variables to exercise capacity, but with greater granularity as to which hemodynamic profile they are associated with. This may explain some the disparate findings among previous reports. This hypothesis generating concept suggests that HFpEF patients may benefit differently from interventions aimed at afterload reduction and chronotropic manipulation based on their hemodynamic phenotype. For example, patients with higher increases in heart rate and stroke volume during exercise, may not benefit from beta blocker treatment. Notably, LV filling pressures (PCWP) both at rest and during exercise were not different between phenotypes.

Limitations

The inclusion criteria were in part based on LVEF≥40% which includes patients with heart failure with mid-range ejection fraction as defined in the recent ESC HF guidelines[38], however in sensitivity analysis our results were consistent in patients with LVEF below and above 50%. Thermodilution was used to measure CO. Dynamic tricuspid regurgitation during exercise was not assessed, and hence may have influenced these measurements. Importantly, hemodynamics were assessed during supine exercise, which alters the response of both SV and HR, and can shift the interrelationship between heart rate and stroke volume, compared to upright exercise which is what patients perform during most activities of daily living[39]. Furthermore, the maximal workload achievable during exercise was assessed by the physician and patient, which may have led to sub-maximal performance in some patients. Beta blocker use was prevalent in our population, making it difficult to generalize our findings to patients not using beta blockers. Our healthy controls were selected to have a BMI between 20-30 kg/m^2, whereas no BMI limit was imposed on the HFpEF patients as multiple population studies have shown HFpEF patients in general tend to be overweight/obese[40]. Based on the patient characteristics our population experienced moderate-

severe symptoms which should be considered when applying the findings to other patient populations.

Hemodynamic data were collected from 3 different trials, hence data collection from HFpEF patients and healthy subjects was not performed at the same laboratories. Of, note the exercise protocols were different between HFpEF patients and healthy participants.

Conclusion

Changes in heart rate and stroke volume in response to peak exercise vary in patients with HFpEF. HFpEF patients with a retained ability to increase their heart rate in response to exercise did so at the expense of an increase in stroke volume, with almost 1/3 of patients displaying negative changes, ie. an impaired stroke volume reserve. This suggests that invasive hemodynamic exercise testing may be useful to identify which HFpEF patients may benefit from interventions targeting stroke volume and chronotropic response.

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DB: Consultant to corvia for hemodynamic core laboratory.

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Table 1. Patient characteristics.

	Controls (n=42)	HFpEF (n=108)	p-value
Age	59±11	70±8	<0.0001
Sex (females)	22/20 (52% females)	64/44 (59% females)	0.44
BMI (kg/m2)	25±3	34±7	<0.0001
BSA (m2)	1.90±0.17	2.01±0.25	0.01
Medical history			
Atrial fibrillation	0	45 (42%)	<0.0001
COPD	0	16 (15%)	<0.0001
Diabetes	0	46 (43%)	<0.0001
NYHA class			<0.0001
II	N/A	18 (17%)	
III	N/A	89 (82%)	
IV	N/A	1 (1%)	
Heart rate (bpm)	63±9	70±14	0.005
Systolic BP	138±16	138±23	0.97
Diastolic BP	79±9	71±14	0.003
VO2-max (ml/kg/min)	32±7	16±4	<0.0001
eGFR (ml/min/1.73m2)	76±13	57±21	<0.0001
Hemoglobin (g/dl)	14±1	13±2	<0.0001
NT-proBNP (pg/ml)	59 [50, 120]	390 [218, 941]	<0.0001
Echocardiography			
LVEF (%)	62±7	52±10	<0.0001
LVEDVi (ml/m2)	70±16	69±21	0.72
LAi (ml/m2)	23±8	39±22	<0.0001
EA	1.2±0.4	1.5±1.2	0.11
E/e'	9±3	15±6	<0.0001
TAPSE (cm)	2.6±0.4	2.0±0.5	<0.0001
Medication			
Betablocker use	0	81 (84%)	<0.0001
ACEi/AT2rb use	0	68 (76%)	<0.0001
Loop diuretic use	0	56 (52%)	<0.0001

Table 2. Hemodynamic variables at rest.

	Controls (n=42)	HFpEF (n=108)	p-value
MAP (mmHg)	93±9	93±14	0.96
SVi (ml/m2)	43±8	41±13	0.24
CI (l/min/m2)	2.7±0.4	2.8±0.8	0.48
RAP (mmHg)	5±2	9±3	<0.0001
mPAP (mmHg)	15±3	26±8	<0.0001
PCWP (mmHg)	9±3	19±6	<0.0001
SVR (dyn x s/cm5)	1437±281	1329±415	0.13
PVR (Wood)	1.2±0.5	1.5±0.9	0.08

Table 3. The association of selected baseline characteristics with the heart rate response to exercise.

HRR (bpm)	Univariable		Multivariable	(R^2:0.20, p=0.001)
	Coefficient	p-value	Coefficient	p-value
Age (Y)	-0.3 (-0.7, 0.2)	0.26	-0.4 (-0.9, 0.0)	0.057
Female	1.0 (-6.5, 8.6)	0.79	6.5 (-0.6, 13.6)	0.07
BMI (kg/m^2)	-0.4 (-0.9, 0.1)	0.15	-1.0 (-1.6, -0.4)	0.001
Heart rate (bpm)	-0.5 (-0.7, -0.2)	0.001		
Stroke volume (ml)	0.09 (-0.03, 0.21)	0.15	0.15 (0.03, 0.27)	0.018
SysBP (mmHg)	-0.03 (-0.20, 0.13)	0.70		
DiaBP (mmHg)	0.01 (-0.29, 0.31)	0.94		
GFR (ml/min/1.73m^2)	0.1 (-0.1, 0.3)	0.16		
Hgb (g/dl)	0.8 (-1.2, 2.7)	0.44		
Diabetes (yes)	-2.8 (-10.3, 4.7)	0.46		
Atrial fibrillation (yes)	-1.7 (-9.4, 5.8)	0.65		
ACEi/AT2rb use (yes)	-6.5 (-14.1, 1.1)	0.09		
Beta blocker use (yes)	-9.2 (-17.6, -0.7)	0.03	-8.0 (-15.4, 0.3)	0.059
RAP (mmHg)	-0.9 (-2.0, 0.2)	0.10		
PCWP (mmHg)	-0.3 (-0.8, 0.3)	0.30		
LVEF (%)	0.2 (-0.2, 0.6)	0.33		
LVEDV (ml/m2)	0.2 (0.1, 0.4)	0.007		
LA volume (ml/m2)	0.05 (-0.13, 0.22)	0.60		
E/A	1.5 (-3.0, 6.0)	0.50		
E/e'	-0.4 (-1.0, 0.3)	0.29		
TAPSE (cm)	6.6 (-2.1, 15.2)	0.14		

The following baseline variables were included in the multivariable model prior to stepwise selection: age, sex, BMI, stroke volume (rest), systolic blood pressure, diastolic blood pressure, GFR, hemoglobin, atrial fibrillation and diabetes, use of ACE-inhibitor/angiotensin II receptor blocker or betablocker, right atrial pressure, and PCWP. Adjustments were made for peak watts obtained during exercise.

Table 4. The association of selected baseline characteristics with the changes in stroke volume in response to exercise.

ΔStroke volume (ml)	**Univariable**		**Multivariable**	**(R^2:0.28, p<0.0001)**
	Coefficient	**p-value**	**Coefficient**	**p-value**
Age (Y)	-0.2 (-0.7, 0.3)	0.35		
Female	-3.6 (-12.0, 4.7)	0.39		
BMI (kg/m^2)	0.2 (-0.4, 0.7)	0.59		
Heart rate (bpm)	0.5 (0.2, 0.8)	0.001	0.5 (0.3, 0.8)	0.0001
Stroke volume (ml)	-0.2 (-0.4, -0.1)	0.001		
SysBP (mmHg)	0.07 (-0.11, 0.25)	0.43		
DiaBP (mmHg)	0.14 (-0.18, 0.45)	0.40		
GFR (ml/min/1.73m^2)	0.1 (-0.1, 0.3)	0.27		
Hgb (g/dl)	0.9 (-1.2, 3.1)	0.38		
Diabetes (yes)	4.7 (-3.4, 12.9)	0.25		
Atrial fibrillation (yes)	-2.6 (-11.0, 5.8)	0.54		
ACEi/AT2rb use (yes)	9.3 (0.8, 17.8)	0.03	11.6 (4.0, 19.2)	0.003
Beta blocker use (yes)	8.6 (-1.0, 18.3)	0.08		
RAP (mmHg)	0.04 (-1.14, 1.22)	0.94	1.1 (-0.2, 2.4)	0.09
PCWP (mmHg)	-0.4 (-1.1, 0.2)	0.18	-0.6 (-1.3, 0.4)	0.07
LVEF (%)	-0.3 (-0.8, 0.1)	0.14		
LVEDV (ml/m2)	-0.4 (-0.6, -0.2)	0.0001		
LA volume (ml/m2)	-0.13 (-0.32, 0.05)	0.16		
E/A	-6.2 (-11.5, -0.9)	0.02		
E/e'	-0.1 (-0.9, 0.6)	0.71		
TAPSE (cm)	-2.0 (-11.3, 7.4)	0.67		

The following baseline variables were included in the multivariable model prior to stepwise selection: age, sex, BMI, heart rate (rest), systolic blood pressure, diastolic blood pressure, GFR, hemoglobin, atrial fibrillation, diabetes, use of ACE-inhibitor/angiotensin II receptor blocker or betablocker, right atrial pressure, and PCWP. Adjustments were made for peak watts obtained during exercise.

Table 5. The independent characteristic(s) that were significant to each hemodynamic subgroup (above or below median) are listed

Change in stroke volume	Change in Heart rate	Independent variables
Low	**Low**	**GFR**: OR 0.97 (0.94, 1.00), p=0.049 **HR – rest**: OR 0.95 (0.91, 1.00), p=0.037
Low	**High**	**No ACEi/AT2rb use**: OR 3.4 (1.3, 8.5), p=0.01 **HR – rest**: OR 0.96 (0.92, 1.00), p=0.039
High	**Low**	**HR – rest**: OR 1.08 (1.04, 1.13), p<0.0001
High	**High**	**Age**: OR 0.93 (0.87, 0.99), p=0.022 **No Betablocker use**: OR 3.8 (1.1, 13.5), p=0.041 **ACEi/AT2rb use**: OR 5.6 (1.34, 23.14), p=0.018

Figure 1: The association between changes in heart rate and stroke volume, from baseline (rest) to peak exercise. Red – HFpEF patients. Blue – Healthy participants.

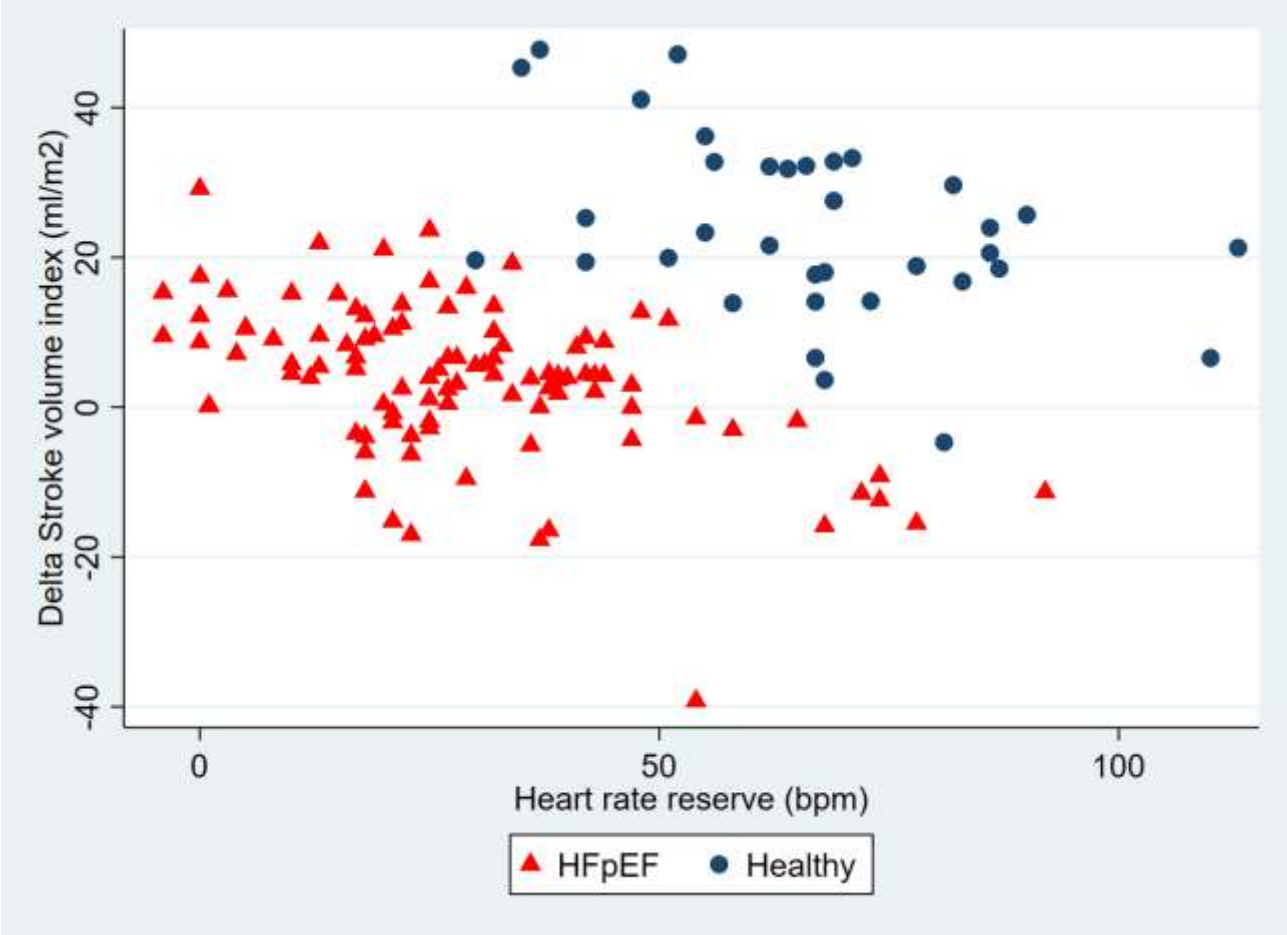

Figure 2: The association between changes in heart rate and workload-corrected pulmonary capillary wedge pressure (PCWL). Red – Patients with HFpEF. Blue – Healthy participants.

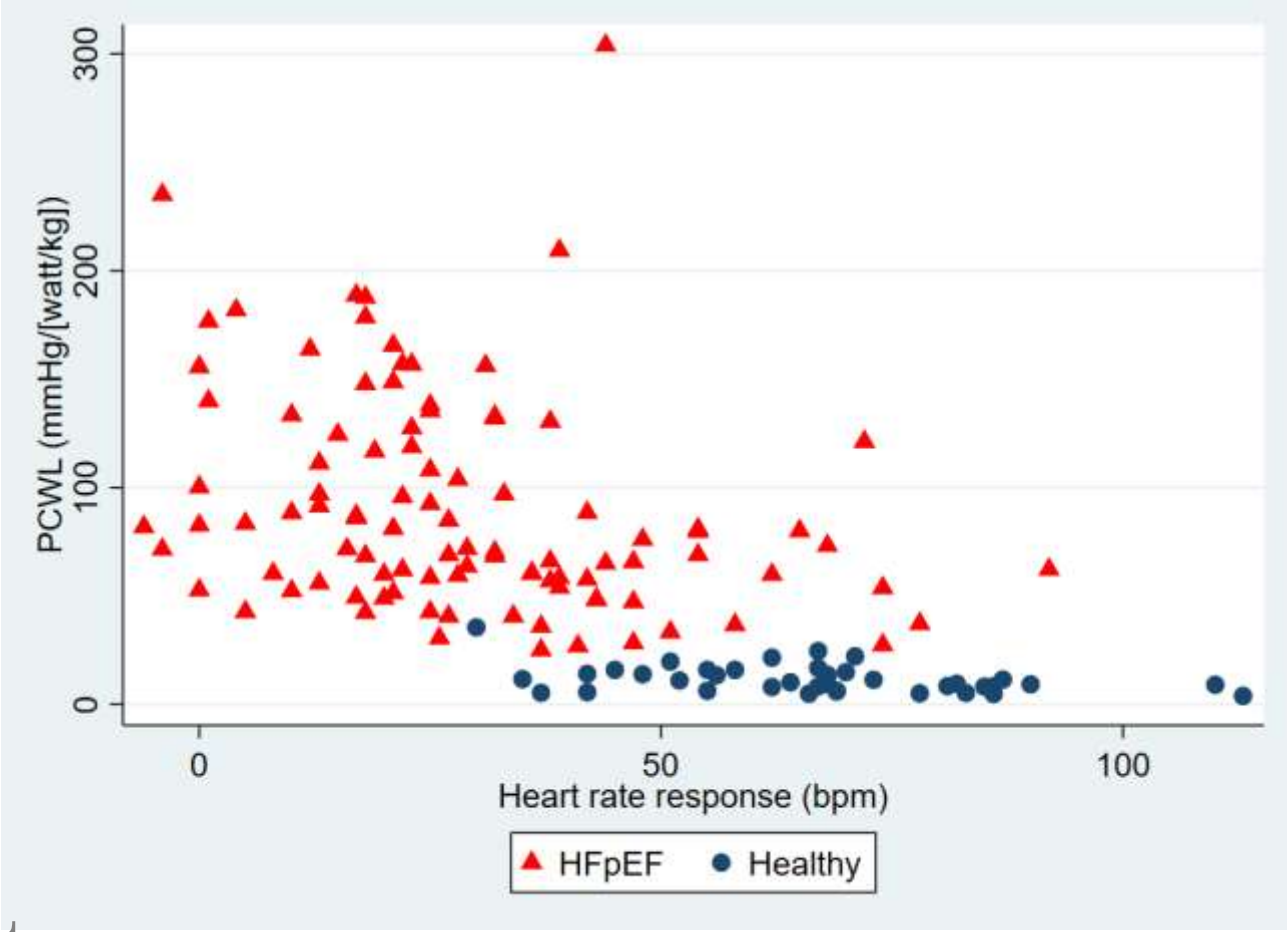

Figure 3. Changes in cardiac index from rest to peak exercise in HFpEF patients (red) grouped according to hemodynamic response (above or below median change) and in healthy participants (blue).

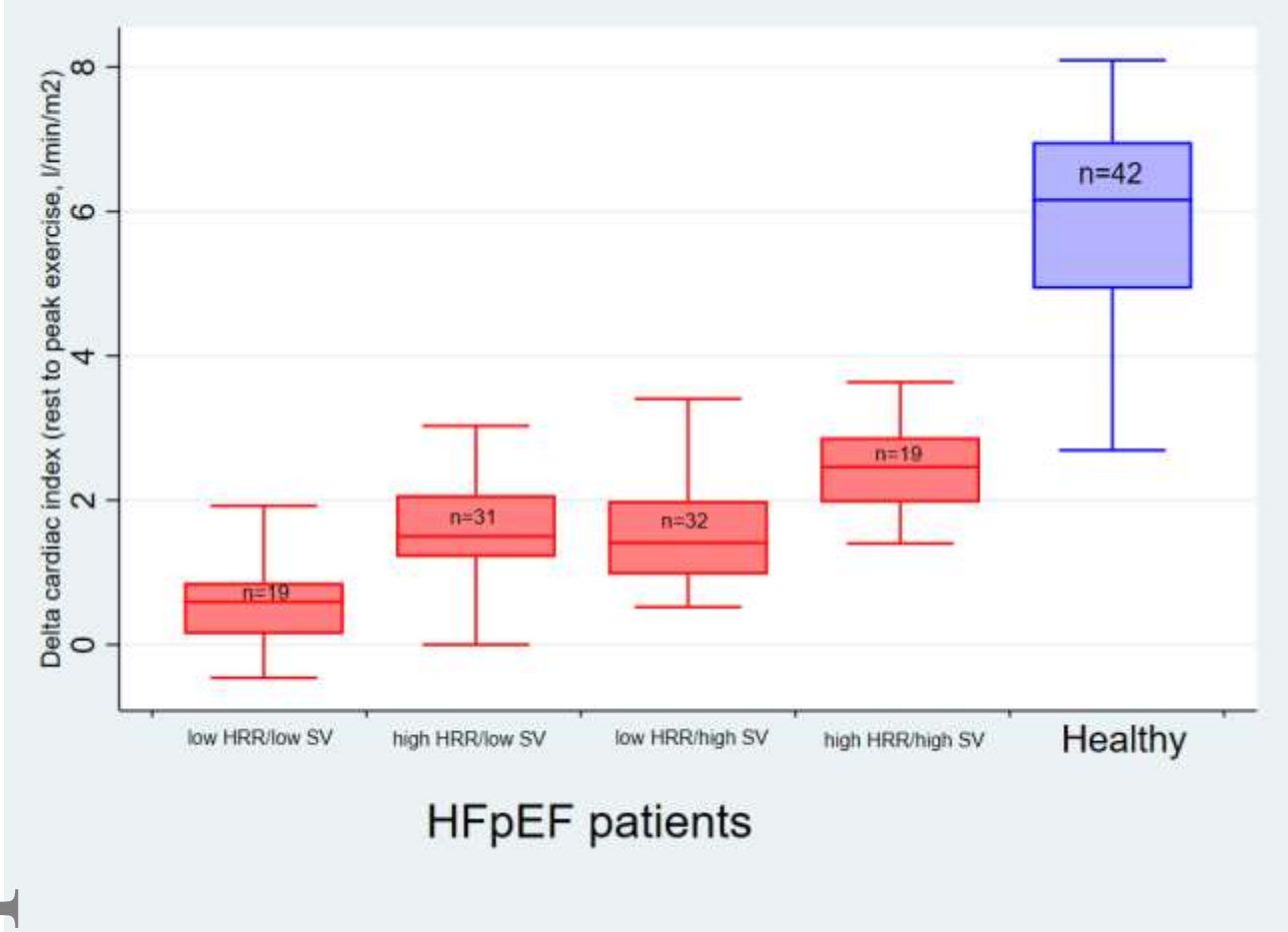

Figure 4. Schematic chart of patients grouped according to their hemodynamic response to exercise (above or below median change).