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

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Abstract

Aims To describe hemodynamic 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 hemodynamic 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-minute walk test distance < 300 meters. Twenty-four (22%) out of 108 patients met the AdHF criteria. On evaluation, clinical characteristics and resting hemodynamics were not different in the two groups. Patients with AdHF had lower work capacity compared to 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 to 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).

Conclusion A significantly higher PCWL and lower CI reserve during exercise was observed in AdHF patients compared to non-advanced. These differences were not apparent at rest. Therapies targeting the hemodynamic compromise associated with advanced HFpEF are needed.

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[2]. For patients with heart failure with preserved ejection fraction (HFpEF) which accounts for approximately half of all HF-cases in the western world[3], the correlation between hemodynamics 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 hemodynamic 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 hemodynamic state in advanced HFpEF, not just at rest, but also during exercise. Using data from two dedicated HFpEF studies incorporating invasive hemodynamic exercise testing, the aim of this

study was to characterize the hemodynamic profile of patients with AdHF as defined by the HFA and to test the hypothesis that patients with advanced disease present with a hemodynamic 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[78]. 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 < 2 L/min/m^2, evidence of pulmonary hypertension with PVR > 4 Woods Units, moderate to severe heart valve disease, infiltrative or hypertrophic cardiomyopathy, atrial fibrillation with resting heart rate >100 bpm (beats per minute), and dialysis or estimated glomerular filtration rate (eGFR) <25 ml/ min/1.73 m^2.

All patients had echocardiographic and invasive hemodynamic 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-minute walk test distance (6MWD) less than 300 meters. The studies

were approved by relevant ethics committees and in accordance with the declaration of Helsinki with informed consent obtained from patients before enrolment.

Hemodynamic evaluation

All patients underwent right heart catheterization with exercise hemodynamic 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 brachial vein and the correct placement was evaluated by visualization of pressure curves with fluoroscopic confirmation when needed. Patients underwent hemodynamic 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 hemodynamic measurements collected included: pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (mPAP), central venous pressure (CVP) and cardiac output (CO) estimated by the thermodilution technique. Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) was reported. All invasive hemodynamic pressures were measured at end-expiration by an independent hemodynamic 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 x DBP] + SBP) / 3. Systemic vascular resistance (SVR) was calculated as 80 x (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 was calculated as CO/HR x 1000, stroke volume index (SVi) as CI/HR x 1000. 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 Watt for every kg the patient weighs. **We calculated PCWP using the formula PCWP/(body weight x watts).**

Ejection fraction 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), categorical variables as numbers (n) and percentages (%) unless indicated otherwise. To test for differences between groups Student t-test was applied to continuous data whereas a Chi-square test was used for categorical data. NT-proBNP was log transformed for analyses since it was not normally distributed and reported as median and interquartile range. Univariable logistic regression analysis was constructed to analyze the association between advanced HFpEF and selected resting hemodynamic parameters. Hemodynamic changes from baseline to maximum workload are reported as absolute delta (Δ)-values. Two-sided p-values were used and a $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (Version 27, IBM Corp.).

Results

The studied population consisted of a total of 108 well-characterized HFpEF-patients from the REDUCE LAP-HF trial (n = 64) and 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 meters 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 fulfillment of only prior HF-hospitalization criteria and low 6MWD criteria. These data are presented in supplementary 1.

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 BMI.

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 hemoglobin-levels (12.0 ± 2.1 vs. 12.9 ± 1.8 g/dL, p = 0.039) compared to patients who did not have AdHF. As expected, higher New York Heart Association (NYHA) class was more prevalent in AdHF, since 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, though patients with AdHF had numerically (but not statistically significant) higher prevalence of COPD. There were no significant differences between groups in medical treatment with loop-diuretics, ACE-inhibitors and angiotensin receptor antagonist.

Resting hemodynamics

Hemodynamic 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 ≥ 15 mmHg) or during exercise (PCWP ≥ 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 analyzed 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 (supplementary 2).

Exercise hemodynamics

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 to 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 to 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 to 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 to in advanced HFpEF patients (ΔCI 1.6 ± 0.9 L/min/m^2 vs. 1.1 ± 0.7, *p = 0.028*) (Figure 3).

Discussion

This study is to our knowledge the first to describe hemodynamic 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 hemodynamic 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 to patients without AdHF. Hence, compared to patients with non-advanced HF, patients with advanced HFpEF are not able to increase cardiac output 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 hemodynamic exercise testing, as there was no resting hemodynamic 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 dyspnea and prior HF hospitalization. A typical hemodynamic 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 dyspnea 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 2-fold lower during exercise compared to 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. Analyzing the hemodynamic 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 hemodynamic response was not attributed to more pronounced systolic dysfunction in advanced HFpEF, i.e., the AdHF group was not dominated by HF with mid-range EF (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 remodeling in advanced HFpEF which would be consistent with greater hemodynamic 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 dyspnea, 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 hemodynamics 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 hemodynamic 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.

Though 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.

HFpEF is a complex disorder with a heterogenous 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 hemodynamics during exercise with an increasing PCWL and a more impaired ability to increase CI as the symptom severity progressed to AdHF. Interventions should not only be focused 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 favorable hemodynamic 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 hemodynamic 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 hemodynamics[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 hemodynamic 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 hemodynamic stress using exercise may be necessary in this patient population unlike the HFrEF population where resting hemodynamic 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 pVO2) for functional limitation and diastolic function will be helpful to better characterize this population. This study, as a start, demonstrated that invasive exercise hemodynamics 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 hemodynamically phenotyped and therefore likely has more abnormal hemodynamics and -given the inclusion criteria for the REDUCE LAP-HF studies- less right heart failure compared to an unselected cohort of HFpEF patients. This may limit the generalizability of our findings. Furthermore, an exclusion criterion was cardiac index 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. Hemoglobin-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 exercise was supine and protocols were similar for e.g. 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 hemodynamic 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 cardiac index reserve than non-advanced HFpEF patients. The HFA criteria for AdHF appear to identify HFpEF patients with greater hemodynamic impairment. Current and future interventions to improve symptoms and outcome of the advanced HFpEF population need to target these specific hemodynamic perturbations.

Disclosures

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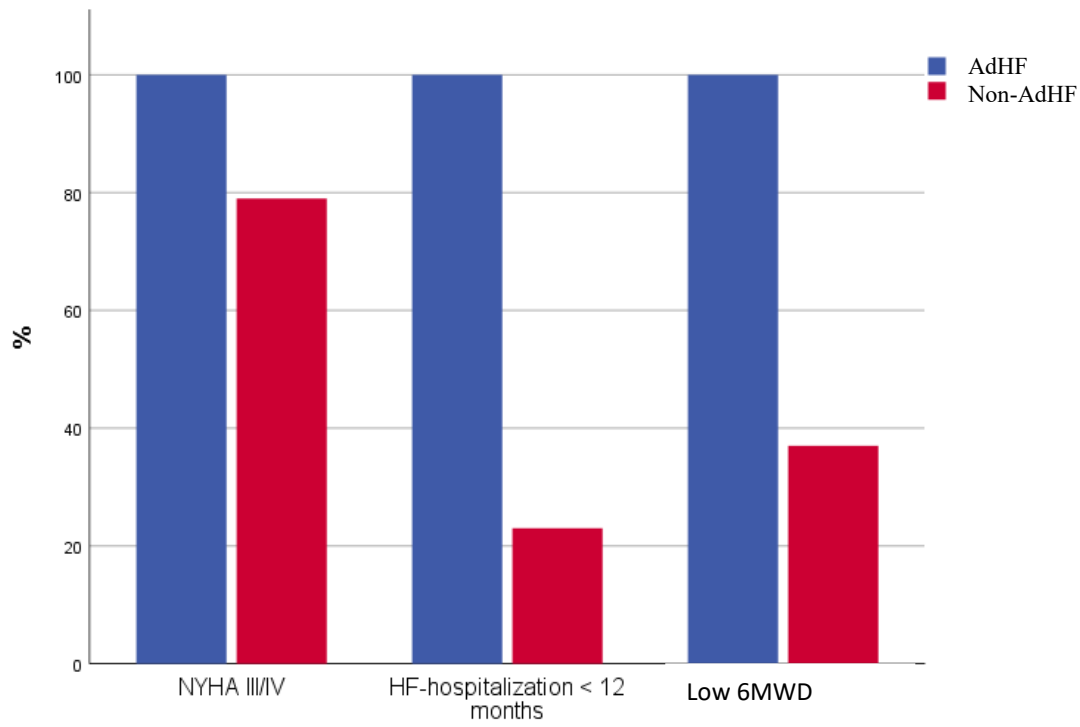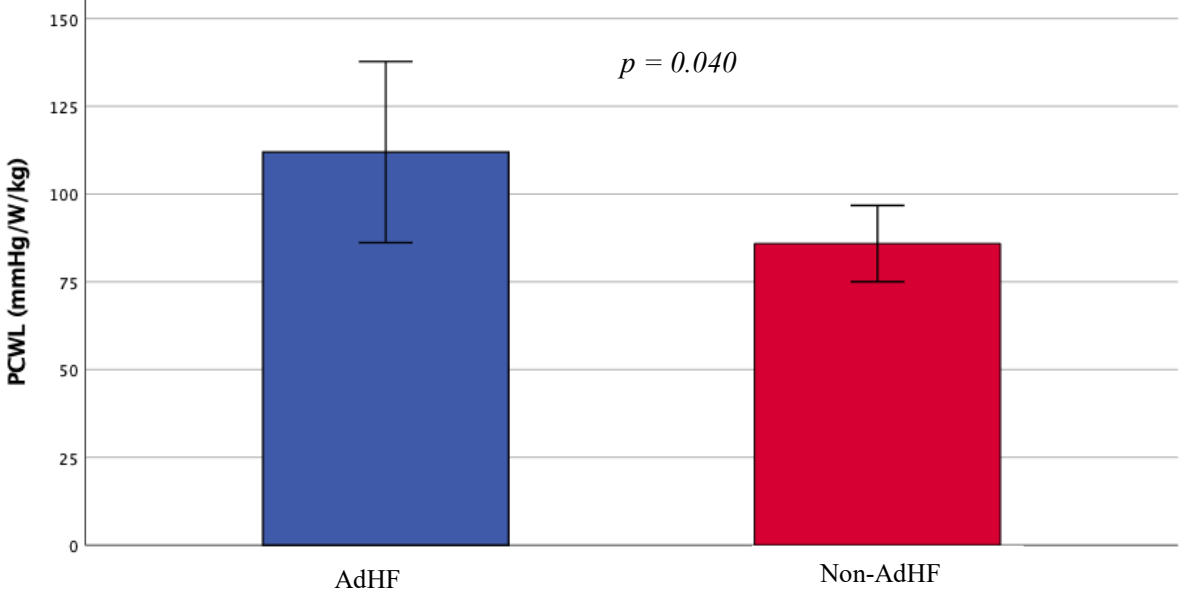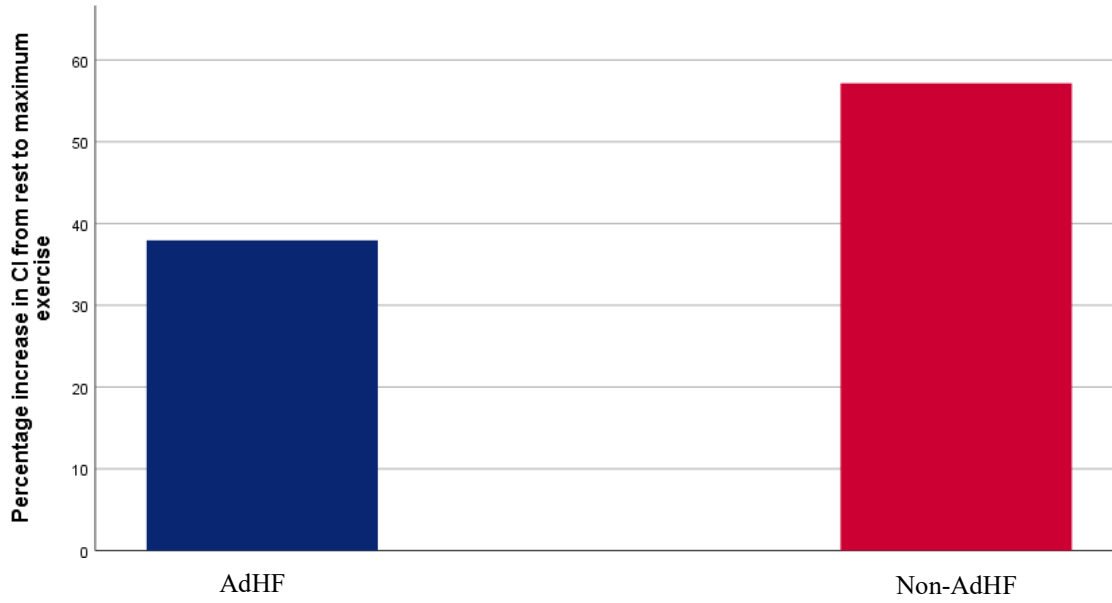**Figure 1:** Proportion of HFpEF patients reaching the individual AdHF criteria.

Figure 2: PCWL in patients with AdHF compared to non-AdHF

Figure 3: Percentage increase in CI from baseline to exercise at maximum workloads in patients with AdHF compared to non-AdHF