HHS Public Access

Author manuscript

Eur J Heart Fail. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Eur J Heart Fail. 2023 February ; 25(2): 185–196. doi:10.1002/ejhf.2747.

Central Hemodynamic Abnormalities and Outcome in Patients with Unexplained Dyspnea

Kazunori Omote, MD, PhD[1,2], **Frederik H. Verbrugge, MD, PhD**[1,3,4], **Hidemi Sorimachi, MD, PhD**[1], **Massar Omar, MD, PhD**[1], **Dejana Popovic, MD, PhD**[1], **Masaru Obokata, MD, PhD**[1], **Yogesh N. V. Reddy, MBBS, MSc**[1], **Barry A. Borlaug, MD**[1]

[1]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States;

[2]Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[3]Centre for Cardiovascular Diseases, University Hospital Brussels, Jette, Belgium;

[4]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium

Abstract

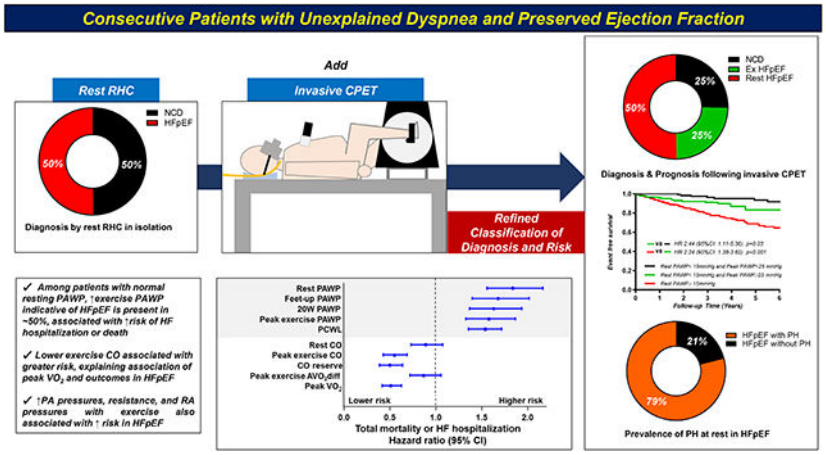
Aims: Little data is available regarding prognostic implications of Invasive exercise testing in heart failure (HF) with preserved ejection fraction (HFpEF). The present study aimed to investigate whether rest/exercise central hemodynamic abnormalities are associated with adverse clinical outcomes.

Methods and results: Patients with exertional dyspnea and EF≥50% (n=764) underwent invasive exercise testing and follow-up for HF hospitalization or death. There were 117 patients with events over a median follow-up of 2.7 (IQR 0.5–4.6) years. Among patients with normal resting PAWP (<15mmHg, n=380 [50%]), increased exercise PAWP (≥25mmHg, n= 187 [24%]) was associated with 2.4-fold higher risk of events compared to those with normal exercise PAWP (<25mmHg, n= 193 [25%]) (HR 2.44; 95%CI, 1.11–5.36; p=0.03), while patients with elevated resting PAWP (≥15mmHg, n=384 [50%]) displayed even higher risk compared to HFpEF with normal resting PAWP (HR 2.24; 95%CI, 1.38–3.65; p=0.001). Similar findings were observed for rest/exercise right atrial pressure, and rest/exercise pulmonary artery pressures. Higher peak VO_2 was associated with decreased risk of events, and this relationship was solely explained by exercise cardiac output. In a multivariable-adjusted Cox model, each 1 SD increase in exercise PAWP was associated with a 41% greater hazard of events (HR 1.41 [95% CI: 1.13–1.76]; p=0.002), while each 1 SD decrease in exercise CO was associated with a 37% increased risk (HR 0.63 [95% CI: 0.47–0.83]; p=0.001).

Conclusions: Hemodynamic abnormalities currently used for diagnosis of HFpEF are associated with increased risk for adverse events. Treatments that reduce central pressures while improving cardiac output reserve may offer greatest benefit to improve outcomes in HFpEF.

Graphical Abstract

Address for correspondence: Barry A. Borlaug, MD, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, Phone: 507-284-4442, Fax: 507-266-0228, borlaug.barry@mayo.edu.



Invasive exercise hemodynamic abnormalities currently used to diagnose or exclude HFpEF was also better for risk stratifications in patients with unexplained dyspnea. AVO_2diff, arterial-venous O_2 content difference; CO, cardiac output; CPET, cardiopulmonary exercise testing; HFpEF, heart failure with preserved ejection fraction; iCPET, invasive CPET; NCD, non-cardiac dyspnea; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PCWL, workload-adjusted PAWP; PH, pulmonary hypertension; RA, right atrial; RHC, right heart catheterization; VO_2, oxygen consumption.

Keywords

invasive hemodynamics; exercise hemodynamics; heart failure; heart failure with preserved ejection fraction; outcome

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is characterized by an inability of the heart to perfuse the body without pathological increases in cardiac filling pressures during exertion.[1–3] This is manifest by elevations in pulmonary artery (PA) wedge pressure (PAWP) during exercise, often associated with blunted cardiac output (CO) reserve,[4–6] impaired peripheral O_2 extraction and uptake in muscle (reduced arterial-venous O_2 content difference, AVO_2 diff),[7, 8] and impaired pulmonary vasodilation.[5, 6, 9] Collectively, these abnormalities interact to limit aerobic capacity (peak oxygen consumption, VO_2) and impair health status in people with HFpEF.[4, 10–12]

While the pathophysiologic significance of these hemodynamic abnormalities is self-evident, their prognostic implications are less well-understood. Elevated PAWP at rest or exercise is used for diagnosis of HFpEF,[2] and increases in PAWP indexed to workload[13] and CO[14, 15] have been associated with greater risk of adverse events, but the prognostic relevance of individual hemodynamic parameters that become abnormal in HFpEF and are used for clinical diagnosis are not well-described. Reduced peak VO_2 is associated with mortality in HFpEF.[16, 17] According to the Fick principle, VO_2 is equal to the product of

central (CO) and peripheral (AVO_2 diff) determinants, but no study has yet evaluated which components is most relevant to outcome in HFpEF.

The present study was undertaken to fill these gaps in the literature, assessing the prognostic value of rest and exercise hemodynamic variables currently used in practice to definitively diagnose or exclude HFpEF, in a large series of consecutive patients undergoing invasive hemodynamic exercise testing for the evaluation of unexplained dyspnea.

METHODS

Study Population

Patients undergoing invasive hemodynamic study during maximal effort supine exercise testing with simultaneous expired gas analysis for the evaluation of unexplained dyspnea at the Mayo Clinic, Rochester, MN, between 2006 and 2018 were retrospectively identified. HFpEF case status was defined by the presence of New York Heart Association (NYHA) functional class II-III dyspnea with activity, preserved left ventricular ejection fraction (LVEF) ≥50%, and elevated left heart filling pressures at rest (PAWP≥15mmHg) and/or with exercise (PAWP ≥25mmHg), fulfilling diagnostic criteria from current guidelines.[2] Patients with non-cardiac dyspnea (NCD) were defined as those with normal hemodynamics at rest and during exercise, including normal PAWP, mean PAP (mPAP) ≤20 mmHg and pulmonary vascular resistance (PVR) <3 WU at rest, and mPAP ≤30 mmHg or total pulmonary resistance <3 WU during exercise.[18]

Two-dimensional, M-mode, Doppler, and tissue Doppler echocardiography was performed according to the American Society of Echocardiography guidelines in all patients.[19] Those with any history of reduced ejection fraction (<50%), valvular heart disease (greater than moderate left-sided regurgitation, greater than mild stenosis), infiltrative, restrictive, or hypertrophic cardiomyopathy, constrictive pericarditis, primary pulmonary arterial hypertension (non-Group 2), and NYHA class IV were excluded. The study was approved by the Mayo Clinic Institutional Review Board and all participants provided consent for data use through completion of research authorization forms. All the authors had full access to the data and take responsibility for its integrity.

Catheterization Protocol

Patients underwent invasive hemodynamic exercise testing with simultaneous expired gas analysis during supine cycle ergometry to volitional exhaustion, using methods we have previously described.[5, 20] Right atrial (RA) pressure (RAP), PAP, and PAWP were measured at end-expiration at rest, and both at end-expiration and as an average of at least 3 respiratory cycles during exercise. For the primary analysis, exercise pressures are averaged over the respiratory cycle. The ratio of PAWP at peak exercise to workload normalized to body weight (PCWL [mmHg/watts/kg]) was calculated as described previously.[13] A 4–6 Fr radial arterial cannula was used to measure arterial blood pressure (BP) and obtain arterial blood gas samples throughout the test. Arterial venous O_2 difference (AVO_2 diff) was directly measured as the difference between systemic arterial and PA O_2 contents (=saturation×hemoglobin×1.34). Oxygen consumption (VO_2) was measured using expired

gas analysis (MedGraphics, St. Paul, MN), with values taken as the mean from 30 seconds preceding arterial and venous blood sampling in each phase. Cardiac output was calculated using the direct Fick method ($CO=VO_2/AVO_2$ diff). Pulmonary vascular resistance [PVR=(mean PAP-PAWP)/CO] and PA compliance (PAC=stroke volume/PA pulse pressure) were calculated. Total pulmonary resistance (TPR) was defined by the quotient of mean PAP/CO. While PVR is mainly determined by the resistance of the pulmonary vasculature, TPR is determined by downstream left atrial pressure, as well as PVR, and in many cases, dominated by LV filling pressures.

After baseline data were acquired, hemodynamic assessment and expired gas analysis were performed during exercise, starting at 20 W workload for 5 minutes, and increasing 20 W increments in 2–3 min stages to volitional exhaustion. Increases in PAWP and mean PAP were normalized to changes in CO during exercise (PAWP/CO slope, PAP/CO slope) by subtracting rest data from peak exercise data, with abnormal slopes defined as values >2 mmHg/l/min and >3 mmHg/l/min, respectively, based upon prior studies.[14, 15] A few patients (22 [2.9%]) experience reduction in CO with exercise, which would result in a negative slope. For these patients, we substituted +0.1 l/min for the change in CO with exercise for the purposes of outcome analysis, ensuring that these patients would be considered as abnormal, and divided the observed changes in PAWP or PAP by this denominator.

Outcome Assessment

Patient follow-up was initiated on the day of invasive hemodynamic cardiopulmonary exercise testing. Mortality data were ascertained from medical records, death certificates, obituaries, and notices of death in the local newspapers. Data on all deaths were obtained from the State of Minnesota annually. Heart failure hospitalizations were determined from the Mayo Clinic electronic medical record and adjudicated by a single cardiologist (K.O.). Patient follow-up was initiated on the day of cardiac catheterization. Patients were censored at last follow-up contact.

Statistical Analysis

Data are presented as mean ± standard deviation (SD), median (interquartile range, IQR) or number (%). Between-group differences were compared by unpaired t-test, Wilcoxon rank-sum test, $\chi 2$ or Fisher's exact test as appropriate. Event rates were compared using Kaplan–Meier curve analysis. Risk of the composite outcome was compared among 3 patient groups defined *a priori*: (1) NCD (normal rest and exercise hemodynamics, defined above), (2) HFpEF with normal resting PAWP (<15 mmHg), but abnormal exercise PAWP (≥25 mmHg), and (3) HFpEF defined by abnormal resting PAWP (≥15 mmHg). Risk was also compared in HFpEF based upon externally-validated diagnostic cutpoints, including leg raise PAWP≥ or <19 mmHg,[21] and by grouping patients with HFpEF by PAWP during exercise above and below the median. Similar comparisons were made using other hemodynamic measures in HFpEF above and below the group median values for other hemodynamic and O_2 transport measures, as compared to NCD. To further evaluate prognostic implications for hemodynamic abnormalities in a continuous manner, independent of partition values used to define the study groups (i.e., NCD or

HFpEF) univariable and multivariable Cox proportional hazards models were created to assess prognostic relationships independent of relevant baseline group differences including age, sex, body mass index, atrial fibrillation, EF, and estimated glomerular filtration rate. Integrated variables including PCWP/CO slope and mean PAP/CO with non-normal distributions were log-transformed. A two-sided *P* value of <0.05 was considered statistically significant. All data were analyzed using JMP14.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subject Characteristics

Consistent with multiple prior studies, patients with HFpEF were older, more obese, had more comorbidities, and displayed poorer kidney function and higher N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels compared to patients with NCD (Table 1). As compared to patients with HFpEF that became apparent only by exercise hemodynamics (Ex HFpEF; resting PAWP<15mmHg and exercise PAWP≥25mmHg), those with HFpEF evident at rest (rest HFpEF, resting PAWP≥15mmHg) were more obese, anemic and had higher NT-proBNP levels. The prevalence of PH (defined by mean PAP>20 mmHg) was 79% among patients with HFpEF overall, 63% among those with rest HFpEF and 16% among those with HFpEF diagnosed only during exercise. While LVEF was similar in all groups, patients with HFpEF displayed greater LV mass and impaired diastolic function with higher E/e' and larger left atrial volume index, these were more pronounced in patients with rest HFpEF as compared to Ex HFpEF. Subjects with rest HFpEF displayed more impaired RV systolic function as compared to subjects with Ex HFpEF and NCD (Table 1).

Baseline and Exercise Hemodynamics

Patients with HFpEF displayed higher central pressures, with lower CO at rest, where patients with rest HFpEF displayed more elevated central pressure as compared to Ex HFpEF (Table 2). With exercise, as compared to subjects with NCD, patients with HFpEF displayed greater increase in left- and right-side filling pressures and more blunted increased in CO with exercise, resulting in impaired functional capacity, and these changes were more pronounced in patients with rest HFpEF as compared to Ex HFpEF. Abnormalities in hemodynamics at peak exercise were similar at a common matched submaximal objective exercise workload (20W) (Supplemental Table 1).

Risk of Outcome by Categorical Hemodynamic Classifications

Over a median follow-up period of 2.7 years (IQR 0.5–4.6), 117 patients experienced the composite endpoint, including 61 deaths without HF hospitalization (8%) and 56 HF hospitalizations with or without death (7%). Patients with HFpEF and elevated resting PAWP (n=380 [50%]) displayed higher risk of events compared to NCD (n=193 [25%], HR 5.48; 95%CI, 2.75–10.9; p<0.0001) and to patients with normal resting PAWP (n=187 [24%], HR 2.24; 95%CI, 1.38–3.65; p=0.001) (Figure 1). However, patients with normal rest PAWP but elevated PAWP with exercise displayed a 2.4-fold greater risk of events as compared to NCD (HR 2.44; 95%CI, 1.11–5.36; p=0.03). Similarly, greater elevation in

PAWP during leg raise, low-level exercise (20W), and peak exercise were all associated with greater risk for adverse events in patients with HFpEF (Figure 1).

Patients with HFpEF and increasing PA and RA pressures at rest, low-level exercise, and peak exercise displayed progressively greater risk of adverse events, with both HFpEF groups displaying higher risk that patients with NCD (Figure 2, Supplemental Figures 1 and 2). Patients with worsening PAC compliance and PVR at rest and during exercise were also found to display higher risk for adverse events (Supplemental Figures 3 and 4).

Patients with HFpEF and peak VO_2 above the group median (>8.9 ml/min/kg, n=264) displayed higher risk of events than patients with NCD (HR 2.40; 95% CI, 1.13–5.08; p=0.03), and patients with HFpEF and peak VO_2 below the group median (≤8.9 ml/min/kg, n=263) displayed incrementally higher risk than HFpEF patients with peak VO_2 above the median (HR 2.61; 95% CI, 1.68–4.07; p<0.0001). There was no statistically significant association between resting CO (HR 0.80; 95% CI, 0.54–1.17; p=0.3) or resting AVO_2 diff (HR 0.88; 95% CI, 0.60–1.29; p=0.5) and risk of events in patients with HFpEF (Figure 3, Supplemental Figure 5). There was no association between exercise AVO_2 diff and event rates in patients with HFpEF (HR 1.37; 95% CI, 0.92–2.06; p=0.1) (Supplemental Figure 5), but lower cardiac output during exercise in HFpEF was associated with progressively greater risk (HR 2.35; 95% CI, 1.50–3.68; p=0.0002) (Figure 3).

Abnormal PAWP/CO slope (>2mmHg/l/min) and mPAP/CO slope (>3 mmHg/l/min) defined using established cutpoints did not differentiate risk among patients with HFpEF (HR 1.28; 95% CI, 0.72–2.25; p=0.4, and HR 1.23; 95% CI, 0.73–2.08; p=0.4, respectively) (Supplemental Figure 6). However, comparing groups according to median observed values in the HFpEF group revealed a trend for higher incidence of composite events with PAWP/CO slope >4.2 mmHg/l/min (HR 1.43; 95% CI, 0.94–2.15; p=0.09) and higher risk in those with mean PAP/CO slope >5.5 mmHg/l/min (HR 1.75; 95% CI, 1.15–2.67; p=0.009; Supplemental Figure 6).

Risk of Outcome by Continuous Hemodynamic Measures

When examined as continuous measures rather than by predefined groups, increasing PAWP, PA pressure, RA pressure, and PVR were all associated with increased risk of events, as was increasing PCWL, lower PA compliance and lower peak VO_2 (Table 3, Figure 4). In multivariable linear regression analyses, peak VO_2 was related to both exercise CO (β=0.94 per 1 l/min, p<0.0001) and exercise AVO_2 diff (β=0.56 per 1 ml/dl, p<0.0001). However, only exercise CO was associated with risk of adverse events (HR 0.55; 95% CI, 0.43–0.69; p<0.0001), as there was no association of risk and exercise AVO_2 diff (HR 0.87; 95% CI, 0.72–1.06; p=0.2) (Table 3, Figure 4). In an univariable Cox model, there were statistically significant associations between continuous values of log peak PAWP/CO slope, log peak mean PAP/CO slope and risk of events (HR 1.40; 95% CI, 1.21–1.60; p<0.0001 and HR 1.39; 95% CI, 1.20–1.61; p<0.0001, respectively) (Table 3, Figure 4).

In a multivariable Cox model, each 1 SD increase in PAWP, PCWL, RA pressure, mean and systolic PAP, resting PVR, and log peak PCWP/CO slope, and each 1 SD decrease in rest PA compliance and peak exercise CO remained significantly associated with risk for adverse

events after adjustment for age, sex, body mass index, atrial fibrillation, LVEF, hemoglobin and estimated glomerular filtration rate (Table 3).

Most associations between hemodynamics and risk of adverse outcome were consistently observed using pressures during exercise measured at end-expiration rather than an average of respiratory cycles (Supplemental Table 2). In a multivariable-adjusted Cox model, log mean PAP/CO slope measured at end-expiration was significantly associated with risk for adverse events (HR 1.18; 95% CI, 1.005–1.38; p=0.04), while the same variable using the average of respiratory cycles was no longer statistically significant (HR 1.16; 95% CI, 0.98–1.37; p=0.08).

DISCUSSION

The present study provides new insights into the prognostic implications of invasive exercise hemodynamic abnormalities currently used to diagnose or exclude HFpEF, from a large consecutive series of individuals with unexplained dyspnea (Graphical Abstract). The data reveal greater risk for adverse events as hemodynamic abnormalities at rest and with exercise worsen. Patients with elevated PAWP at rest display the greatest risk, but importantly, the presence of elevated PAWP during exercise or leg-rise is shown to be associated with increased risk of adverse events among patients with normal resting PAWP. In addition, we also provide a comprehensive analysis of all other hemodynamic data that are available from rest/exercise invasive testing, most particularly, cardiac output and AVO_2 difference reserve, as well as pulmonary vascular function and right heart filling pressures. Importantly, aerobic capacity, measured as peak VO_2, was correlated with both exercise CO and AVO_2diff, but only exercise CO was associated with adverse events, emphasizing the importance of CO reserve in HFpEF. These data further validate the importance of invasive exercise hemodynamics, expanding the clinical significance from diagnosis to include risk stratification. These data further emphasize the importance of limitations in CO reserve, in addition to elevated central hemodynamics as key treatment targets to improve clinical outcomes in HFpEF.

Prognostic Influence of Left Heart Filling Pressures

Hemodynamic abnormalities represent the physiologic force linking alterations in myocardial structure, function, and loading conditions to symptoms, functional impairment, and organ damage in HF.[22] In patients with HFpEF, increases in PAWP and PA pressure during exercise lead to development of lung congestion that acutely promotes dyspnea,[11, 23] chronically alters pulmonary vascular structure and function,[24–26] and eventually leads to development of clinically overt right-sided HF.[27, 28] In addition to congestive abnormalities related to high filling pressures, impairments in O_2 delivery to the tissues are also common in HFpEF, related to limitations in CO reserve, anemia, and abnormalities in pulmonary and skeletal muscle gas diffusion.[4, 12, 25] For these reasons, invasive exercise testing has emerged as the gold standard method to diagnose or exclude HFpEF,[1–3] and has further been proposed as a key method to help phenotype patients based upon physiologic responses to stress.[12]

Despite this established value for diagnosis and pathophysiologic phenotyping, there is less data available regarding the prognostic implications of exercise hemodynamics in HFpEF. Dorfs et al. first reported that elevation in PAWP indexed to workload during exercise was associated with increased risk of all-cause mortality.[13] While this observation has supported the importance of exercise PAWP elevation, it has remained unclear if the finding was driven more by PAWP elevation (numerator), or by the denominator of peak workload achieved during exercise, especially as it is well established that exercise capacity is also a powerful predictor of mortality.[16, 17, 29] Two separate studies demonstrated a that PAWP/CO slope>2 during upright exercise was associated with greater risk of cardiovascular events.[14, 15] As with the Dorfs study, it was again unclear whether the authors' finding was related to pathologic PAWP increase (numerator), blunted CO increase (denominator), or some combination of both.[14] The present study now resolves these questions. Importantly, among patients with normal PAWP at rest, those with abnormal increases in PAWP during exercise to currently-endorsed cutpoints (≥25 mmHg) displayed 2.4-fold greater risk for the combined endpoint of HF hospitalization or death compared to those without exertional PAWP elevation, providing further evidence to the diagnostic cutpoints for exercise PAWP in consensus guidelines.[2]

Aerobic Capacity, O_2 Transport, and Outcome

Peak VO_2 is well known to predict risk of adverse outcome in HFpEF, just as in HFrEF.[16, 17, 29] According to the Fick principle, VO_2 is equal to the product of CO and AVO_2diff. While both components are known to correlate with peak VO_2 in HFpEF,[4, 8, 12] to our knowledge, no study has yet reported on the prognostic impact of these individual determinants of VO_2 in this patient population. While resting PAWP and PA pressures were associated with outcome, we found that patients with HFpEF and low resting CO had similar risk of events as HFpEF patients with normal resting CO (Figure 3A). Conversely, impairments in CO reserve (i.e. the ability to augment CO with exercise) were strongly predictive of adverse outcome, similar to prior observations in HFrEF.[30, 31] Patients with HFpEF are well-known to display abnormalities in myocardial stress reserve with exercise, often despite apparently normal resting values,[32–34] explaining this limitation, and by confirming the prognostic impact of this reserve limitation, the current data reinforce the clinical significance for impairments in CO reserve in HFpEF.

In contrast to exercise CO, there was no association between AVO_2diff at rest or exercise and risk for adverse outcomes. Multiple (though not all) studies have shown that the ability to augment AVO_2 difference with exercise is blunted in patients with HFpEF, contributing to impairments in exercise capacity.[7, 8, 12] In the present study, we observed highly significant associations with peak VO_2, but no association between exercise AVO_2 difference. However, not all patients were able to attain an RER at peak exercise indicating a true "maximal" workload. This may result in lower AVO_2 difference as compared to what would be expected at higher RER, which could influence the prognostic value of peak AVO_2 difference. It should also be remembered that AVO_2 difference increases as CO decreases, because there is prolonged capillary transit time to allow for O_2 diffusion in the tissues, functioning as an "auto-correcting" adaptation to tissue hypoperfusion.[4, 12] It is also important to consider that relationships with HF hospitalizations or death are not equivalent to relationships

with exercise capacity, quality of life, or health status, and peripheral impairments are well-known to play important roles in these aspects of the HFpEF syndrome.[7, 8, 12]

Integrated Measures

Applying partition values previously shown to be associated with risk during upright exercise, mean PAP/CO slope (>3 mmHg/l/min)[15] and PAWP/CO slope (>2 mmHg/l/min)[14] were both associated with increased risk of events in univariate analysis in the overall group (i.e. including both NCD and HFpEF), but this was not maintained in the multivariable Cox analysis, except for mean PAP/CO using end-expiratory pressure.[14, 15] However, these slopes were determined based upon peak exercise and resting data alone, rather than through linear regression of multipoint pressure and flow measures throughout the totality of exercise, and this methodologic difference may explain some of the discrepant findings.

Other reasons for the different findings between the present study and the prior two studies[14, 15] are not clear, but may relate in part to differences in body position during exercise, and the method of deriving the pressure-flow slopes as well as differences in patient characteristics. The prior studies included patients who were much younger, less obese, and that displayed much lower comorbidity burden than in the present study, and also included a more heterogenous sample, including patients with other disease states such as precapillary pulmonary hypertension.[14, 15] In this study, the pressure-flow slopes derived relied on subtraction of peak from baseline values. This is quite distinct from the multiple matched PCWP and CO measurements used in these two studies, which may have less variability through use of repeated measures.

A potentially even more relevant difference is body position. The earlier studies were performed upright, whereas exercise was performed in the supine position in the present study. Pressures are lower at rest, and pulmonary vascular pressures increase in a more linear fashion during exercise when upright, but in the supine position, venous return is higher at rest and maximized earlier during exercise, such that pressures are higher at rest, rise more dramatically at lower workloads, and then tend to plateau, resulting in a curvilinear relationship.[35] While the absolute change of CO during exercise was similar in the present and the prior studies,[15] the increase in pulmonary vascular pressures was greater in the present study with supine exercise. This suggests that a higher cutpoint for PAWP/CO and mean PAP/CO slope may be necessary for supine exercise, and this is supported by the stronger associations with outcome using higher cutpoints (>4.2 mmHg/L/min, >5.5 mmHg/L/min) in the present analysis. However, even using these higher cutpoints, risk stratification using these integrated measures was not superior to using individual pressures or exercise CO measures and did not remain independently associated with outcome in the multivariable Cox modeling, with the exception of end-expiratory mean PAP/CO slope. This reinforces the importance of considering body position in the interpretation of invasive exercise hemodynamic data for both clinical and research purposes.

Limitations

Individuals participating in this study were referred for invasive testing at a tertiary referral center, which may introduce bias. The observational nature of the data does not provide

ability to discern causality in the associations with outcome. The NCD population was not truly normal in that they had prevalent comorbidities and by the fact that they were referred to invasive exercise stress testing for evaluation of exertional dyspnea, but this would only be expected to bias the results toward the null, as events would be expected to be less common in a cohort of completely healthy volunteers. Deaths and HF hospitalizations were identified and adjudicated through exhaustive chart review. While this captures events occurring within the Mayo Health system and other health systems that using the common EPIC electronic health record platform, it is possible that some events were not captured. While this may decrease our estimate for the annual event rate, this limitation applies equally to HFpEF and NCD patients, resulting in no bias regarding risk stratification. Many of the hemodynamic indices evaluated in this study may also be estimated noninvasively using echocardiography and magnetic resonance imaging in place of invasive testing, which may also have prognostic importance, but the variability and accuracy is less robust for these methods compared to invasive exercise testing. Pulmonary vascular pressure-flow relationships were estimated by subtracting resting pressures and CO from corresponding values at peak exercise, rather than by applying linear regression to multiple datapoints throughout all exercise stages as shown in the previous studies.[14, 15] While values estimated in this way would differ from regression-based estimates, this method better aligns with the analysis that is performed in clinical laboratories were multipoint linear regression is not used in reporting. Finally, as typically observed in practice, not all patients (cases and controls) were able to attain an RER>1.05 at peak exercise. This may result in lower CO and AVO_2 difference as compared to what would be expected at higher RER, which could influence the associations between CO and AVO_2 difference with outcomes.

Conclusions

Increases in PAWP at rest and during exercise to levels currently used for diagnostic evaluation of HFpEF are associated with increased risk of adverse events among patients with exertional dyspnea and preserved EF. Similar associations with adverse outcome exist for additional hemodynamic variables, including RA and PA pressure, and PA compliance at rest and during exercise. While resting CO does not discriminate risk in patients with HFpEF, limited ability to augment CO with exercise is independently associated with adverse outcomes and appears to principally explain the association between peak VO_2 and outcomes in HFpEF. These data provide new insight into the prognostic implications for hemodynamic abnormalities observed in patients with HFpEF and support their importance as therapeutic targets to improve outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the staff of the Mayo Clinic Earl Wood Catheterization Laboratory and the patients who agreed to participate in research, allowing for this study to be completed.

Sources of Funding

B.A.B. is supported by R01 HL128526 and U01 HL160226 from the NHLBI and W81XWH2210245 from the United States Department of Defense. H.S. is supported by a research fellowship from the Uehara Memorial Foundation, Japan. K.O. is supported by Japan Heart Foundation / Bayer Yakuhin Research Grant Abroad and the JSPS Overseas Research Fellowships from the Japan Society for the Promotion of Science. F.H.V. is supported by a Fellowship of the Belgian American Educational Foundation (B.A.E.F.) and by the Special Research Fund (BOF) of Hasselt University (BOF19PD04).

Disclosures

Dr. Borlaug receives research support from the National Institutes of Health (NIH) and the United States Department of Defense, as well as research grant funding from AstraZeneca, Axon, GlaxoSmithKline, Medtronic, Mesoblast, Novo Nordisk, and Tenax Therapeutics. Dr. Borlaug has served as a consultant for Actelion, Amgen, Aria, Axon Therapies, BD, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Eli Lilly, Imbria, Janssen, Merck, Novo Nordisk, NGM, NXT, and VADovations, and is named inventor (US Patent no. 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure.

References

1. Pfeffer MA, Shah AM and Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019;124:1598–1617. [PubMed: 31120821]
2. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P and Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297–3317. [PubMed: 31504452]
3. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020;17:559–573. [PubMed: 32231333]
4. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD and Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail. 2013;15:776–85. [PubMed: 23426022]
5. Borlaug BA, Kane GC, Melenovsky V and Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J. 2016;37:3293–3302.
6. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB and Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. Circ Heart Fail. 2015;8:278–85. [PubMed: 25550438]
7. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS and Lewis GD. Mechanisms of Exercise Intolerance in Heart Failure with Preserved Ejection Fraction: The Role of Abnormal Peripheral Oxygen Extraction. Circ Heart Fail. 2015;8:286–94. [PubMed: 25344549]
8. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM and Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol. 2011;58:265–74. [PubMed: 21737017]
9. Gorter TM, Obokata M, Reddy YNV, Melenovsky V and Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J. 2018;39:2825–2835. [PubMed: 29947750]
10. Reddy YNV, Olson TP, Obokata M, Melenovsky V and Borlaug BA. Hemodynamic Correlates and Diagnostic Role of Cardiopulmonary Exercise Testing in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2018;6:665–675. [PubMed: 29803552]
11. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC and Borlaug BA. Haemodynamics, dyspnea, and pulmonary reserve in heart failure with preserved ejection fraction. Eur Heart J. 2018;39:2810–2821. [PubMed: 29788047]
12. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD and Lewis GD. Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: Diagnosing and Ranking

Its Causes Using Personalized O2 Pathway Analysis. Circulation. 2018;137:148–161. [PubMed: 28993402]

13. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B and 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. 2014;35:3103–12. [PubMed: 25161181]
14. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R and Lewis GD. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail. 2018;11:e004750. [PubMed: 29695381]
15. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Farrell R, Sbarbaro JA, Schoenike MW, Houstis NE, Baggish AL, Shah RV, Nayor M, Malhotra R and Lewis GD. Exercise Pulmonary Hypertension Predicts Clinical Outcomes in Patients With Dyspnea on Effort. J Am Coll Cardiol. 2020;75:17–26. [PubMed: 31918830]
16. Guazzi M, Myers J and Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol. 2005;46:1883–90. [PubMed: 16286176]
17. Nadruz W Jr., West E, Sengelov M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H and Shah AM. Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. J Am Heart Assoc. 2017;6.
18. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grunig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A and Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J. 2017;50.
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39 e14. [PubMed: 25559473]
20. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V and Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017;135:825–838. [PubMed: 28039229]
21. van de Bovenkamp AA, Wijkstra N, Oosterveer FPT, Vonk Noordegraaf A, Bogaard HJ, van Rossum AC, De Man FS, Borlaug BA and Handoko ML. The Value of Passive Leg Raise During Right Heart Catheterization in Diagnosing Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2022;in press.
22. Verbrugge FH, Guazzi M, Testani JM and Borlaug BA. Altered Hemodynamics and End-Organ Damage in Heart Failure: Impact on the Lung and Kidney. Circulation. 2020;142:998–1012. [PubMed: 32897746]
23. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, Melenovsky V, Carter RE and Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. Eur Heart J. 2019;40 3721–3730. [PubMed: 31609443]
24. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM and Redfield MM. Global Pulmonary Vascular Remodeling in Pulmonary Hypertension Associated with Heart Failure and Preserved or Reduced Ejection Fraction. Circulation. 2018;137:1796–1810. [PubMed: 29246894]
25. Olson TP, Johnson BD and Borlaug BA. Impaired Pulmonary Diffusion in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2016;4:490–8. [PubMed: 27256752]
26. Jain CC, Tschirren J, Reddy YNV, Melenovsky V, Redfield M and Borlaug BA. Subclinical Pulmonary Congestion and Abnormal Hemodynamics in Heart Failure With Preserved Ejection Fraction. JACC Cardiovasc Imaging. 2021.
27. Melenovsky V, Hwang SJ, Lin G, Redfield MM and Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014;35:3452–62. [PubMed: 24875795]

28. Obokata M, Reddy YNV, Melenovsky V, Pislaru S and Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J. 2019;40:689–697. [PubMed: 30544228]
29. Guazzi M, Bandera F, Ozemek C, Systrom D and Arena R. Cardiopulmonary Exercise Testing: What Is its Value? J Am Coll Cardiol. 2017;70:1618–1636. [PubMed: 28935040]
30. Chomsky DB, Lang CC, Rayos GH, Shyr Y, Yeoh TK, Pierson RN 3rd, Davis SF and Wilson JR. Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. Circulation 1996;94:3176–83. [PubMed: 8989126]
31. Lang CC, Agostoni P and Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J Card Fail. 2007;13:672–9. [PubMed: 17923361]
32. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD and Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56:845–54. [PubMed: 20813282]
33. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A and Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 2009;54:402–9. [PubMed: 19628114]
34. Burrage MK, Hundertmark M, Valkovic L, Watson WD, Rayner J, Sabharwal N, Ferreira VM, Neubauer S, Miller JJ, Rider OJ and Lewis AJM. Energetic Basis for Exercise-Induced Pulmonary Congestion in Heart Failure With Preserved Ejection Fraction. Circulation. 2021.
35. Hasler ED, Muller-Mottet S, Furian M, Saxer S, Huber LC, Maggiorini M, Speich R, Bloch KE and Ulrich S. Pressure-Flow During Exercise Catheterization Predicts Survival in Pulmonary Hypertension. Chest. 2016;150:57–67. [PubMed: 26892603]
36. Vanderpool RR, Saul M, Nouraie M, Gladwin MT and Simon MA. Association Between Hemodynamic Markers of Pulmonary Hypertension and Outcomes in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol. 2018.
37. Al-Naamani N, Preston IR, Paulus JK, Hill NS and Roberts KE. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015;3:467–74. [PubMed: 26046840]
38. Huang W, Oliveira RKF, Lei H, Systrom DM and Waxman AB. Pulmonary Vascular Resistance During Exercise Predicts Long-Term Outcomes in Heart Failure With Preserved Ejection Fraction. J Card Fail. 2017;24:169–176. [PubMed: 29180305]
39. Malhotra R, Dhakal BP, Eisman AS, Pappagianopoulos PP, Dress A, Weiner RB, Baggish AL, Semigran MJ and Lewis GD. Pulmonary Vascular Distensibility Predicts Pulmonary Hypertension Severity, Exercise Capacity, and Survival in Heart Failure. Circ Heart Fail. 2016;9:pii: e003011. doi: 10.1161/CIRCHEARTFAILURE.115.003011. [PubMed: 27301469]
40. Reddy YNV, Obokata M, Koepp KE, Egbe AC, Wiley B and Borlaug BA. The beta-Adrenergic Agonist Albuterol Improves Pulmonary Vascular Reserve in Heart Failure With Preserved Ejection Fraction. Circ Res. 2019;124:306–314. [PubMed: 30582447]

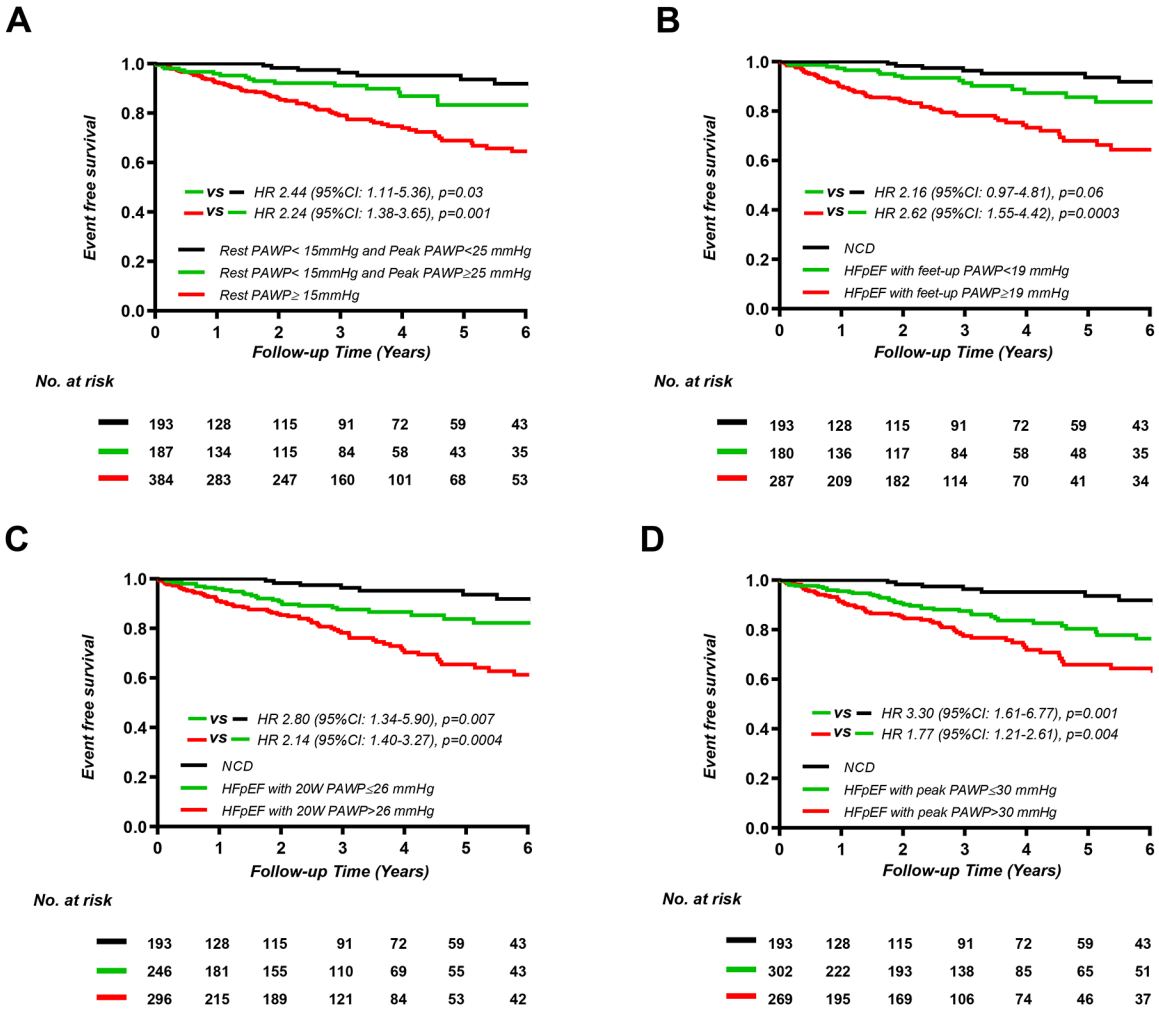


Figure 1.

Kaplan-Meier analysis for composite of all-cause death and heart failure hospitalization categorized by current cutoff point of diagnosis or median values of pulmonary artery wedge pressure (PAWP) (A) at rest (n=764), (B) feet-up (n=660), (C) 20W exercise (n=735), and peak exercise (n=764). HFpEF, heart failure with preserved ejection fraction; NCD, non-cardiac dyspnea.

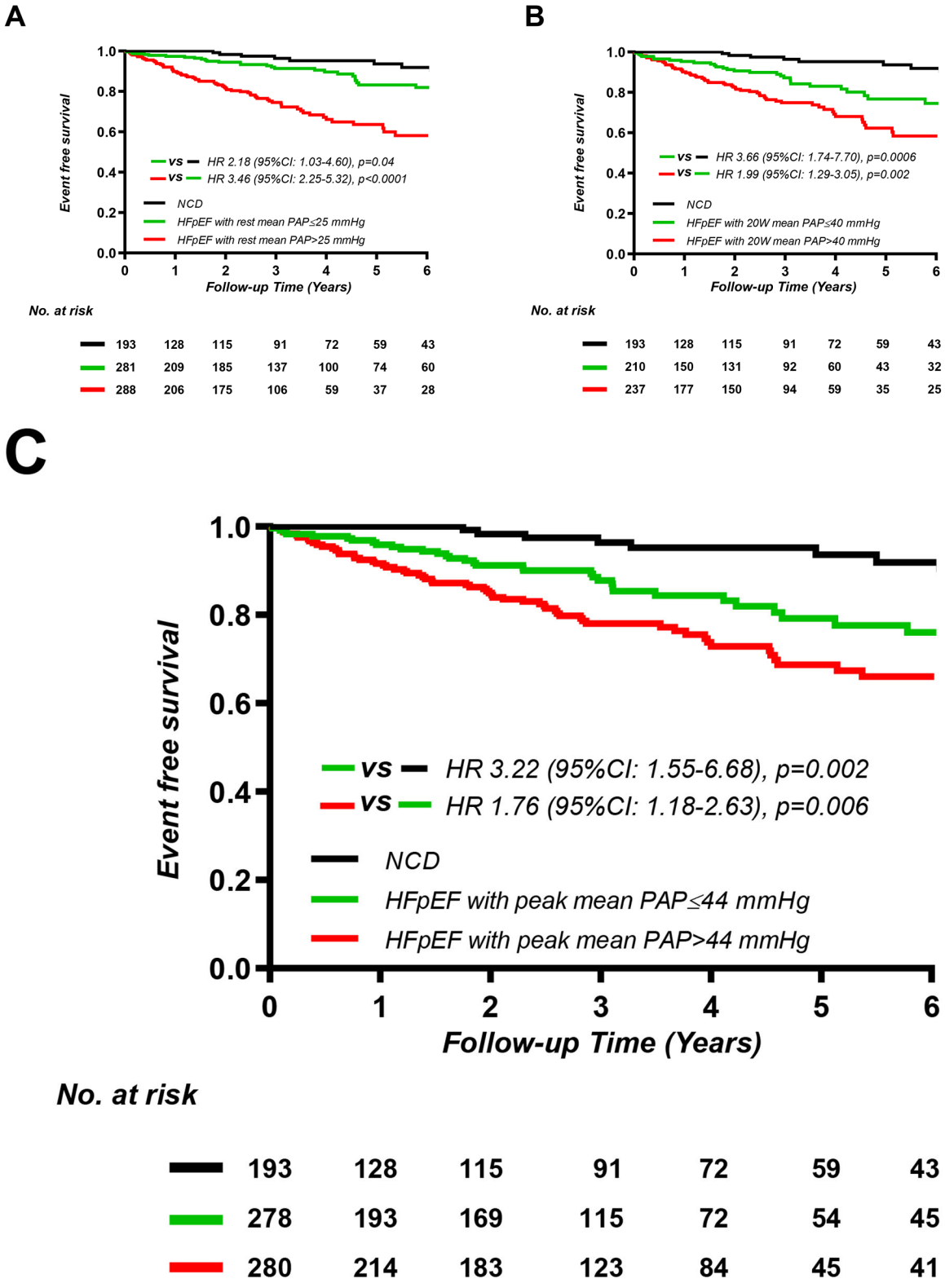


Figure 2.

Kaplan-Meier analysis for composite of all-cause death and heart failure hospitalization categorized by median values of mean pulmonary artery pressure (PAP) (A) at rest (n=762), (B) 20W exercise (n=640), and peak exercise (n=751).
HFpEF, heart failure with preserved ejection fraction; NCD, non-cardiac dyspnea

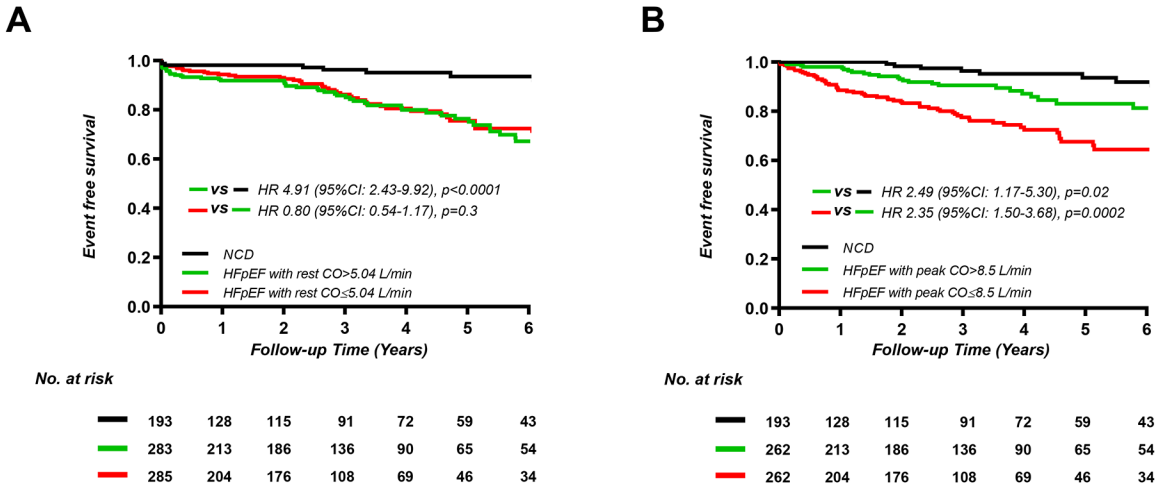


Figure 3.

Kaplan-Meier analysis for composite of all-cause death and heart failure hospitalization categorized by median values of cardiac output (CO) (A) at rest (n=761), (B) peak exercise (n=717).

HFpEF, heart failure with preserved ejection fraction NCD, non-cardiac dyspnea.

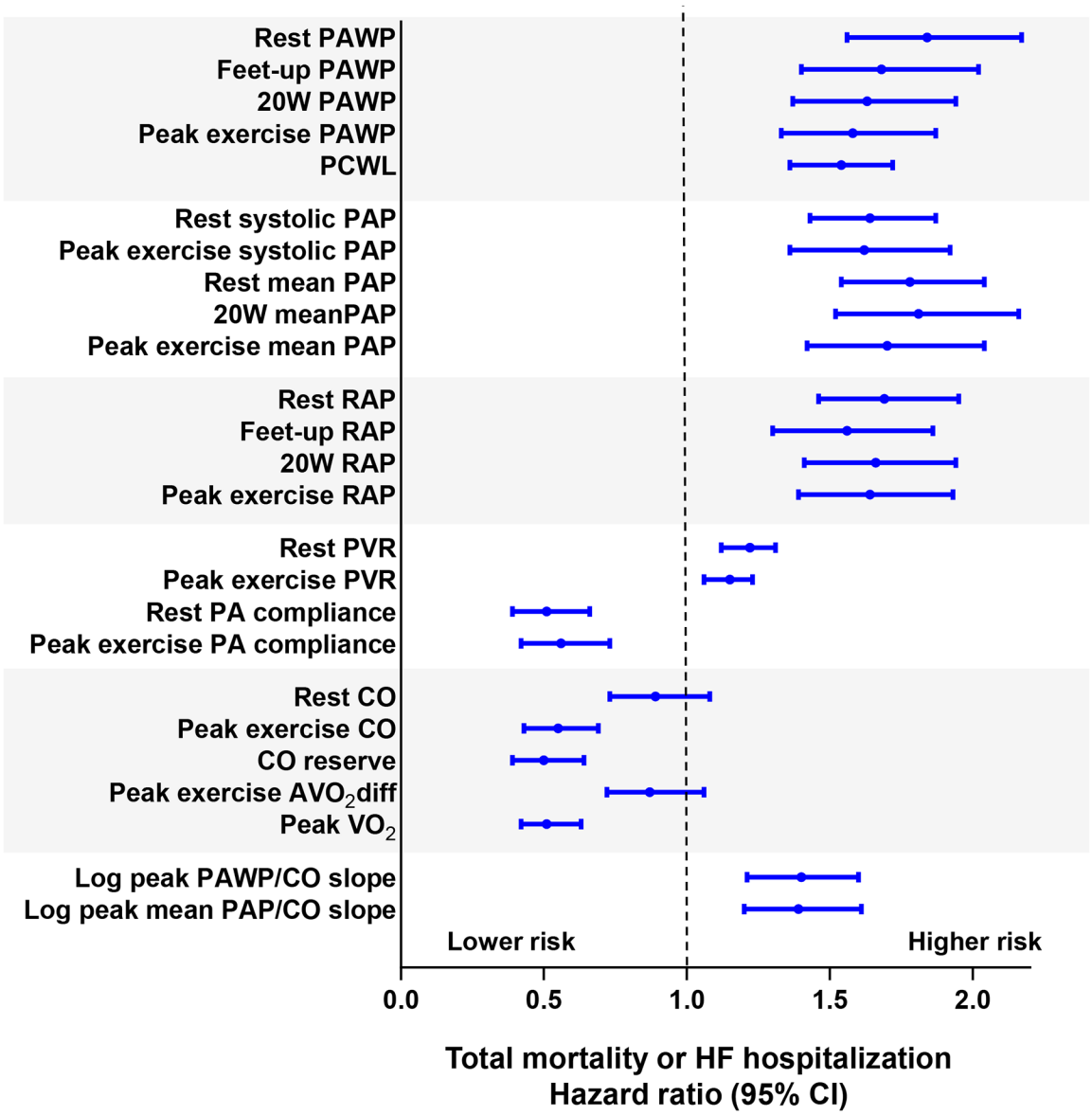


Figure 4.

Univariable Cox models were used to determine the hazard ratio (each 1 SD increase) for the heart failure hospitalization or death. AVO_2 diff indicates arterial-venous O_2 content difference; CO, cardiac output; PA, pulmonary artery; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; PVR, pulmonary vascular resistance; RAP, right atrial pressure and VO_2, oxygen consumption volume.

Table 1:

Baseline Characteristics

	NCD (n=193)	Ex HFpEF (n=187)	Rest HFpEF (n=384)	P value
Age (years)	55±14	68±10 *	68±11 *	<0.0001
Women, n (%)	112 (58%)	105 (56%)	219 (57%)	0.9
Body mass index (kg/m^2)	27.5±5.3	32.1±6.1 *	33.7±7.7 *†	<0.0001
Comorbidities, n (%)				
Coronary disease	41 (21%)	74 (40%)	126 (33%)	0.0006
Diabetes mellitus	25 (13%)	50 (27%)	102 (27%)	0.0005
Hypertension	120 (62%)	170 (91%)	364 (95%)	<0.0001
Atrial fibrillation	11 (6%)	42 (22%)	166 (43%)	<0.0001
Medications, n (%)				
Renin-angiotensin system blocker	52 (27%)	72 (39%)	194 (51%)	<0.0001
Beta-Blocker	49 (25%)	89 (48%)	231 (60%)	<0.0001
Diuretic	42 (22%)	90 (48%)	238 (62%)	<0.0001
Laboratories				
Hemoglobin (g/dL)	13.6±1.4	13.3±1.5	12.9±1.6 *†	<0.0001
Estimated GFR (mL/min/1.73m^2)	78±20	67±18 *	62±21 *	<0.0001
NT-pro BNP (pg/mL) (n=548)	75 (30, 158)	146 (64, 485) *	371 (119, 1208) *†	<0.0001
Echocardiography				
LV diastolic dimension (mm)	48±5	48±5	49±5 *	0.02
LV mass index (g/m^2)	84±18	90±21 *	92±23 *	0.0009
LA volume index (mL/m^2)	29±10	33±12 *	38±16 *†	<0.0001
LVEF (%)	65±5	65±6	64±6	0.3
E/e’	7 (6, 9)	9 (7, 12) *	12 (9, 16) *†	<0.0001
TAPSE (mm)	22±4	22±5	20±5 *†	0.001
RV s’ (cm/s)	13±3	13±3	12±3 *†	0.0005
TR velocity (m/s)	2.4±0.3	2.6±0.3 *	2.8±0.5 *†	<0.0001

Data are mean ± SD, median (interquartile range), or n (%).E/e', ratio of early diastolic filling pulsed wave doppler to early diastolic mitral annular tissue doppler velocity; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; Ex HFpEF, HFpEF that became evident only during exercise testing; Rest HFpEF, HFpEF that was diagnosed based upon resting hemodynamics alone; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; NCD, non-cardiac dyspnea; NT-pro BNP, N-terminal-pro-B-type natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation and s', systolic mitral annular tissue doppler velocity.

*P< 0.05 vs NCD.

†P< 0.05 vs Ex HFpEF.

Eur J Heart Fail. Author manuscript; available in PMC 2024 February 01.

Table 2:

Invasive hemodynamics at rest and during exercise

	NCD (n=193)	Ex HFpEF (n=187)	Rest HFpEF (n=384)	P value
Rest				
Vital signs				
Heart rate (bpm)	73±13	69±11 *	70±12 *	0.002
Systolic BP (mm Hg)	135±22	144±23 *	147±24 *	<0.0001
Central pressures				
RAP (mm Hg)	5±2	7±3 *	12±4 *†	<0.0001
Feet-up RAP (mm Hg)	7±3	10±3 *	16±6 *†	<0.0001
PA systolic pressure (mm Hg)	26±6	32±7 *	45±14 *†	<0.0001
PA mean pressure (mm Hg)	16±4	21±5 *	30±8 *†	<0.0001
PAWP (mm Hg)	9±3	11±2 *	20±4 *†	<0.0001
Feet-up PAWP (mm Hg)	12±4	16±4 *	23±5 *†	<0.0001
Vascular function				
PVR (WU)	1.2 (0.9, 1.6)	1.7 (1.2, 2.5) *	1.9 (1.1, 3.1) *	<0.0001
PAC (mL/mm Hg)	5.1±2.0	4.2±1.8 *	3.4±1.9 *†	<0.0001
PA Ea (mm Hg/mL)	0.3±0.1	0.4±0.1 *	0.6±0.3 *†	<0.0001
Oxygen Transport				
VO_2 (mL/min/kg)	2.8±0.6	2.5±0.6 *	2.5±0.6 *	<0.0001
A-Vo_2 diff (mL/dL)	4.0±0.8	4.4±0.8 *	4.7±1.0 *†	<0.0001
CO (L/min)	5.7±1.6	5.3±1.4 *	5.1±1.7 *	0.0006
Peak Exercise				
Vital signs				
Heart rate (bpm)	118±24	105±19 *	98±21 *†	<0.0001
Systolic BP (mm Hg)	170±32	183±32 *	175±33 †	0.0006
Peak workload (W)	69±37	50±29 *	40±25 *†	<0.0001
RER	1.04±0.13	1.02±0.01	1.00±0.12 *	0.002

Eur J Heart Fail. Author manuscript; available in PMC 2024 February 01.

	NCD (n=193)	Ex HFpEF (n=187)	Rest HFpEF (n=384)	P value
Central pressures				
RAP (mm Hg)	7±4	15±6 *	22±8 *†	<0.0001
PA systolic pressure (mm Hg)	40±10	60±13 *	68±17 *†	<0.0001
PA mean pressure (mm Hg)	25±6	41±8 *	47±11 *†	<0.0001
PAWP (mm Hg)	15±5	30±5 *	32±7 *†	<0.0001
PAWP/CO slope	1.1 (0.5, 1.9)	4.4 (3.0, 7.5) *	3.8 (2.0, 7.4) *	<0.0001
Mean PAP/CO slope	1.8 (1.1, 2.5)	4.8 (3.2, 7.8) *	5.9 (3.0, 10.5) *	<0.0001
PCWL (mmHg/watts/kg)	17 (11, 28)	64 (39, 97) *	90 (54, 137) *†	<0.0001
Vascular function				
PVR (WU)	0.9 (0.6, 1.2)	1.1 (0.6, 1.9) *	1.7 (1.1, 2.9) *†	<0.0001
PAC (mL/mm Hg)	4.0±1.6	3.1±1.7 *	2.6±1.4 *†	<0.0001
PA Ea (mm Hg/mL)	0.4±0.2	0.6±0.2 *	0.8±0.4 *†	<0.0001
Oxygen Transport				
VO_2 (mL/min/kg)	13.5±5.3	10.4±3.1 *	8.9±3.2 *†	<0.0001
A-VO_2 diff (mL/dL)	9.3±2.0	9.8±2.0	10.0±2.4 *	0.0009
CO (L/min)	11.4±3.3	9.9±3.5 *	8.5±3.2 *†	<0.0001

Data are mean ± SD, median (interquartile range), or n (%). AVO_2 diff indicates arterial-venous O_2 content difference; BP, blood pressure; CO, cardiac output; Ea, elastance; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; NCD, non-cardiac dyspnea; PA, pulmonary artery; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; RV, right ventricular; and VO_2, oxygen consumption volume.

* P< 0.05 vs NCD.

† P< 0.05 vs Ex HFpEF.

Table 3:

Univariable and multivariable models for death and HF hospitalization

	Univariable Model		Multivariable Model*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Rest PAWP	1.84 (1.56–2.17)	<0.0001	1.50 (1.22–1.83)	<0.0001
Feet-up PAWP	1.68 (1.40–2.02)	<0.0001	1.28 (1.01–1.62)	0.04
20W PAWP	1.63 (1.37–1.94)	<0.0001	1.32 (1.07–1.63)	0.01
Peak exercise PAWP	1.58 (1.33–1.87)	<0.0001	1.30 (1.05–1.62)	0.02
PCWL	1.54 (1.36–1.72)	<0.0001	1.66 (1.34–2.05)	<0.0001
Rest systolic PAP	1.64 (1.43–1.87)	<0.0001	1.29 (1.09–1.54)	0.005
Peak exercise systolic PAP	1.62 (1.36–1.92)	<0.0001	1.26 (1.01–1.58)	0.04
Rest mean PAP	1.78 (1.54–2.04)	<0.0001	1.45 (1.21–1.74)	<0.0001
20W mean PAP	1.81 (1.52–2.16)	<0.0001	1.44 (1.16–1.79)	0.0009
Peak exercise mean PAP	1.70 (1.42–2.04)	<0.0001	1.33 (1.06–1.66)	0.01
Rest RAP	1.69 (1.46–1.95)	<0.0001	1.43 (1.19–1.72)	0.0002
Feet-up RAP	1.56 (1.30–1.86)	<0.0001	1.29 (1.02–1.60)	0.03
20W RAP	1.66 (1.41–1.94)	<0.0001	1.34 (1.08–1.64)	0.008
Peak exercise RAP	1.64 (1.39–1.93)	<0.0001	1.37 (1.10–1.70)	0.005
Rest PVR	1.22 (1.12–1.31)	<0.0001	1.18 (1.0004–1.38)	0.0495
Peak exercise PVR	1.15 (1.06–1.23)	0.0001	1.10 (0.93–1.30)	0.3
Rest PAC	0.51 (0.39–0.66)	<0.0001	0.72 (0.53–0.96)	0.03
Peak exercise PAC	0.56 (0.42–0.73)	<0.0001	0.77 (0.58–1.04)	0.09
Rest CO	0.89 (0.73–1.08)	0.3	-	-
Peak exercise CO	0.55 (0.43–0.69)	<0.0001	0.67 (0.51–0.89)	0.007
CO reserve	0.50 (0.39–0.64)	<0.0001	0.65 (0.50–0.85)	0.002
Peak exercise AVO2 difference	0.87 (0.72–1.06)	0.2	-	-
Peak VO2	0.51 (0.42–0.63)	<0.0001	0.53 (0.38–0.73)	0.0001
Log 20W PAWP/CO slope	0.10 (0.97–1.32)	0.1		
Log 20W Mean PAP/CO slope	0.12 (0.57–1.31)	0.1		
Log PAWP/CO slope	)1.40 (1.21–1.60)	<0.0001	1.20 (1.02–1.41)	−0.03
Log Mean PAP/CO slope	1.39 (1.20–1.61)	<0.0001	−1.16 (0.98–1.37)	−0.08

	Univariable Model		Multivariable Model*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
20W PAWP/CO slope >2 mmHg/L/min	1.91 (1.06–3.47)	0.03	1.45 (0.78–2.71)	0.2
20W Mean PAP/CO slope >3 mmHg/L/min	2.04 (1.10–3.78)	0.02	1.46 (0.79–2.72)	0.2
PAWP/CO slope >2 mmHg/L/min	1.98 (1.23–3.21)	0.005	1.16 (0.68–1.99)	0.6
Mean PAP/CO slope >3 mmHg/L/min	2.03 (1.27–3.23)	0.003	1.22 (0.74–2.00)	0.4
PAWP/CO slope >4.2 mmHg/L/min**	1.86 (1.26–2.75)	0.002	1.25 (0.83–1.90)	0.3
Mean PAP/CO slope >5.5 mmHg/L/min**	2.42 (1.63–3.61)	<0.0001	1.39 (0.91–2.13)	0.1

Hazard ratios (HR) shown are for a 1 standard deviation change in each hemodynamic parameter, unless otherwise indicated.

CI indicates confidence interval; CO, cardiac output; HR, hazard ratio; PA, pulmonary artery; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; RAP, right atrial pressure; VO_2, oxygen consumption volume; and CO reserve = peak CO – rest CO.

*Multivariable Model was adjusted by age, gender, body mass index, prevalence of atrial fibrillation, left ventricular ejection fraction, hemoglobin and estimated glomerular filtration rate.

**Cutoff value was calculated from each of the median value in participants with HFpEF.