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Exercise intolerance in HFpEF: arterial stiffness and abnormal left ventricular hemodynamic responses during exercise

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Abstract

BACKGROUND: Arterial stiffness is thought to contribute to the pathophysiology of heart failure with preserved ejection fraction (HFpEF). We sought to examine arterial stiffness in HFpEF and hypertension and investigate associations of arterial and left ventricular hemodynamic responses to exercise.

METHODS: A total of 385 symptomatic individuals with EF ≥ 50% underwent upright cardiopulmonary exercise testing with invasive hemodynamic assessment of arterial stiffness and load (aortic augmentation pressure, augmentation index, systemic vascular resistance index, total arterial compliance index, effective arterial elastance index, and pulse pressure amplification) at rest and during incremental exercise. An abnormal hemodynamic response to exercise was defined as a steep increase in pulmonary capillary wedge pressure relative to cardiac output (ΔPCWP/ΔCO > 2 mmHg/L/min). We compared rest and exercise measures between HFpEF and hypertension in multivariable analyses.

RESULTS: Among 188 HFpEF participants (age 61±13, 56% women), resting arterial stiffness parameters were worse compared to 94 hypertensive participants (age 55 ± 15, 52% women); these differences were accentuated during exercise in HFpEF (all p≤0.0001). Among all participants, exercise measures of arterial stiffness correlated with worse ΔPCWP/ΔCO. Specifically, a 1-SD higher exercise augmentation pressure was associated with 2.15-fold greater odds of abnormal LV hemodynamic response (95% CI 1.52–3.05, p<0.001). Further, exercise measures of systemic vascular resistance index, elastance index, and pulse pressure amplification correlated with lower peak VO_2.

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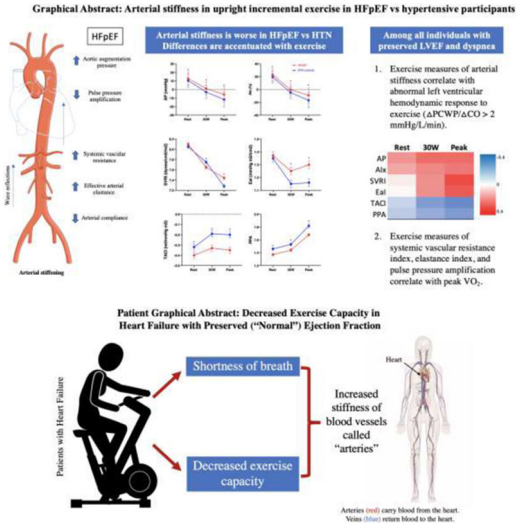
CONCLUSIONS: Exercise accentuates elevated arterial stiffness in HFpEF, which in turn correlate with left ventricular hemodynamic responses. Unfavorable ventricular-vascular interactions during exercise in HFpEF may contribute to exertional intolerance and inform future therapeutic interventions.

Graphical Abstract:



Arterial stiffness and load are accentuated with exercise in heart failure with preserved ejection fraction compared with hypertensive participants and correlate with left ventricular hemodynamic responses to upright incremental exercise. Patients with heart failure exercised on a stationary bicycle while we measured their heart and lung function and their blood pressure. Compared with patients with high blood pressure, patients with heart failure had stiffer blood vessels. Stiffer blood vessels may be related to the shortness of breath and difficulty exercising experienced by patients with heart failure.

Keywords

Arterial stiffness; arterial load; HFpEF; exercise capacity; heart failure; hypertension

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition with no known effective treatments, in no small part due to substantial phenotypic heterogeneity that challenges broad therapeutic approaches.(1–3) A hallmark of HFpEF is exertional intolerance. The pathophysiology of reduced exercise capacity in HFpEF is multifactorial, with contributions from chronotropic incompetence, impaired stroke volume augmentation, abnormal ventricular-arterial coupling and impaired peripheral oxygen extraction during exercise.(4–10) None of these putative mechanisms of exercise intolerance are adequately characterized during rest alone, though repeated measurements during exercise, in contrast, permit quantification of the deficits and their contribution to exercise intolerance. Several recent studies have shown that exercise may uncover abnormal physiologic responses such as elevated cardiac filling pressures that are not evident at rest.

(11,12) Increased arterial stiffness and arterial load, out of proportion from aging or chronic hypertension alone, have been recognized as important contributors to the hemodynamic abnormalities observed in HFpEF.(13–16)

The extent to which measures of arterial stiffness and load are increased in HFpEF during exercise and their relationship to continuous invasive cardiac hemodynamic measures during exercise remains unclear. While a prior study correlated supine submaximal exercise to invasive hemodynamics in the HFpEF population, no studies to date have evaluated whether arterial waveform abnormalities during continuous upright exercise relate to exercise capacity.(15) Utilizing a comprehensively phenotyped sample of patients undergoing cardiopulmonary exercise testing (CPET) with continuous invasive arterial waveform assessment and hemodynamic monitoring, we sought to 1) examine resting and exercise arterial waveform measures that reflect arterial stiffness and pulsatile and non-pulsatile arterial load among symptomatic HFpEF patients and hypertensive controls and 2) determine the association of arterial waveform measures during exercise with left ventricular (LV) hemodynamic responses to exercise and exercise capacity. We hypothesized that abnormalities in measures of arterial stiffness at rest would be accentuated during exercise provocation in relation to hypertensive controls. Further, we also hypothesized that abnormal arterial stiffness and load during exercise would be directly associated with worse exercise capacity and abnormal rise in LV filling pressures during exercise, suggesting unfavorable ventricular-vascular interaction as a potential mechanism underlying exertional intolerance in HFpEF.

METHODS:

Study Sample

The study sample included 483 consecutive patients with exertional dyspnea (New York Heart Association class II-IV symptoms) and left ventricular ejection fraction (LVEF) ≥50% who underwent clinically indicated cardiopulmonary exercise testing to maximal effort (defined as respiratory exchange ratio >1.0) with invasive hemodynamic monitoring and arterial stiffness measurements at Massachusetts General Hospital between 2009 to 2017. Participants were excluded if they had one or more of the following: pulmonary arterial hypertension in the absence of left heart disease (n=8), history of heart or lung transplantation (n=9), complex adult congenital heart disease (n=2), mitochondrial disease (n=13), undergoing evaluation for lung transplant (n=7), moderate or greater aortic or mitral valve disease or prior valve replacement (n=39), or oxygen-dependent lung disease (n=18), leaving 385 participants for analysis. Informed consent was obtained from all participants, and the Massachusetts General Hospital Institutional Review Board approved the study.

Cardiopulmonary Exercise Testing

All participants underwent insertion of a pulmonary artery catheter via the internal jugular vein and systemic arterial catheter via the radial artery, followed by maximal upright cycle ergometry at 5 to 15 W/min continuous ramp after an initial 3-minute period of unloaded exercise as previously described.(17) Serial gas exchange (MedGraphics, St. Paul, MN) and minute-by-minute hemodynamic measures were assessed during exercise. Hemodynamic

measures included pulmonary capillary wedge pressure (PCWP), pulmonary artery (PA) pressure, and cardiac output calculated utilizing the direct Fick method. Pulmonary artery catheter measurements were obtained at end-expiration.

HFpEF was defined as impaired peak VO_2 (<80% predicted) with either (1) elevated PCWP at rest (supine PCWP ≥ 15mmHg) or (2) abnormally steep increase in PCWP relative to cardiac output (CO) during exercise (ΔPCWP/ΔCO slope > 2.0 mmHg/L/min with peak PCWP ≥ 15mmHg, calculated using multi-point measures of PCWP and CO during CPET, average of 10±2 measures per individual) as previously described.(18,19) The hypertensive control group included individuals with normal rest PCWP, exercise ΔPCWP/ΔCO slope ≤ 2.0 mmHg/L/min, and elevated resting blood pressure (≥140/90mmHg) or treatment with anti-hypertensive medication. Participants who were not classified as either HFpEF (n=188) or HTN (n=94) were included in analyses examining the association of arterial stiffness parameters with PCWP/CO slope and peak VO_2 among the entire cohort of 385 participants with exertional dyspnea. In sensitivity analyses, we reclassified HFpEF using the following hemodynamic criteria: PCWP/CO slope >2 mmHg/L/min and peak PCWP ≥25mmHg as per previous studies(15,20).

Arterial Stiffness and Load Assessment

Peripheral arterial pressure measures were ascertained using invasive radial arterial catheter. Central aortic pressure waveforms at rest, 30 Watts, and peak exercise were derived from invasive radial artery pressure tracings using a mathematical transfer function as previously described and validated at rest and during exercise (SphygmoCor, Atcor Medical).(21,22) Pressure tracings were additionally manually reviewed for quality control. Surrogate measures of arterial stiffness were calculated using simultaneously measured hemodynamic parameters. Higher values of augmentation pressure (AP) and augmentation index (Aix) indicate greater wave reflection and late-systolic load.(23) Non-pulsatile load, or the steady component of vascular resistance, was quantified by systemic vascular resistance index (SVRI=80*[mean arterial pressure – right atrial pressure]/cardiac index). Further parameters measured included: pulse pressure amplification (PPA=peripheral-to-central PP ratio; decreased with increased aortic wave reflection), total arterial compliance index (TACI = stroke volume index/central pulse pressure; a metric of aortic stiffness), and effective arterial elastance index (EaI = end systolic pressure/stroke volume index; dependent on resistive load and heart rate).(24,25) Worse overall arterial stiffness is indicated by a higher effective arterial elastance index and lower total arterial compliance index and pulse pressure amplification. We lump these parameters together as “arterial stiffness” for ease of description, acknowledging that overall left ventricular afterload is composed of a steady resistive component and a pulsatile component described by parameters including systemic vascular resistance, arterial compliance, impedance, and wave reflection amplitude.(23)

Clinical and Biomarker Assessment:

At the time of CPET, participants underwent history and physical examination, measurement of body mass index (BMI), and fasting blood draw, including N-terminal pro-B type natriuretic peptide (Roche, NT-proBNP, intra-assay coefficient of variation 2.4–3.8%) and high-sensitivity C-reactive protein (Roche, hsCRP, intra-assay coefficient of variation 0.4–

8.4%). Blood specimens were immediately processed and stored at −80°C. Echocardiography within one year of CPET was utilized for abstraction of LVEF and presence of structural heart disease (left ventricular hypertrophy, left atrial enlargement, and diastolic dysfunction).(26)

Statistical Analysis:

Baseline clinical characteristics were summarized for the total sample. HFpEF and HTN subgroups were compared using t-tests or Chi^2 tests as appropriate. Arterial stiffness parameters at rest, 30W, and peak exercise were summarized using raw means and adjusted means accounting for age, sex, BMI, and presence of diabetes mellitus (DM). Aortic augmentation pressure and index were additionally adjusted for heart rate.(27) We examined the association of arterial stiffness parameters with peak VO_2, and PCWP/CO slope as a measure of LV hemodynamic response using partial correlation coefficients first adjusting for age and sex (and heart rate for augmentation pressure and index), then further adjusting for BMI and DM as covariates. Our primary outcomes were augmentation pressure and index at rest and 30W of exercise between HFpEF and HTN, yielding four comparisons with a Bonferroni correction for significance of p=0.0125. In secondary analyses, we examined associations of arterial stiffness with abnormal PCWP/CO slope. We evaluated whether HFpEF status modifies the association of arterial stiffness with outcomes at peak exercise (PCWP/CO slope and peak VO_2) utilizing an interaction term (HFpEF*arterial stiffness parameter) in multivariable Cox models. Data were log-transformed where necessary. Analyses were conducted using STATA v. 15.1 (College Station, TX). A p value of < 0.05 was considered significant.

RESULTS

Of 385 individuals with exertional dyspnea and LVEF≥50% who underwent CPET with arterial stiffness assessment, the mean age was 56±15 years, and 58% were women (Table 1). Among these individuals, 188 had HFpEF (age 61±13 years, 56% women), and 94 met criteria for the hypertensive control group (age 55±15 years, 52% women). Participants with HFpEF had a greater burden of comorbid conditions, including diabetes mellitus (21%), obesity (53%) and prior cardiovascular hospitalization (39%) compared with hypertensive controls (P<0.05 for all). Compared with hypertensive controls, the HFpEF group had a higher median NT-proBNP concentration (99 pg/mL [46–260 pg/mL] vs 42 pg/mL [23–113 pg/mL], p=0.0001).

Exercise capacity is worse in HFpEF compared to hypertensive controls

HFpEF participants had lower peak VO_2 (15.1±3.7 ml/kg/min) compared with hypertensive controls (20.7±4.8 ml/kg/min), with correspondingly lower % predicted peak VO_2 and maximum work achieved (Table 1). There were no differences between HFpEF and hypertensive control groups in resting heart rate, resting or peak systolic blood pressure, or cardiac output (Table 2). Peak heart rate was lower among HFpEF participants (130±25 beats/minute) compared to hypertensive controls (147±21 beats/min). As expected, individuals with HFpEF had steeper PCWP/CO slopes (3.1±1.7 mmHg/L/min) compared to hypertensive controls (1.2±0.4 mmHg/L/min, P<0.05).

Exercise unmasks greater arterial stiffness in HFpEF compared with hypertensive controls

Rest and exercise hemodynamic and arterial stiffness parameters are displayed in Tables 2 and 3 and Figure 1. Figure 1 and Table 3 present adjusted means after accounting for age, sex, BMI, and DM (and heart rate where applicable) of primary outcomes augmentation pressure and index at rest and 30W and secondary outcomes of compliance index, systemic vascular resistance index, elastance index and pulse pressure amplification throughout exercise. At rest, there were no differences in SVRI or EaI between HFpEF participants and hypertensive controls ($P>0.05$), but other resting measures of arterial stiffness (augmentation pressure and index, compliance index, and pulse pressure amplification) were significantly worse amongst HFpEF participants ($P<0.05$ for all in multivariable-adjusted analyses, Table 3). Progression to 30W and peak exercise further delineated differences between the two groups, with more abnormal measures of all parameters of arterial stiffness ($P\leq0.0001$ for all at peak) among patients with HFpEF. Specifically, at peak exercise, adjusted augmentation pressure was 5.75 mmHg higher among HFpEF patients vs hypertensive controls, with an absolute difference of 7.7% in augmentation index. In sensitivity analyses using PCWP/CO slope >2 mmHg/L/min and peak PCWP ≥25mmHg to define HFpEF (79% of original HFpEF definition), we found no substantive differences when compared with primary results. Specifically, we again show worse arterial stiffness among HFpEF patients at 30W and peak exercise, with no differences among resting measures (Supplemental Table 1).

Measures of arterial stiffness correlate with left ventricular hemodynamic response to exercise and exercise capacity

We next examined the association of arterial stiffness with LV hemodynamic responses with exercise among all individuals with exertional dyspnea and LVEF≥50% who underwent CPET (n=385) (Table 4, Figure 2). Resting measures of arterial stiffness (augmentation pressure and index, compliance index, and pulse pressure amplification) were associated with PCWP/CO slope (augmentation pressure, $r=0.17$, $p=0.001$; augmentation index, $r=0.14$, $p=0.008$; compliance index, $r=-0.10$, $p=0.04$; pulse pressure amplification, $r=-0.12$, $p=0.02$), whereas no association was found with systemic vascular resistance index or elastance index. Compared to resting assessments, both low-level exercise (30W) and peak exercise revealed consistently stronger correlations between all measures of arterial stiffness with PCWP/CO slope (at peak: augmentation pressure, $r=0.24$; augmentation index, $r=0.22$; systemic vascular resistance index, $r=0.30$, elastance index, $r=0.27$, compliance index, $r=-0.27$, pulse pressure amplification, $r=-0.23$; $p<0.0001$ for all). In exploratory analyses, we found that the association of exercise arterial stiffness and PCWP/CO slope was apparent among individuals with HFpEF, whereas these associations were not significant among hypertensive controls (Supplemental Table 2, Supplemental Figure 1). In the test for interaction of HFpEF status with arterial stiffness parameter, at peak exercise, HFpEF status modified the association of augmentation index, systemic vascular resistance index, elastance index, and compliance index with PCWP/CO slope ($p\leq0.02$ for all).

There were only modest correlations between rest measures of compliance and elastance indices with peak VO_2 (compliance index, $r=0.10$, $p=0.049$; elastance index, $r=-0.11$, $p=0.04$). By contrast, exercise measures of systemic resistance and arterial stiffness were significantly associated with peak VO_2 (systemic vascular resistance index, $r=-0.29$,

p<0.0001; elastance index, r=−0.13, p=0.01; compliance index, r=0.12, p=0.03; pulse pressure amplification, r=0.23, P<0.0001). There were no significant correlations between augmentation pressure and index throughout exercise and peak VO_2. HFpEF status only modified the association of systemic vascular resistance index with peak VO_2 at peak exercise (p=0.006); tests for interaction with other arterial stiffness parameters were not significant.

In exploratory analyses, we also demonstrate correlations between all measures of arterial stiffness other than PPA and peak PCWP and delta PCWP (peak PCWP – rest PCWP); these correlations similarly strengthen from rest to low-level (30W) to peak exercise (Supplemental Table 3). Resting parameters of all measures of arterial stiffness correlate with stroke volume reserve (stroke $volume_{peak}$/stroke $volume_{rest}$).

Arterial stiffness predictors of an abnormal PCWP/CO response to exercise

Among the whole sample (n=385 participants), we next examined the association of arterial stiffness with abnormal LV hemodynamic response to exercise, defined as an abnormally steep PCWP/CO slope > 2mmHg/L/min (Supplemental Table 4, Figure 3).(18,28) We found that most rest measures of arterial stiffness, other than elastance index and systemic vascular resistance index, were associated with abnormal PCWP/CO response to exercise. Specifically, a 1-SD higher augmentation pressure was associated with a 2-fold increased odds of having abnormally steep PCWP/CO response to exercise (multivariable-adjusted OR 1.98, 95% CI 1.42, 2.75, P=<0.001). Moreover, we found that arterial stiffness measures ascertained at 30W and peak exercise displayed increased odds of an abnormal PCWP/CO response for each individual parameter (P<0.001 for all). For example, a 1-SD higher systemic vascular resistance index at 30W and peak exercise was associated with 1.8- and 2.2-fold increased odds of abnormal PCWP responses to exercise, respectively (OR 1.8, 95% CI 1.35–2.38, p<0.001 at 30W; and OR 2.16, 95% CI 1.58–2.96, p<0.001 at peak exercise).

DISCUSSION:

We ascertained continuous invasive measures of arterial stiffness during exercise in a large sample that included patients with hemodynamically-confirmed HFpEF and hypertensive controls. We demonstrate the following: (1) at rest, measures of arterial stiffness are worse in HFpEF participants compared with hypertensive controls; (2) exercise provocation accentuates differences in arterial stiffness among patients with HFpEF compared to hypertensive controls, even at low-level exercise; and (3) measures of arterial stiffness ascertained during exercise are directly related to an abnormal increase in PCWP during exercise and correlate with a lower peak VO2. Our data provide the most direct evidence to date that abnormal vascular responses to exercise may contribute to impaired cardiac performance during exercise and overall exercise intolerance in HFpEF.

Arterial stiffening has been previously highlighted as an important component to the diverse range of hemodynamic and metabolic abnormalities that may be observed in patients with HFpEF.(13–16) Higher wave reflection amplitude with increased late-systolic load to the left ventricle has been shown to be associated with myocardial hypertrophy and fibrosis, heart

failure, and cardiovascular mortality.(23,29) In prior studies, resting arterial stiffness parameters were similar between HFpEF and hypertensive participants without HF.(30) Less is known about exercise responses: one prior study suggested abnormal ventriculoarterial coupling during exercise in 23 patients with HFpEF compared with 15 controls using noninvasive measures of vascular stiffness.(31) In a study by Reddy et al. of invasively measured arterial stiffness among individuals with HFpEF vs hypertensive controls, there were no differences in aortic pulse pressure or augmentation index at rest or during exercise, although other measures of arterial stiffness were worse with exercise in HFpEF and directly related to increased supine PCWP during exercise.(15) We extend these prior reports by studying a larger sample of individuals with HFpEF and hypertensive controls with detailed assessment of invasively measured arterial stiffness and hemodynamics during upright exercise. Upright exercise permits greater exposure to exercise and repeated serial measures of arterial stiffness and hemodynamics while permitting patients to achieve true peak VO_2 (i.e. peak VO_2 was 15ml/kg/min in HFpEF, consistent with previous HFpEF studies of upright exercise,(32) compared to 8.6 ml/kg/min in the one other study of invasive arterial waveform analysis(15)).

Our study is also unique in that we examined direct associations of arterial stiffness with multi-point measurements of PCWP/CO slope. We acknowledge that prior studies involving exercise hemodynamics in HFpEF participants have utilized a PCWP during exercise ≥ 25 mmHg as cutoff(15,20). However, utilization of flow-corrected definitions of HFpEF during exercise, such as the PCWP/CO slope, allows for capture of a prognostically significant integrated hemodynamic measure of left heart performance, preferable to an isolated measurement of PCWP alone during exercise.(18,19,33)

Our findings underscore important interactions between cardiac performance and the systemic vasculature as previously noted.(34) In our study, we assess arterial elastance, Ea, as a lumped measurement of the mean resistive and pulsatile components of afterload. While Ea has been shown to be dominated by the nonpulsatile systemic vascular resistance and heart rate with negligible influence by pulsatile afterload,(35) pulsatile afterload has shown to be most strongly correlated with left ventricular diastolic relaxation.(36) In our study, we demonstrate that arterial stiffness, quantified by surrogates of wave reflection and late systolic load (augmentation pressure and index and pulse pressure amplification), metrics of stiffness (total arterial compliance index and effective arterial elastance index), and nonpulsatile load (systemic vascular resistance index), are independently associated with abnormal left ventricular hemodynamic response to exercise (the PCWP/CO slope), as well as the absolute peak PCWP and difference in PCWP between rest and peak exercise. These associations are unmasked or accentuated at low intensity exercise to 30W, providing opportunity for more widespread practical assessment of arterial stiffness as a diagnostic strategy in patients with dyspnea on exertion. Whether pulsatile or nonpulsatile components of arterial stiffness and load may identify high risk patients and guide therapies remains to be studied.

In addition, this is the first study to demonstrate that measures of arterial stiffness during exercise are related to peak VO_2, even after adjustment for age, sex, BMI, and diabetes status. A prior study on exercise training in HFpEF demonstrated improvement in peak VO_2

without change in flow-mediated arterial dilation or carotid artery distensibility (37), though other measures of arterial load were not directly assessed. As peak VO_2 carries prognostic value in HFpEF(38), future studies may examine whether measuring surrogates of arterial stiffness similarly identifies patients with HFpEF at highest risk of adverse outcomes.

Beyond lending further insights into the pathophysiology of HFpEF, understanding contributions of arterial stiffness and load may inform therapeutic strategies.(39,40) Prior studies have highlighted that central pressures are higher in individuals with cardiovascular risk factors or disease,(41) respond differently to antihypertensive therapy,(42,43) and more strongly correlate with cardiovascular outcomes than peripheral pressures.(44–47) As a proof-of-concept, in patients with heart failure with reduced ejection fraction (HFrEF), aortic waveform-guided medical therapy as compared to standard brachial cuff pressures improved exercise capacity and functional status.(48,49) Whether these findings can be extrapolated to the HFpEF population has yet to be determined, though specific vasoactive agents are known to target large artery stiffness, including inorganic nitrites and nitrates in the HFpEF population (15,50) and phosphodiesterase type 5 inhibition, ivabradine, and sodium-glucose cotransport 2 inhibitors across broader samples (51–54). Whether phenotype-specific selection of HFpEF participants with the highest degree of arterial stiffness may help target vasoactive interventions in the future remains to be seen (40).

There are several limitations to this study. We included consecutive ambulatory participants referred for CPET in the context of chronic dyspnea on exertion. In this setting, we acknowledge that our HFpEF group may represent participants earlier in the disease course with hemodynamic abnormalities during exercise only (evidenced for example by only modest elevations in natriuretic peptide levels, only 40% diuretic use, and low prevalence of prior HF hospitalizations), and that generalizability to broader populations is unclear. Clinical heterogeneity among HFpEF samples may explain potential differences in findings of abnormal arterial stiffness during rest between HFpEF and hypertensive controls compared to prior studies. We did not adjust for use of antihypertensive agents which may have differential effects on ventricular arterial coupling.(55) We do not have advanced echocardiographic or magnetic resonance imaging data on these participants, limiting our ability to correlate arterial stiffness parameters to advanced non-invasive imaging parameters. It is also important to note that the associations of arterial stiffness and abnormal PCWP response to exercise and peak VO_2 are not necessarily causal as ours is an observational study. Regardless of these limitations, one of the strengths of our study was the rigorous ascertainment of invasive arterial stiffness and hemodynamic measurements throughout exercise, facilitating multi-point analysis of PCWP/CO responses rather than a single static measurement.

In sum, we demonstrate that patients with HFpEF appear to have greater vascular stiffness compared with hypertensive controls, and that these differences in vascular stiffness are particularly pronounced during exercise provocation. We also show that worse arterial stiffness is associated with abnormal increases in PCWP relative to CO with exercise. We also demonstrate that systemic vascular resistance, pulse pressure amplification, and arterial elastance are correlated with lower peak VO_2. Our findings support the clinical relevance of arterial stiffness as a contributor to the hallmark exertional intolerance and abnormal LV

hemodynamic exercise responses in HFpEF. Future studies are needed to examine whether targeted therapeutic interventions against increased arterial stiffness may alter symptomatology and clinical outcomes in the HFpEF population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures:

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ABBREVIATIONS:

Aix	aortic augmentation index
AP	aortic augmentation pressure
CO	cardiac output
CPET	cardiopulmonary exercise testing
EaI	effective arterial elastance index
HFpEF	heart failure with preserved ejection fraction
PCWP	pulmonary capillary wedge pressure
PPA	pulse pressure amplification
SVRI	systemic vascular resistance index
TACI	total arterial compliance index

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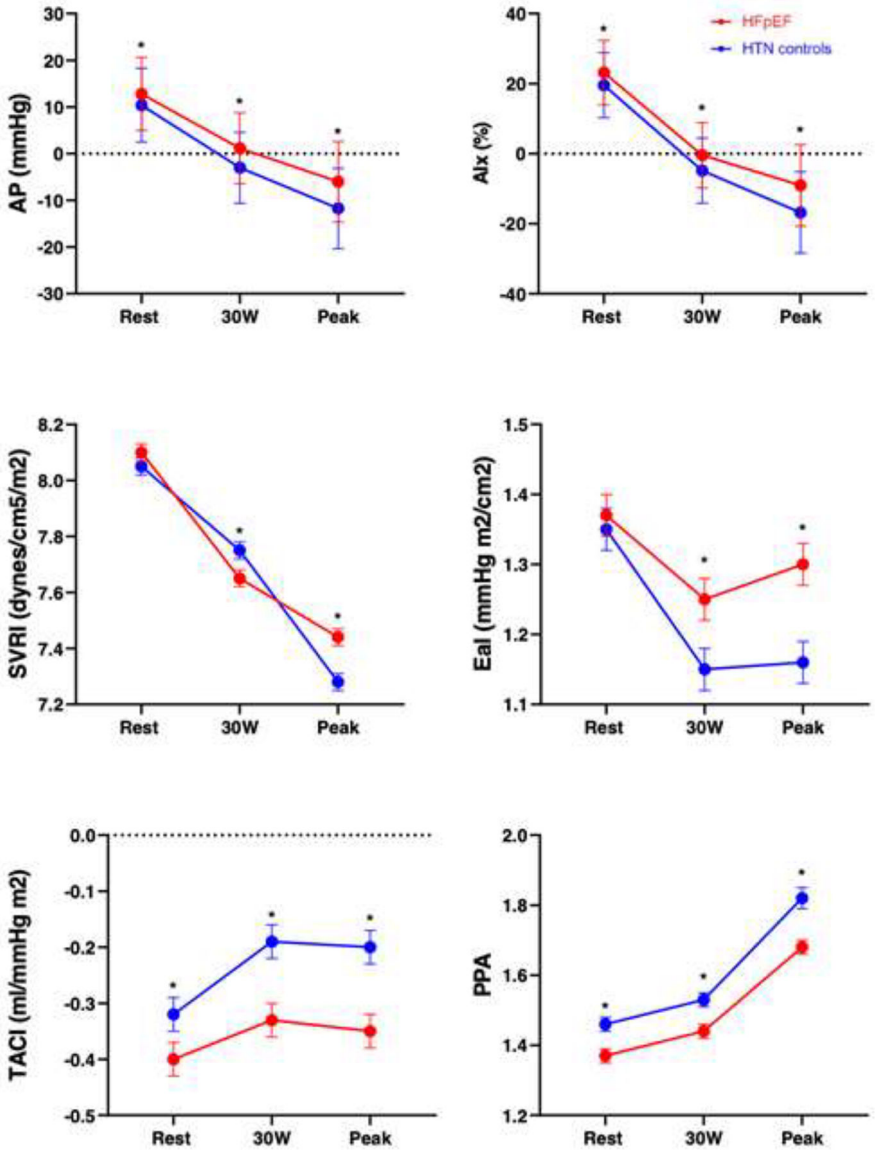

Figure 1.

Arterial stiffness and load parameters at rest, 30W, and peak exercise in HFpEF participants and hypertensive controls. * denotes $p<0.05$ difference between HFpEF and hypertensive controls.

Abbreviations: Aix, augmentation index; AP, aortic augmentation pressure; EaI, elastance index; HTN, hypertension; PPA, pulse pressure amplification; SVRI, systemic vascular resistance index; and TACI, total arterial compliance index.

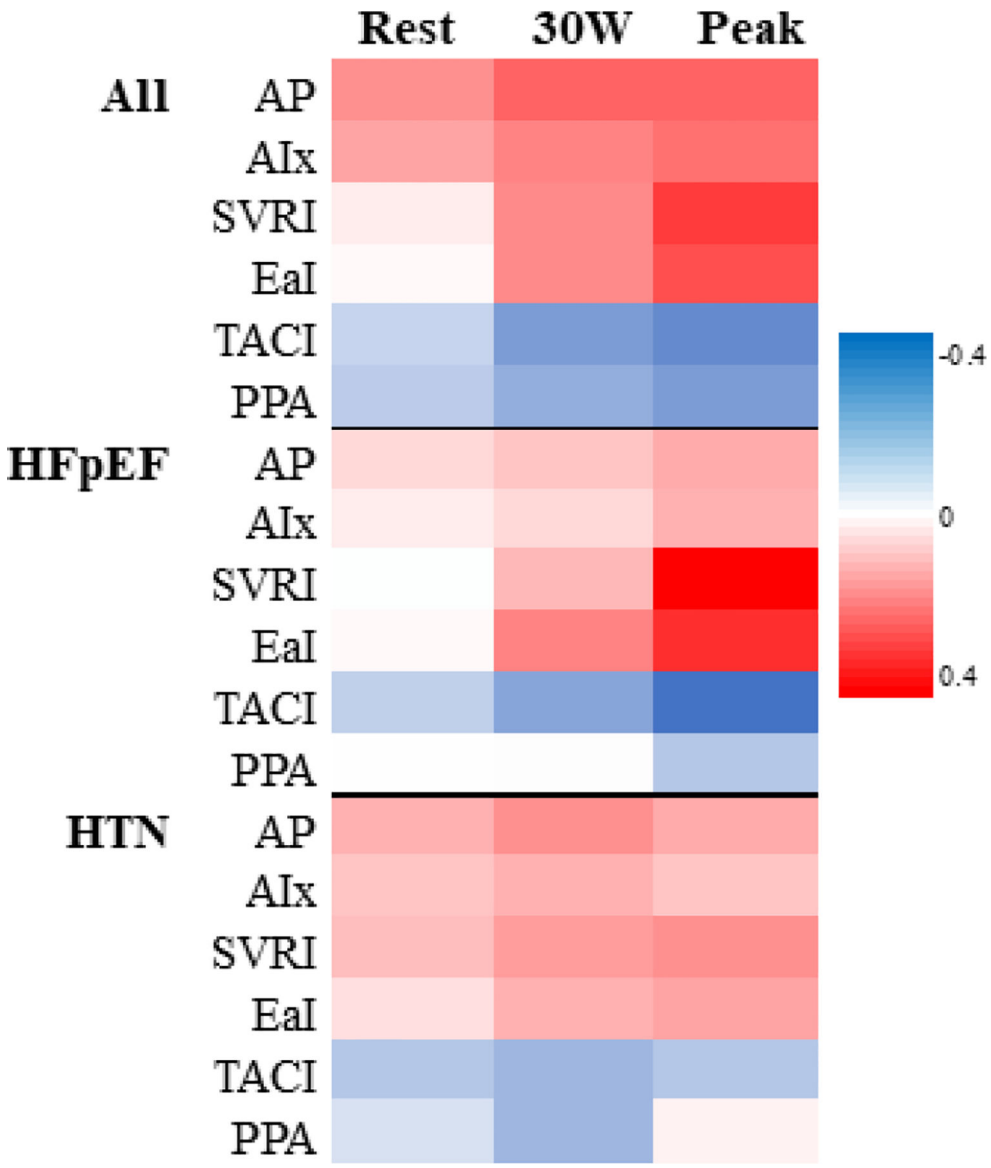

Figure 2.

Arterial stiffness and load and PCWP/CO slope correlations during exercise. Analyses are adjusted for age, sex, body mass index, and presence of diabetes mellitus. Augmentation pressure and index are also adjusted for heart rate. The red and blue shading represent positive and negative correlations, respectively.

Abbreviations: Aix, augmentation index; AP, aortic augmentation pressure; EaI, elastance index; HTN, hypertension; PPA, pulse pressure amplification; SVRI, systemic vascular resistance index; and TACI, total arterial compliance index.

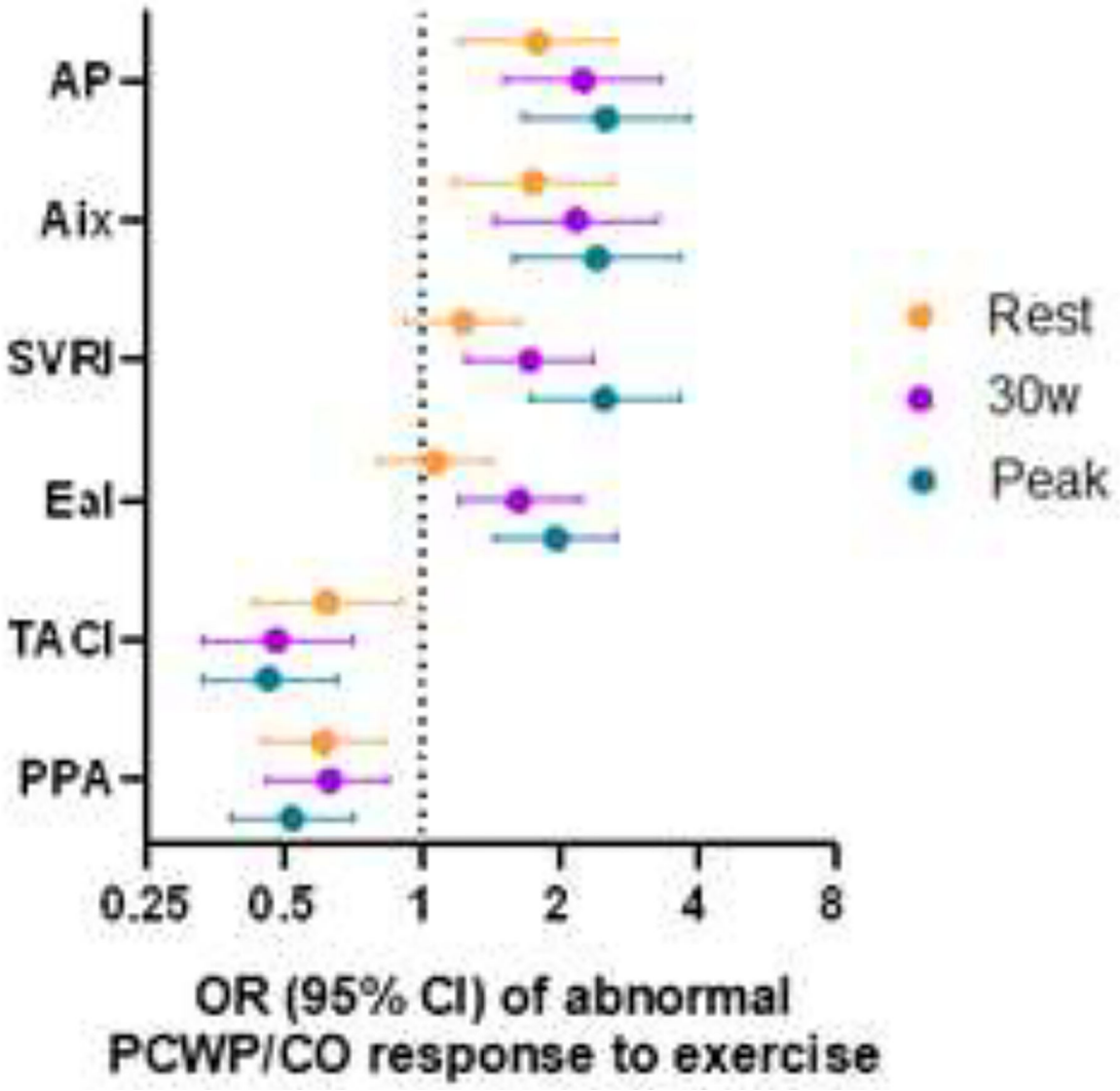

Figure 3.

Parameters of arterial stiffness and arterial load are associated with abnormal PCWP/CO response to exercise. Odds ratio (OR) is per one-standard deviation increase in predictor variable.

Abbreviations: Aix, augmentation index; AP, aortic augmentation pressure; EaI, elastance index; HTN, hypertension; PPA, pulse pressure amplification; SVRI, systemic vascular resistance index; and TACI, total arterial compliance index.

Table 1.

Clinical characteristics and CPET parameters of HFpEF and hypertensive control participants

	Total sample n=385	HFpEF subgroup n=188	HTN control subgroup n=94	P-value*
Clinical characteristics				
Women, n (%)	224 (58)	106 (56)	49 (52)	0.50
Age, years	56 ± 15	61 ± 13	55 ± 15	0.001
BMI, kg/m^2	29.5 ± 6.5	31.3 ± 6.7	27.1 ± 5.1	<0.0001
Hypertension, n (%)	313 (81)	170 (90)	94 (100)	0.002
Diabetes Mellitus, n (%)	62 (16)	40 (21)	9 (9)	0.01
Current Smoker, n (%)	13 (4)	4 (2)	4 (4)	0.31
Prior MI, n (%)	17 (4)	10 (5)	4 (4)	0.70
Prior CV admission, n (%)	121 (31)	74 (39)	21 (22)	0.004
Prior HF admission, n (%)	23 (6)	14 (7)	4 (4)	0.14
Diuretic, n (%)	109 (28)	76 (40)	14 (15)	<0.001
Beta blocker use, n (%)	121 (31)	79 (42)	26 (28)	<0.001
Nitrate use, n (%)	18 (6)	16 (9)	2 (2)	0.02
Calcium channel blocker use, n (%)	58 (15)	29 (16)	20 (21)	0.008
ACEi or ARB use, n (%)	104 (27)	60 (32)	28 (30)	<0.001
NT-proBNP, pg/mL, median (IQR)	67 (30–167)	99 (46–260)	42 (23–113)	0.0001
CRP, pg/mL, median (IQR)	1.8 (0.8–4.9)	3.0 (1.2–5.9)	1.3 (0.5–3.0)	0.0001
Echocardiographic characteristics				
LVEF, %	65 ± 7	65 ± 8	65 ± 6	0.40
LV hypertrophy	20%	28%	17%	0.047
Left atrial enlargement	32%	40%	27%	0.05
Diastolic dysfunction	32%	40%	26%	0.04
CPET characteristics				
Peak VO_2, ml/kg/min	17.2 ± 5.2	15.1 ± 3.7	20.7 ± 4.8	0.0001
% pred VO_2, Wasserman, %	76.7 ± 16.3	75.1 ± 15.5	84.8 ± 14.1	0.0001
VE/VCO_2 slope	36.2 ± 8.3	36.8 ± 8.6	34.9 ± 6.6	0.10
Max work, watts	107 ± 38	98 ± 35	126 ± 37	0.0001
Respiratory exchange ratio	1.15 ± 0.1	1.15 ± 0.1	1.15 ± 0.08	0.73
Stroke volume reserve	1.35 + 0.78	1.38 + 1.05	1.35 + 0.28	0.11
PCWP/CO slope, mmHg/L/min	2.1 ± 1.6	3.1 ± 1.7	1.2 ± 0.4	<0.0001

Table displays mean ± standard deviation unless otherwise specified

*P-value for HFpEF vs HTN control comparison

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CO, cardiac output; CRP, C-reactive protein; CV, cardiovascular; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; RER, respiratory exchange ratio; VE/VCO_2 slope, ventilator efficiency; and VO_2, oxygen consumption.

Table 2.

Exercise parameters among HFpEF and hypertensive participants

	HFpEF			HTN control		
	Rest	**30W**	**Peak**	**Rest**	**30W**	**Peak**
Hemodynamic parameters						
SBP, mmHg	152 ± 22	168 ± 28	192 ± 30	150 ± 19	161 ± 25	192 ± 22
DBP, mmHg	77 ± 12 *	81 ± 14	91 ± 18	80 ± 10	83 ± 12	92 ± 13
HR, bpm	75 ± 14	96 ± 18	126 ± 25 *	78 ± 14	96 ± 16	142 ± 23
PCWP, mmHg	15 ± 6 *	15 ± 6 *	25 ± 7 *	10 ± 3	9 ± 3	17 ± 5
CO, L/min	5.2 ± 1.5 *	8.1 ± 2.2	11.0 ± 3.2 *	5.5 ± 1.5	8.3 ± 1.9	13.3 ± 2.9

* denotes $p<0.05$ difference between HFpEF and HTN controls. Table displays raw values.

Abbreviations: CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; HTN, hypertension; PCWP, pulmonary capillary wedge pressure; and SBP, systolic blood pressure.

Table 3.

Adjusted arterial stiffness and load parameters during exercise among HFpEFand hypertensive participants

	HFpEF	HTN control	P-value
AP (mmHg)			
Rest	12.80 (7.8)	10.39 (7.9)	p=0.05
30w	1.15 (7.6)	−3.01 (7.6)	p=0.0003
Peak	−6.00 (8.6)	−11.75 (8.6)	p=0.0001
Aix (%)			
Rest	23.14 (9.2)	19.55 (9.3)	p=0.01
30w	0.45 (9.3)	−4.83 (9.3)	p=0.0002
Peak	−9.06 (11.6)	−16.81 (11.6)	p=0.0001
SVRI (dynes-sec*m^2/cm^5)			
Rest	8.10 (0.03)	8.05 (0.03)	p=0.14
30w	7.65 (0.03)	7.75 (0.03)	p=0.005
Peak	7.44 (0.03)	7.28 (0.03)	p<0.0001
EaI (mmHg*m^2/ml)			
Rest	1.37 (0.03)	1.35 (0.03)	p=0.61
30w	1.25 (0.03)	1.15 (0.03)	p=0.004
Peak	1.30 (0.03)	1.16 (0.03)	p=0.0001
TACI ml/mmHg*m^2)			
Rest	−0.40 (0.03)	−0.32 (0.03)	p=0.03
30w	−0.33 (0.03)	−0.19 (0.03)	p=0.0002
Peak	−0.35 (0.03)	−0.20 (0.04)	p<0.0001
PPA (mmHg)			
Rest	1.37 (0.02)	1.46 (0.02)	p=0.001
30w	1.44 (0.02)	1.53 (0.02)	p=0.0006
Peak	1.68 (0.02)	1.82 (0.03)	p<0.0001

Values are expressed as mean (standard error), and values are adjusted for age, sex, body mass index, and presence of diabetes mellitus. AP and Aix also are adjusted for heart rate. Abbreviations: Aix, augmentation index; AP, aortic augmentation pressure; EaI, elastance index; HTN, hypertension; PPA, pulse pressure amplification; SVRI, systemic vascular resistance index; and TACI, total arterial compliance index.

Table 4.

Association of arterial stiffness and load with exercise cardiac performance, including PCWP/CO slope and peak VO_2

	Rest r (P-value)	30W r (P-value)	Peak r (P-value)
PCWP/CO slope			
AP	0.17 (0.001)	0.24 (<0.0001)	0.24 (<0.0001)
Aix	0.14 (0.008)	0.19 (0.003)	0.22 (<0.0001)
SVRI	0.03 (0.60)	0.18 (0.001)	0.30 (<0.0001)
EaI	0.01 (0.78)	0.18 (0.0007)	0.27 (<0.0001)
TACI	−0.10 (0.04)	−0.23 (<0.0001)	−0.27 (<0.0001)
PPA	−0.12 (0.02)	−0.19 (0.0003)	−0.23 (<0.0001)
Peak VO_2			
AP	−0.05 (0.29)	−0.05 (0.30)	−0.08 (0.14)
Aix	−0.09 (0.09)	−0.07 (0.22)	−0.07 (0.15)
SVRI	−0.10 (0.06)	−0.08 (0.17)	−0.29 (<0.0001)
EaI	−0.11 (0.04)	−0.13 (0.02)	−0.13 (0.01)
TACI	0.10 (0.049)	0.12 (0.03)	0.12 (0.03)
PPA	0.04 (0.42)	0.02 (0.70)	0.23 (<0.0001)

Values are expressed as partial correlation coefficient, r, (p-value). Values are adjusted for age, sex, body mass index, and presence of diabetes mellitus. AP and Aix also are adjusted for heart rate. Abbreviations: Aix, augmentation index; AP, aortic augmentation pressure; CO, cardiac output; EaI, elastance index; HTN, hypertension; PCWP, pulmonary capillary wedge pressure; PPA, pulse pressure amplification; SVRI, systemic vascular resistance index; TACI, total arterial compliance index; and VO2, oxygen consumption.