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Research paper

Arterial stiffness assessment in coronary microvascular dysfunction and heart failure with preserved ejection fraction: An initial report from the WISE-CVD continuation study

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is the most common cardiac complication in patients with coronary microvascular dysfunction (CMD), yet its underlying pathways remain unclear. Aortic pulse-wave velocity (aPWV) is an indicator of large artery stiffness and a predictor for cardiovascular disease. However, aPWV in CMD and HFpEF is not well characterized and may provide understanding of disease progression.

Methods: Among participants without obstructive coronary artery disease, we evaluated 51 women with suspected CMD and 20 women and men with evidence of HFpEF. All participants underwent aPWV measurement (SphygmoCor, Atcor Medical) with higher aPWV indicating greater vascular stiffness. Cardiac magnetic resonance imaging (CMRI) assessed left ventricular (LV) ejection fraction, CMD via myocardial perfusion reserve index (MPRI), and ventricular remodeling via LV mass-volume ratio. . Statistical analysis was performed using Wilcoxon rank sum tests, Pearson correlations and linear regression analysis.

Results: Compared to the suspected CMD group, the HFpEF participants were older (65 ± 12 vs 56 ± 11 yrs., $p = 0.002$) had higher BMI (31.0 ± 4.3 vs 27.8 ± 6.7 kg/m^2, $p = 0.013$), higher aPWV (10.5 ± 2.0 vs 8.0 ± 1.6 m/s, $p = 0.05$) and lower MPRI (1.5 ± 0.3 vs1.8 ± 0.3, $p = 0.02$), but not remodeling. In a model adjusted for cardiovascular risk factors, the HFpEF group had a lower LVEF (estimate -4.78, $p = 0.0437$) than the suspected CMD group.

Conclusions: HFpEF participants exhibit greater arterial stiffness and lower myocardial perfusion reserve, with lower LVEF albeit not remodeling, compared to suspected CMD participants. These findings suggest arterial stiffness may contribute to progression from CMD to HFpEF. Prospective work is needed and ongoing.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death of men and women and is linked to arterial stiffness [1]. In contrary to systolic dysfunction and obstructive CAD, women are more likely to present with HFpEF [2] and CMD in the setting of no obstructive CAD, compare to men [3]. HFpEF is increasingly prevalent condition which accounts for almost one-half of all heart failure, particularly in women [4]. The contributors to HFpEF are unclear but may be related to vascular stiffness.

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Modern-day lifestyle risk factors – including hypertension – contribute to left ventricular remodeling, diastolic dysfunction and consequently HFpEF [5]. Aortic pulse wave velocity (aPWV) has been established as the gold standard for assessing arterial stiffness [6]. The aPWV is a direct measure of large arterial stiffness. Augmentation index (AAI) is a surrogate measure of arterial rigidity that could be affected by the ventricular ejection and peripheral hemodynamics in addition to the properties of large arteries [7]. Previous investigations in women with symptoms and signs of myocardial ischemia in the absence of obstructive coronary artery disease (INOCA) from the Women's Ischemia Syndrome Evaluation (WISE) revealed aortic systolic pressure, as an index of aortic stiffness, was associated with CMD indicated by low coronary flow reserve (CFR) [8,9].

Previous investigation documented the development of heart failure hospitalization, validated to be HFpEF, as the most common adverse cardiac event in follow-up after a diagnosis of CMD [10]. Aortic stiffness increases left ventricular (LV) afterload and workload, resulting in escalation of myocardial oxygen demand, LV hypertrophy and myocardial dysfunction [9]. Prior work also demonstrates the link between hypertension and large artery stiffness with lower CFR and myocardial ischemia [11]. We have previously reported lower CFR is related higher aortic stiffness in women with suspected CMD [8]. However, relations between arterial stiffness, myocardial perfusion and ventricular remodeling in patients with CMD vs HFpEF in the absence of obstructive CAD have not been described. To explore this further, using an initial cross-sectional design, we hypothesized that arterial stiffness contributes to both CMD and HEpEF, and therefore may be a contributor to progression from CMD to HFpEF.

2. Methods

We recruited 51 women with suspected CMD and 20 women and men with HFpEF in a single center (NCT02582021). The CMD group included women with signs or symptoms of myocardial ischemia undergoing clinically indicated coronary angiography and function testing [3] . The HFpEF group included women and men diagnosed with HFpEF as defined by the European Society of Cardiology (ESC) [12]. The study received full IRB approval and all participants consented to participate in the study.

2.1. Cardiac magnetic resonance imaging (CMRI)

Stress and rest CMRI were obtained using 3.0 Tesla scanners (Magnetom Verio and Biograph mMR, Siemens Healthcare, Erlangen, Germany) in the supine position with electrocardiogram (ECG)-gating, previously published [13]. Participants were asked to withhold cardiac medications 24–48 h and caffeine 24 h prior to CMRI as previously described [13]. First-pass perfusion imaging was performed and optimized to reduce subendocardial dark-rim artifact as previously published [14]. Adenosine was infused at a rate of 140 μg/kg/min using an MRI-compatible Medfusion pump for three minutes prior to the first-pass perfusion scan and was continued until end of the perfusion data acquisition, as previously described [13].

Three left-ventricular short-axis slices (basal, mid, and apical) were acquired. Blood pressures were recorded at rest and during vasodilatory stress. The rest scan was acquired at least ten minutes after the stress scan, with identical scan parameter settings and slice positions.

Primary measures of interest for CMRI were defined as myocardial perfusion reserve index (MPRI), LV mass, LV mass/volume ratio, and secondary outcome measures included, LV end diastolic volume (LVEDV), and systolic function (LV ejection fraction).

2.2. CMRI myocardial perfusion reserve index (MPRI)

LV cavity contours and an 18-segment model (six segments per slice) were used to calculate subendocardial MPRI, subepicardial MPRI, transmural (whole, mean) MPRI as previously published [15]. Dedicated software (CVI42, Circle Cardiovascular Imaging, Calgary, Ontario, Canada) was used for analysis of the MPRI. As per prior report, a MPRI threshold of <1.84 was used to define coronary vascular dysfunction [14,16].

2.3. Cardiac morphology and function

Short-axis cine images were placed and manually adjusted to derive LV volumes and LV mass using CVI42 software, as previously described [13]. Papillary muscles were not contoured for measurement of LV mass and were included in the left ventricular (LV) volume measurement.

2.4. Aortic stiffness testing

Aortic stiffness was assessed non-invasively by calculating aortic pulse wave velocity (PVW) and aortic augmentation index (AAIs) via Brachial- Femoral method using SphygmoCor system (AtCor Medical, Sydney, Australia). Brachial systolic pressure (bSP) and diastolic pressure (DP) were measured in the left arm with appropriately-sized cuff using a validated, automatic oscillometric BP monitor (Omron R3, Omron Healthcare, Kyoto, Japan). Three blood pressure reads were performed ≥2 min apart: the average of the last two reads was calculated for this inquiry. Participants did not eat, smoke or drink caffeinated beverage at least 2 h before measurements.

Data was collected while participants were placed in the quiet, temperature-controlled room after resting ≥15 min in supine position. Radial artery pressure waveforms were measured at the wrist, using applanation tonometry with a high-fidelity micro-manometer (Millar Instruments, Houston, TX) [17]. The multiple aPWV measures were averaged per participant.

2.5. Statistical analysis

Variables were summarized using mean ± standard deviation (SD) or counts (percentages) where appropriate. The HFpEF and suspected CMD groups were compared for Table 1 using *t*-tests for continuous variables and Fisher's Exact test for categorical. Table 2 used linear regression with the row variable as the outcome and group and age as explanatory variables. Multiple linear regression models were made for EF, LV EDV indexed by BSA. These models included group and adjusted for age, history of hypertension, dyslipidemia, diabetes and smoking. Model estimates are in Table 3. All tests used a significance level of 0.05.

Table 1
Baseline characteristics in suspected CMD and HFpEF groups.

	Suspected CMD group (n:51)	HFpEF group (n:20)	*p*-Value
Age (yrs ± SD)	**56 ± 11**	**65 ± 12**	**0.002**
Race			0.311
American Indian or Alaska Native	2 %	5 %	
Black or African American	4 %	10 %	
Hispanic/Latino	8 %	15 %	
White	86 %	70 %	
Male	0 %	45 %	**<0.0001**
BMI (kg/m^2)	27.8 ± 6.7	31.0 ± 4.3	**0.013**
HF	6.25 %	47.37 %	**0.0003**
Current smoker	3.92 %	10 %	0.314
Current/former smoker	21.6 %	40 %	0.141
Family history of CAD	52.9 %	15 %	**0.004**
History of hypertension	38 %	75 %	**0.008**
Diabetes	7.8 %	15 %	0.394
Dyslipidemia	20.4 %	33 %	0.336

BMI: Body Mass Index; HF: Heart Failure; CAD: Coronary Artery Disease. The bold font indicates statistical significance. Heart failure with preserved ejection fraction (HFpEF) coronary microvascular dysfunction (CMD).

Table 2
Cardiac MRI stress testing and aortic hemodynamic variables for suspected CMD vs HEpEF groups.

Variables Data presented are mean ± standard deviation or %	Suspected CMD (n:51)	HFpEF (n:20)	Age adjusted *P* values
Resting Heart Rate (bpm)	59.8 ± 9.6	70.4 ± 10.3	**0.003**
Resting Systolic Pressure (mmHg)	125.7 ± 15.4	140.4 ± 21.6	0.23
Resting Diastolic Pressure (mmHg)	74.8 ± 9.2	85.0 ± 11.6	**0.04**
Resting Mean Pressure (mmHg)	90.8 ± 11.1	103.6 ± 14.7	**0.03**
Resting Pulse Pressure (mmHg)	50.8 ± 10.7	55.4 ± 15.6	0.88
Aortic Systolic Pressure (mmHg)	116.6 ± 14.3	129.5 ± 20.5	0.33
Aortic Pulse Pressure (mmHg)	41.0 ± 9.0	43.4 ± 14.1	0.48
Aortic Pulse Wave Velocity (cm/s)	8.0 ± 1.6	10.5 ± 2.0	**0.05**
Aortic Augmentation Index (%)	35.2 ± 11.2	32.2 ± 9.7	**0.04**
LVEF (%)	62.1 ± 5.6	58.6 ± 8.1	**0.039**
LV mass/ vol. ratio (gr/cm^3)	0.65 ± 0.1	0.74 ± 0.1	0.06
MPRI	1.8 ± 0.3	1.5 ± 0.3	**0.02**
MPRI≤1.84	55 %	87.5 %	0.1062

LVEF: Left Ventricular Ejection Fraction; LV mass/vol. ratio: Left Ventricular mass to left ventricular volume ratio; MPRI: myocardial perfusion reserve index. The bold font indicates statistical significance. Heart failure with preserved ejection fraction (HFpEF) coronary microvascular dysfunction (CMD) magnetic resonance imaging (MRI).

Table 3
Multivariable linear regression of outcome EF (%) on all row variables.

Model effect	Estimate	Standard error	P-value
Model intercept	60.0	4.58	<0.0001
Slope Age per year (%/year)	0.049	0.08	0.56
Group CCTA vs CRT (%)	−4.78	2.31	0.0437
Ever smoker vs not (%)	−2.56	2.19	0.25
Hx hypertension vs not (%)	−0.72	1.93	0.71
Hx diabetes vs not (%)	−0.28	3.13	0.93
Hx Dyslipidemia vs not (%)	2.16	2.49	0.39

3. Results

3.1. Baseline characteristics

Baseline group clinical characteristics were summarized in Table 1. As expected, the mean age was older in the HFpEF vs suspected CMD group. The traditional major cardiovascular diseases risk factors including age, hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity were higher in the HFpEF group with the exception of family history of CAD which was statistically significantly higher in suspected CMD group.

3.2. Hemodynamic characteristics

Age-adjusted variables are summarized in the HFpEF vs the suspected CMD group in Table 2. In the HFpEF group the heart rate, systolic and diastolic pressure were significantly higher compared to suspected CMD group. Aortic pulse wave velocity was significantly higher in the HFpEF group compared to the suspected CMD group. Aortic augmentation index (AAI) was statistically significant lower in the HFpEF group. While LVEF in the HFpEF group was lower than the suspected CMD group, LV mass/volume ratio was significantly lower in the suspected CMD group. Myocardial perfusion measured by CMRI in both groups was MPRI≤1.8, although it was significantly more often met the abnormally low threshold in the HFpEF group (55 % in suspected CMD group vs 87.5 % in than HFpEF group) (Table 2).

3.3. Multivariable modeling

A model with LVEF as the outcome (Table 3) demonstrated a difference in LVEF between the groups, adjusted for age, smoking, history of hypertension, diabetes and dyslipidemia, with the HFpEF group having a lower LVEF (estimate −4.78, $p = 0.0437$), however this was not observed for LVEDV/BSA. None of the other covariates were significantly associated with EF in this model.

4. Discussion

In an initial cross-sectional analysis of arterial stiffness in both HFpEF and suspected CMD groups, we observed comparatively relatively higher arterial stiffness and lower myocardial perfusion reserve, albeit not remodeling in the HFpEF group. Our findings also demonstrate adjusted lower LVEF but not different ventricular remodeling in the HFpEF compared to the suspected CMD group. These findings support the hypothesis that arterial stiffness may contribute to progression from CMD to HFpEF and suggest that prospective work be undertaken to test this potential contributor.

Central aortic stiffness measured by aPWV velocity is positively associated with age [18] . The AAI represents the arterial rigidity associated with ventricular ejection [17]. Our current findings are consistent with our prior report in the WISE study of increased arterial stiffness associated with increased myocardial energy demand to overcome increased left ventricular afterload, likely due to reduced nitric oxide production contributing to CMD [8]. The current results extend these observations to a HFpEF group demonstrating a higher large arterial stiffness and lower myocardial perfusion reserve compared to the suspected CMD group.

Prior work by Nichols et al. [8] described that altered large arterial flexibility – associated with different risk factors including but not limited to age, smoking, obesity- induces changes in arterial properties and consequently increase LV afterload demanding the ventricle to produce additional, but wasted, energy that intensifies indices of myocardial oxygen demand and reduced nitrite oxide production. The increased large arterial stiffness increases afterload which can subsequently increase myocardial energy demand to overcome increased LV afterload [8]. As a result, increased afterload can cause LV wasted energy, and consequently increased myocardial oxygen demand and eventually cause myocardial ischemia leading to endothelial and diastolic dysfunction [8,19]. Ongoing prospective investigation is investigating these potential contributors to HFpEF in patients with CMD.

5. Limitations

Our relatively small sample sizes results may not be generalizable to all patients. The suspected CMD group was exclusively women while the HFpEF group were includes both men and women. No control group was included in this study.

6. Conclusions

We demonstrate in an initial cross-sectional analysis of arterial stiffness in HFpEF and suspected CMD relatively higher arterial stiffness and lower myocardial perfusion reserve in the HFpEF group. These findings suggest arterial stiffness may be a contributor to progression from CMD to HFpEF. Prospective work is needed and ongoing.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Ethical statement

All authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association and the manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

Since Dr. Pepine is a co-author, the peer review of this manuscript was managed by the guest editor Dr. Samir Alam.

CRediT authorship contribution statement

P. Rezaeian: Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **C.L. Shufelt:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **J. Wei:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – review & editing. **C. Pacheco:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. **G. Cook-Wiens:** Data curation, Formal analysis, Project administration, Resources, Validation, Writing – review & editing. **D. Berman:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. **B. Tamarappoo:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. **L.E. Thomson:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. **M.D. Nelson:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. **R.D. Anderson:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. **J. Petersen:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. **E.M. Handberg:** Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – review & editing. **C.J. Pepine:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. **C.N. Bairey Merz:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

Dr. Bairey Merz has disclosures from iRhythm and SHL Telemedicine. Dr. Pepine: Research Grant from Gilead Sciences, Inc., Pfizer, Park-Davis, Sanofi-Aventis, Fujisawa HealthCare Inc., Baxter, Brigham & Women's Hospital, AstraZeneca, NIH/NHLBI, Amorcyte/Neostem, Cytori, InfraReDx, NHLBI/NCRR CTSA grant 1UL1RR029890, AHA. Consultant/Advisory Board: NIH Study Section of Cardiovascular Sciences Small Business Activities 2RG1 CVS-K-10, Lilly/Cleveland Clinic DSMB Member for a Phase 2 Efficacy and Safety Study of Ly2484595, Medtelligence, NHLBI Study Section for Progenitor Cell Biology Consortium, NHLBI DSMB Chair for Freedom Trial. Dr. Handberg receives research grants from Aastrom Biosciences, Amorcyte, Biocardia, Brigham and Women's Hospital, Capricor, Cytori Therapeutics, Department of Defense, Direct Flow Medical, Duke Clinical Research Institute, East Carolina University, Everyfit Inc., Medtronic, Merck & Co., Mesoblast, National Institutes of Health (NIH), NIH through University of Rochester, NIH through Brigham and Women's Health, NIH through University of Texas, PCORI, and Sanofi Aventis; Research grant and educational grant from Gilead Sciences; Unrestricted educational grants for the Vascular Biology Working Group from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Ionis, and Relypsa; and Consultant fees from Bristol-Myers Squibb Company.

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