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Maladaptive left ventricular remodeling in women: An analysis from the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction study☆,☆☆

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ABSTRACT

Background: Women represent approximately half of heart failure hospitalizations and are disproportionately affected by heart failure with preserved ejection fraction (HFpEF). Women with signs and symptoms of ischemia, preserved left ventricular ejection fraction (LVEF), and no obstructive coronary artery disease (CAD) often have elevated left ventricular end-diastolic pressure (LVEDP). However, isolated elevated LVEDP in the absence of coronary microvascular dysfunction (CMD) is not understood.

Methods: Among 244 women with signs and symptoms of ischemia, no obstructive CAD, and preserved LVEF who underwent invasive coronary reactivity testing (CRT), 43 (18%) women had no evidence of CMD. LVEDP was measured at time of CRT, and left ventricular (LV) volumes and mass were assessed by cardiac magnetic resonance (CMR) imaging.

Results: Of the 43 women without CMD, 24 (56%) had elevated LVEDP [mean 18 mm Hg (SD = 3)] compared to 19 (44%) with normal LVEDP [11 mm Hg (SD = 3)]. The elevated LVEDP group had a comparatively higher systolic and diastolic blood pressure, lower LV end-diastolic volume index (EDVI), and higher mass-to-volume ratio. Other functional parameters were not significantly different.

Conclusions: Among women with signs and symptoms of ischemia without obstructive CAD, absence of CMD, and preserved LVEF, isolated elevated LVEDP is associated with a significantly higher systolic and diastolic blood pressure, higher LV mass-to-volume ratio and lower LV EDVI. These results suggest these women have maladaptive remodeling to blood pressure. Given the relatively high prevalence of HFpEF in women, these hypothesis-generating results suggest that further study of ventricular remodeling is warranted.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Heart failure represents a significant and growing public health problem in the United States, with 1 in 5 men and women at risk for developing it in their lifetimes [1]. Women represent approximately half of heart failure hospitalizations, but are disproportionately affected by heart failure with preserved ejection fraction (HFpEF) and have twice the likelihood of developing the disease compared to men [2–4]. The spectrum of pathophysiologic changes in HFpEF includes varying degrees of cardiomyocyte stiffness, myocardial interstitial fibrosis, and coronary microvascular dysfunction (CMD) that all contribute to diastolic dysfunction [3,5]. This altered myocardial relaxation can manifest in part as elevated left ventricular end-diastolic pressure (LVEDP) [6,7].

Prior work in the Women's Ischemic Syndrome Evaluation (WISE) original cohort has shown that in prognostic follow-up of women with preserved left ventricular ejection fraction (LVEF) and no obstructive coronary artery disease (CAD), hospitalization for heart failure was the most prevalent adverse outcome over the 5-year follow-up period [8]. Better characterization of ventricular function in this cohort is needed.

We have previously shown that LVEDP is linearly related to measured LV end-diastolic volume in a subset of the WISE original cohort, but measurements of LV mass were not available, and results were not stratified by myocardial ischemia or presence of CMD [9]. Additionally, in another subset of the WISE original cohort, we found no association between coronary flow reserve (CFR), an invasive measure of CMD, and echocardiographic measures of LV remodeling in a relatively small sample size [10]. Cardiac magnetic resonance (CMR) imaging provides superior ability to quantify LV anatomy and function, and CMR was performed in a large sample of women enrolled in the National Heart, Lung, and Blood Institute-sponsored prospective multicenter WISE-Coronary Vascular Dysfunction (WISE-CVD) study. To understand relations in ventricular anatomy and function in the absence of obstructive CAD or CMD, we investigated relationships between LV volumes and mass measured by CMR in women with symptoms and signs of ischemia, but no obstructive CAD or CMD.

2. Methods

2.1. Study design

Among the total 406 WISE-CVD participants, we included 244 women with complete CRT, LVEDP, and CMR measures [11]. The study protocol was approved by the institutional review committee at Cedars-Sinai Medical Center, Los Angeles, California and the University of Florida, Gainesville, Florida, and all women provided written informed consent.

Women were eligible for participation if they were 18 years of age or older with signs and symptoms of myocardial ischemia prompting a clinically indicated coronary angiogram for suspected coronary artery disease. The full list of exclusion criteria has been previously published [11].

Long-acting nitrates, short-acting calcium-channel blockers, alpha-blockers, beta-blockers, and ACE-I/angiotensin-II-receptor antagonists were withdrawn 24 h and long acting calcium-channel blockers were held for 48 h prior to CRT, LVEDP, and CMRI testing which was conducted in the morning after an overnight fast. Sublingual nitroglycerin was not taken within 4 h prior to testing and participants were caffeine-free and nicotine-free for 24 h prior to vasodilator stress.

2.2. CRT protocol

Invasive CRT was conducted as previously published [12]. All women had no obstructive CAD. Abnormal LVEDP was defined as ≥15 mm Hg, approximating the threshold used by the American College of Cardiology Foundation and American Heart Association [13]. Absence of CMD was defined as having normal coronary responses to intracoronary adenosine and acetylcholine, defined as a change in baseline coronary flow reserve of ≥2.5, coronary blood flow response ≥50%, and/or acetylcholine coronary diameter response >0%.

2.3. CMR

CMR was performed as previously published [11]. As indicated above, CMR was performed after an overnight fast. CMR data were analyzed in a dedicated core laboratory with review of all data contours by an experienced reader.

2.4. Statistical methods

Values included in this study are summarized as mean ± standard deviation or percentage where appropriate. Women with elevated LVEDP values were compared to those with normal values using two sample *t*-tests and Fisher's exact test. Analysis of linear correlation between variables was performed using Pearson's correlation coefficient. Multiple linear regression models were made to evaluate the association of the outcomes of LV mass-to-volume ratio, SBP, DBP, EDV index, and ESV index with the explanatory factor LVEDP, adjusted for other clinical variables. Standard stepwise selection was used to select variables with the largest F statistic to the model and used a level of 0.15 to keep variables in the model. Regression analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). p values ≤0.05 were considered statistically significant.

3. Results

Overall, among the 43 women with no CMD, 24 (56%) had elevated LVEDP [≥15 mm Hg; mean 18 mm Hg (SD = 3)] compared to 19 (44%) with normal LVEDP [<15 mm Hg; mean 11 mm Hg (SD = 3)]. Clinical characteristics of the women with elevated LVEDP and those with normal LVEDP are presented in Table 1. The elevated LVEDP group had significantly higher resting systolic blood pressure ($p = 0.02$) and diastolic blood pressure ($p = 0.02$). There were no additional significant differences noted between the two groups with regard to co-morbidities and medication history.

The LV end-diastolic volume index (EDVI) was significantly lower in women with elevated LVEDP ($p = 0.03$). LV end-systolic volume index (ESVI) was not statistically significant between the two groups [mean 21 (SD = 6) in the elevated LVEDP group versus mean 25 (SD = 9), $p = 0.06$]. LV mass-to-volume ratio was significantly greater in women with elevated LVEDP compared to women with normal LVEDP ($p = 0.0003$). The remaining functional parameters tested were not different (Table 2).

The correlation coefficients for the significant functional parameters tested are shown in Fig. 1. An incrementally higher LVEDP showed a positive correlation with LV mass-to-volume ratio ($p = 0.0015$; $r = 0.49$), resting systolic blood pressure ($p = 0.011$; $r = 0.38$), and resting diastolic blood pressure ($p = 0.019$, $r = 0.36$). Conversely, a higher LVEDP was negatively associated with LV EDVI ($p = 0.027$; $r = -0.35$) and LV ESVI ($p = 0.031$; $r = -0.35$). Additionally, increase in mass-to-volume ratio showed a positive correlation with resting systolic blood pressure ($p = 0.0048$; $r = 0.44$).

Table 1
Clinical findings in women without CMD with normal and elevated left ventricular end-diastolic pressure (n = 43).

Variable	LVEDP <15 mm Hg (n = 19) [Mean ± (SD)]	LVEDP ≥15 mm Hg (n = 24) [Mean ± (SD)]	p-Value
Age	52.3 (7.4)	55.5 (11.2)	0.35
Postmenopausal	8/16 (50%)	15/21 (71.4%)	0.31
Systolic blood pressure (mm Hg)	121 (18)	135 (20)	0.02
Diastolic blood pressure (mm Hg)	70 (9)	79 (13)	0.02
History of diabetes mellitus (%)	0	9.5	0.50
History of hypertension (%)	26.7	40	0.49
History of dyslipidemia (%)	9.1	21.4	0.60
Creatinine (mg/dL)	0.78 (0.11)	0.73 (0.10)	0.26
Body mass index (kg/m^2)	26 (5)	29 (9)	0.21
Body surface area (m^2)	1.70 (0.17)	1.80 (0.20)	0.10
Any anti-hypertensive medication (%)	56	71	0.49
ACE-inhibitor (%)	6	20	0.35
Angiotensin receptor blocker (%)	0	10	0.49
Beta blocker (%)	6	35	0.053
Calcium channel blocker (%)	25	15	0.68
Diuretic (%)	13	15	1
Nitrate (%)	31	33	1
Ranolazine (%)	0	10	0.49

Abbreviations: ACE, angiotensin-converting enzyme; LVEDP, left-ventricular end-diastolic pressure.