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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 mmHg (SD=3)] compared to 19 (44%) with normal LVEDP [11 mmHg (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.

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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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.

Keywords

ischemic heart disease; left ventricular end-diastolic pressure; cardiac magnetic resonance imaging; women

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 lifetimes¹. 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 include 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 period⁸. 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 CMD⁹. 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 size¹⁰. 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 measures¹¹. 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 published¹¹.

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calcium-channel blockers, alpha-blockers, beta-blockers, and ACE-I/angiotensin-II-receptor antagonists were withdrawn 24 hours and long acting calcium-channel blockers were held for 48 hours prior to CRT, LVEDP, and CMRI testing which was conducted in the morning after an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

2.2 CRT protocol

Invasive CRT was conducted as previously published¹². All women had no obstructive CAD. Abnormal LVEDP was defined as ≥ 15 mmHg, approximating the threshold used by the American College of Cardiology Foundation and American Heart Association¹³. 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 $\geq 50\%$, and/or acetylcholine coronary diameter response $\geq 0\%$.

2.3 CMR

CMR was performed as previously published¹¹. 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 $\pm$ 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 mmHg; mean 18 mmHg (SD=3)] compared to 19 (44%) with normal LVEDP [<15 mmHg; mean 11 mmHg (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 Figure 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 ($p=0.0048$; $r=0.44$).

Overall time between CRT and CMR testing was mean 46 days (SD=119) and median 20 days (range -233 to 525 days). 35 people had both CRT and CMR within three months of each other, four people had these done further apart, only two of them more than a year apart. The correlation of LVEDP and age was not significant ($r=-0.1$, $p=0.57$), nor was the difference in average LVEDP between post-menopausal and pre-menopausal groups (14.8 vs 15, t test $p=0.92$). The previous correlations in the results were adjusted for age and menopausal status, and other clinical factors using multiple linear regression.

Stepwise selection for LV mass-to-volume ratio as the outcome selected only LVEDP and history of hypertension as significant explanatory factors. Forcing LV mass-to-volume ratio to be adjusted for age and postmenopausal status in addition to LVEDP and hypertension still shows a significant association of LV mass-to-volume ratio with LVEDP (adjusted slope=0.013 per unit increase in LVEDP, $p=0.0018$, $n=31$) although the other factors were not significant.

The model with SBP as the outcome had LVEDP, age, history of hypertension, and postmenopausal status as covariates and showed the same trend with LVEDP, but without statistical significance for the other factors (adjusted slope=1.95 per unit increase in LVEDP, $p=0.025$, $n=34$).

Stepwise selection for the model with DBP as the outcome had hemoglobin and LVEDP as explanatory factors, although LVEDP was not significant at the 0.05 level. Forcing age and

menopausal status into this model gives four explanatory factors and the trend with LVEDP is still the same as before (adjusted slope=0.87 per unit increase in LVEDP, $p=0.028$, $n=35$).

The model with EDVI as the outcome showed LVEDP, hemoglobin and menopausal status as significant explanatory factors. Forcing age into the model still showed the same trend with LVEDP (adjusted slope= -0.58 per unit increase in LVEDP, $p=0.055$, $n=32$), and age was not significant while the other two factors, hemoglobin and menopausal status were significant.

Stepwise selection in the regression of ESVI indicated LVEDP, menopausal status, hemoglobin and BMI as covariates. Adding age in the model gave five explanatory factors, and only age was not significant at the 0.05 level. LVEDP had a similar trend as in the correlation analysis (adjusted slope= -0.47 per unit increase in LVEDP, $p=0.044$, $n=32$).

The model with SBP as the outcome that adjusts for LV mass-to-volume ratio, age, postmenopausal status, and history of hypertension showed only LV mass-to-volume ratio significant at the 0.05 level, and the positive trend with LV mass-to-volume ratio was still present (adjusted slope=84.1 per unit increase in LV mass-to-volume ratio, $p=0.03$, $n=31$).

4. Discussion

Our results demonstrate that among women with signs and symptoms of ischemia, no obstructive CAD, preserved LVEF, and no CMD, those with elevated LVEDP have a significantly higher blood pressure, LV mass, and LV mass-to-volume ratio as well as lower EDVI compared to the women with normal LVEDP. There is a positive correlation between LVEDP and mass-to-volume ratio as well as systolic and diastolic blood pressure, whereas ESVI and EDVI are negatively correlated with LVEDP. These results are contrary to the prior findings of the original WISE cohort which showed a positive linear relation between LVEDP and end-diastolic volume,⁹ and suggest there may be different mechanisms of LV remodeling in women with and without CMD. In particular, these findings suggest that there is blood pressure-related adverse cardiac remodeling occurring that may precede signs of coronary micro- or macrovascular dysfunction. While prior studies have assessed LV structure and volume in health and disease states in the general population,^{14, 15} this is the first study to assess whether adverse LV remodeling seen in this cohort of women occurs in the absence of CMD, and addresses the question of if blood pressure-related maladaptive remodeling may precede CMD development. Given that hospitalization for HFpEF is the predominant adverse outcome at 5-year follow-up in women with non-obstructive CAD, understanding the mechanisms that contribute to the development of this syndrome remains a critical need.

An increase in the LV mass-to-volume ratio is indicative of concentric remodeling and likely reflects LV morphological changes from elevated blood pressure. It has been previously shown that there exists an independent and continuous relationship between adverse LV remodeling and systolic blood pressure.¹⁶ This finding of early cardiac structural change in the absence of identifiable CMD is important because increased mass-to-volume ratio has been shown to be an independent predictor of adverse cardiovascular events, particularly in

adults under the age of 65 years.¹⁷ In a prospective study of 5,098 individuals followed up for a median of four years, increased mass-to-volume ratio was associated with incident coronary heart disease and stroke.¹⁸ Concentric remodeling, defined as increased LV mass-to-volume ratio, is also significant because it is associated with changes in arterial structure and function, including increased carotid intima-media thickness, atherosclerotic plaque burden, and arterial stiffness.^{19–21} A 2011 meta-analysis of 7,465 individuals with either concentric remodeling or normal geometry showed that individuals with concentric remodeling had significantly higher risk of fatal and non-fatal cardiovascular events.²² Interestingly, a retrospective analysis of 35,602 individuals referred for echocardiography found that normalization of concentric remodeling was associated with improved survival (RR 0.64, 95% CI 0.42 to 0.97, $p=0.03$) while progression to LV hypertrophy increased mortality (RR 1.54, 95% CI 1.01 to 2.47, $p=0.05$).²³ Additionally, there is an association with extracardiac organ damage, including microalbuminuria, retinopathy, and stroke.^{18, 24, 25} Individuals without CAD who have concentric LV changes have reduced exercise capacity compared to those with structurally normal hearts.²⁶ Concentric remodeling has also been implicated in increased rates of arrhythmia and sudden cardiac arrest.²⁷ Thus, despite having no evidence of CMD on invasive CRT, women with elevated LVEDP and LV mass-to-volume ratio should be counseled regarding future cardiovascular risk.

It is known that modifiable cardiovascular risk factors are associated with subclinical changes in LV geometry and systolic function on CMR.²⁸ Elevated blood pressure-related anatomical remodeling likely had a significant impact on our findings. Our study found that blood pressure was significantly higher in women with elevated LVEDP, which may have led to cardiac remodeling.²⁹ Our findings are consistent with prior studies showing that hypertensive patients without systolic dysfunction have high incidence (51%) of elevated LVEDP³⁰. Additionally, we found that incremental increase in systolic blood pressure showed a strong positive correlation with mass-to-volume ratio. Pressure overload of the LV results in increase in relative wall thickness even before an increase in LV mass is detectable. These compensatory early changes allow for maintenance of systolic wall stress in a manner that preserves LVEF¹⁵. While initial cardiac structural changes are beneficial as an adaptive response to hemodynamic overload, prolonged hypertension is a well-known risk factor for maladaptive cardiac remodeling³¹. Previous studies have shown that individuals with hypertension who have evidence of concentric remodeling are at increased risk for adverse cardiovascular events^{32–34}.

Women with signs and symptoms of ischemia, no obstructive CAD, and preserved LVEF have been demonstrated to be at increased risk for heart failure hospitalizations as compared to asymptomatic women identified in the community³⁵. WISE investigators have recently reported that these heart failure hospitalizations are primarily heart failure with preserved ejection fraction (HFpEF)³⁶. Our results suggest that maladaptive remodeling may play a role in this increased frequency of heart failure in this population with signs and symptoms of ischemia but no CMD by CRT. LV diastolic function as measured by isovolumic relaxation time has been shown to be decreased in concentric remodeling³⁷. In a study of 181 hypertensive patients without systolic dysfunction undergoing echocardiography to assess LV geometry, LV end-diastolic volume and end-systolic volume were reduced among patients with evidence of concentric remodeling³⁸. Compared to patients with normal

geometry, those with concentric remodeling had a significantly higher E/E' ratio, a measurement for estimating LV filling pressure, indicating early evidence of diastolic dysfunction. Other indices of LV relaxation have also been shown to be impaired in hypertensive patients without CVD with concentric remodeling present on echocardiography³⁹. In comparison to men, women have poorer diastolic function and greater LV diastolic stiffness and systolic stiffness, suggesting diastolic dysfunction may account for the higher predisposition to HFpEF in women⁴⁰.

4.1 Study limitations

Given the cross-sectional nature of this study, our findings indicate only an association between elevated LVEDP and relevant cardiac parameters, not impact or causality. The sample size of 43 patients is small and may not have been adequately powered to detect all significant differences between the variables tested. However, a significantly higher mass-to-volume ratio was found in patients with elevated LVEDP despite the small sample size. While there was no statistically significant difference in self-reported history of hypertension, women with elevated LVEDP had significantly higher blood pressure measured at baseline. Hypertension remains poorly diagnosed and managed as women are particularly prone to developing resistant hypertension with adverse long-term outcomes⁴¹. Additionally, these self-reported histories may have underestimated the number of truly hypertensive women in the elevated LVEDP cohort under the updated 2017 American College of Cardiology/American Heart Association blood pressure guidelines, which now defines hypertension as systolic and diastolic blood pressure $\geq 130/80$ ⁴². The CRT protocol used in WISE-CVD may have under-diagnosed CMD in this population, as we injected vasoactive agents into the left main coronary artery rather than selective injection into the left anterior descending artery, where the Doppler and coronary diameter measurements were made. Coronary vasospasm testing with high dose acetylcholine was also not performed in this cohort and may have missed this potential cause of ischemia. Other potential causes for ischemia may have included subendocardial ischemia due to elevated LVEDP, subclinical LV hypertrophy, hypoxia, and anemia^{43, 44}. The absence of men in this study limits any assessment of sex-specific differences in LV structure and function that have been previously described^{45, 46}.

4.2 Conclusions

The presence of elevated LVEDP is associated with a significantly higher mass-to-volume ratio and lower EDVI in women with signs and symptoms of ischemia, no obstructive CAD and no CRT evidence of CMD. Prior studies have shown that increased mass-to-volume ratio is independently associated with increased cardiovascular events, especially heart failure. These results suggest that these women may have a maladaptive remodeling process and that this phenotype should not be ignored despite having no evidence of CMD on CRT. Since the women with elevated LVEDP had significantly higher blood pressure, which correlated with increased mass-to-volume ratio, we hypothesize that pre-clinical hypertension-related maladaptive remodeling may be responsible for future development of HFpEF in this population. Our findings are hypothesis generating and have important prognostic implications, as normalization of concentric remodeling is associated with improved survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. 2011; 123:e18–e209. DOI: 10.1161/CIR.0b013e3182009701 [PubMed: 21160056]
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013; 127:143–52. DOI: 10.1161/CIR.0b013e318282ab8f [PubMed: 23283859]
3. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular Disease in Women: Clinical Perspectives. *Circulation research*. 2016; 118:1273–93. DOI: 10.1161/circresaha.116.307547 [PubMed: 27081110]
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *The New England journal of medicine*. 2006; 355:251–9. DOI: 10.1056/NEJMoa052256 [PubMed: 16855265]
5. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013; 62:263–71. DOI: 10.1016/j.jacc.2013.02.092 [PubMed: 23684677]
6. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. *Journal of the American College of Cardiology*. 2015; 66:1918–33. DOI: 10.1016/j.jacc.2015.08.876 [PubMed: 26493665]
7. Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, Reichek N, Rogers WJ, Merz CN, Sopko G, Pepine CJ. Investigators W. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J*. 2001; 141:735–41. S0002870301653250 [pii]. [PubMed: 11320360]

8. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med.* 2009; 169:843–50. DOI: 10.1001/archinternmed.2009.50 [PubMed: 19433695]
9. Doyle M, Weinberg N, Pohost GM, Merz CN, Shaw LJ, Sopko G, Fuisz A, Rogers WJ, Walsh EG, Johnson BD, Sharaf BL, Pepine CJ, Mankad S, Reis SE, Rayarao G, Vido DA, Bittner V, Tauxe L, Olson MB, Kelsey SF, Biederman RW. Left Ventricular Energy Model Predicts Adverse Events in Women With Suspected Myocardial Ischemia: Results From The NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. *Cardiovascular diagnosis and therapy.* 2013; 3:64–72. [PubMed: 24015377]
10. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, Denardo SJ, McGorray SP, Smith KM, Sharaf BL, Nicholls SJ, Nissen SE, Anderson RD. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol.* 2010; 23:511–9. DOI: 10.1111/j.1540-8183.2010.00598.x [PubMed: 21029178]
11. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, Gill EB, Johnson BD, Kenkre T, Handberg EM, Li D, Sharif B, Berman DS, Petersen JW, Pepine CJ, Bairey Merz CN. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. *Circulation Cardiovascular imaging.* 2015; : 8.doi: 10.1161/CIRCIMAGING.114.002481
12. Wei J, Mehta PK, Johnson BD, Samuels B, Kar S, Anderson RD, Azarbal B, Petersen J, Sharaf B, Handberg E, Shufelt C, Kothawade K, Sopko G, Lerman A, Shaw L, Kelsey SF, Pepine CJ, Merz CN. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. *JACC Cardiovascular interventions.* 2012; 5:646–53. DOI: 10.1016/j.jcin.2012.01.023 [PubMed: 22721660]
13. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *Journal of the American College of Cardiology.* 2009; 53:1573–619. DOI: 10.1016/j.jacc.2009.01.004 [PubMed: 19389575]
14. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Santucci A, Santucci C, Reboldi G, Porcellati C. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. *The American journal of cardiology.* 1996; 78:197–202. [PubMed: 8712142]
15. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *Journal of the American College of Cardiology.* 2011; 58:1733–40. DOI: 10.1016/j.jacc.2011.07.022 [PubMed: 21996383]
16. de Marvao A, Dawes TJ, Shi W, Durighel G, Rueckert D, Cook SA, O'Regan DP. Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: A High-Resolution 3D MRI Study. *JACC Cardiovascular imaging.* 2015; 8:1260–9. DOI: 10.1016/j.jcmg.2015.08.007 [PubMed: 26476505]
17. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circulation Cardiovascular imaging.* 2009; 2:191–8. DOI: 10.1161/circimaging.108.819938 [PubMed: 19808592]
18. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *Journal of the American College of Cardiology.* 2008; 52:2148–55. DOI: 10.1016/j.jacc.2008.09.014 [PubMed: 19095132]

19. Cuspidi C, Giudici V, Meani S, Negri F, Sala C, Zanchetti A, Mancia G. Extracardiac organ damage in essential hypertensives with left ventricular concentric remodelling. *Journal of human hypertension*. 2010; 24:380–6. DOI: 10.1038/jhh.2009.87 [PubMed: 19960029]
20. Park HE, Youn TJ, Kim HK, Kim YJ, Sohn DW, Oh BH, Park YB, Cho GY. Different pattern of carotid and myocardial changes according to left ventricular geometry in hypertensive patients. *Journal of human hypertension*. 2013; 27:7–12. DOI: 10.1038/jhh.2011.115 [PubMed: 22237632]
21. Truong QA, Toepker M, Mahabadi AA, Bamberg F, Rogers IS, Blankstein R, Brady TJ, Nagurney JT, Hoffmann U. Relation of left ventricular mass and concentric remodeling to extent of coronary artery disease by computed tomography in patients without left ventricular hypertrophy: ROMICAT study. *Journal of hypertension*. 2009; 27:2472–82. DOI: 10.1097/HJH.0b013e328331054a [PubMed: 19696685]
22. Pierdomenico SD, Di Nicola M, Pierdomenico AM, Lapenna D, Cuccurullo F. Cardiovascular risk in subjects with left ventricular concentric remodeling at baseline examination: a meta-analysis. *Journal of human hypertension*. 2011; 25:585–91. DOI: 10.1038/jhh.2011.24 [PubMed: 21412267]
23. Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. *The American journal of cardiology*. 2006; 97:959–63. DOI: 10.1016/j.amjcard.2005.10.030 [PubMed: 16563894]
24. Cuspidi C, Lonati L, Sampieri L, Pelizzoli S, Pontiggia G, Leonetti G, Zanchetti A. Left ventricular concentric remodelling and carotid structural changes in essential hypertension. *Journal of hypertension*. 1996; 14:1441–6. [PubMed: 8986927]
25. Lam CS, Grewal J, Borlaug BA, Ommen SR, Kane GC, McCully RB, Pellikka PA. Size, shape, and stamina: the impact of left ventricular geometry on exercise capacity. *Hypertension (Dallas, Tex: 1979)*. 2010; 55:1143–9. DOI: 10.1161/hypertensionaha.109.146845
26. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, Poisa P, Rizzoni D, Castellano M, Agabiti-Rosei E. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension (Dallas, Tex: 1979)*. 2004; 43:731–8. DOI: 10.1161/01.HYP.0000121223.44837.de
27. Li L, Shigematsu Y, Hamada M, Hiwada K. Relative wall thickness is an independent predictor of left ventricular systolic and diastolic dysfunctions in essential hypertension. *Hypertension research: official journal of the Japanese Society of Hypertension*. 2001; 24:493–9. [PubMed: 11675942]
28. Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. *Journal of the American College of Cardiology*. 2006; 48:2285–92. DOI: 10.1016/j.jacc.2006.03.072 [PubMed: 17161261]
29. Elhabyan AK, Reyes BJ, Hallak O, Broce M, Rosencrance JG, Lucas BD, Fazal H. Subendocardial ischemia without coronary artery disease: is elevated left ventricular end diastolic pressure the culprit? *Current medical research and opinion*. 2004; 20:773–7. DOI: 10.1185/030079904125003359 [PubMed: 15140345]
30. Rusconi C, Sabatini T, Faggiano P, Ghizzoni G, Oneglia C, Simoncelli U, Gualeni A, Sorgato A, Marchetti A. Prevalence of isolated left ventricular diastolic dysfunction in hypertension as assessed by combined transmitral and pulmonary vein flow Doppler study. *The American journal of cardiology*. 2001; 87:357–60. a10. [PubMed: 11165980]
31. Yoshihara F, Nishikimi T, Yoshitomi Y, Nakasone I, Abe H, Matsuoka H, Omae T. Left ventricular structural and functional characteristics in patients with renovascular hypertension, primary aldosteronism and essential hypertension. *American journal of hypertension*. 1996; 9:523–8. [PubMed: 8783775]
32. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Annals of internal medicine*. 1991; 114:345–52. [PubMed: 1825164]
33. Pierdomenico SD, Lapenna D, Bucci A, Manente BM, Cuccurullo F, Mezzetti A. Prognostic value of left ventricular concentric remodeling in uncomplicated mild hypertension. *American journal of hypertension*. 2004; 17:1035–9. DOI: 10.1016/j.amjhyper.2004.06.016 [PubMed: 15533730]

34. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, Santucci A, Santucci C, Reboldi G, Porcellati C. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *Journal of the American College of Cardiology*. 1995; 25:871–8. DOI: 10.1016/0735-1097(94)00424-o [PubMed: 7884090]
35. Gori M, Lam CS, Gupta DK, Santos AB, Cheng S, Shah AM, Claggett B, Zile MR, Kraigher-Krainer E, Pieske B, Voors AA, Packer M, Bransford T, Lefkowitz M, McMurray JJ, Solomon SD. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *European journal of heart failure*. 2014; 16:535–42. DOI: 10.1002/ehf.67 [PubMed: 24574260]
36. Bakir M, Nelson MD, Jones E, Li Q, Wei J, Sharif B, Minissian M, Shufelt C, Sopko G, Pepine CJ, Merz CN. Heart failure hospitalization in women with signs and symptoms of ischemia: A report from the women's ischemia syndrome evaluation study. *International journal of cardiology*. 2016; 223:936–939. DOI: 10.1016/j.ijcard.2016.07.301 [PubMed: 27589041]
37. de Simone G, McClelland R, Gottdiener JS, Celentano A, Kronmal RA, Gardin JM. Relation of hemodynamics and risk factors to ventricular-vascular interactions in the elderly: the Cardiovascular Health Study. *Journal of hypertension*. 2001; 19:1893–903. [PubMed: 11593112]
38. Cho IJ, Pyun WB, Shin GJ. The influence of the left ventricular geometry on the left atrial size and left ventricular filling pressure in hypertensive patients, as assessed by echocardiography. *Korean circulation journal*. 2009; 39:145–50. DOI: 10.4070/kcj.2009.39.4.145 [PubMed: 19949603]
39. de Simone G, Kitzman DW, Chinali M, Oberman A, Hopkins PN, Rao DC, Arnett DK, Devereux RB. Left ventricular concentric geometry is associated with impaired relaxation in hypertension: the HyperGEN study. *European heart journal*. 2005; 26:1039–45. DOI: 10.1093/eurheartj/ehi019 [PubMed: 15618056]
40. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, Smith KM, Olson MB, Johnson BD, Sopko G, Handberg E, Pepine CJ, Kerensky RA. National Heart L and Blood I. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*. 2004; 109:722–5. DOI: 10.1161/01.CIR.0000115525.92645.16 [PubMed: 14970106]
41. Smith SM, Huo T, Delia Johnson B, Bittner V, Kelsey SF, Vido Thompson D, Noel Bairey Merz C, Pepine CJ, Cooper-Dehoff RM. Cardiovascular and mortality risk of apparent resistant hypertension in women with suspected myocardial ischemia: a report from the NHLBI-sponsored WISE Study. *Journal of the American Heart Association*. 2014; 3:e000660.doi: 10.1161/jaha.113.000660 [PubMed: 24584740]
42. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Oviagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2017; doi: 10.1016/j.jacc.2017.11.006
43. Arant CB, Wessel TR, Olson MB, Bairey Merz CN, Sopko G, Rogers WJ, Sharaf BL, Reis SE, Smith KM, Johnson BD, Handberg E, Mankad S, Pepine CJ. National Heart L and Blood Institute Women's Ischemia Syndrome Evaluation S. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation Study. *J Am Coll Cardiol*. 2004; 43:2009–14. DOI: 10.1016/j.jacc.2004.01.038 [PubMed: 15172405]
44. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, von Mering GO, Smith KM, Pauly DF, Handberg EM, Mankad S, Olson MB, Johnson BD, Merz CN, Sopko G, Pepine CJ. Coronary microvascular reactivity is only partially predicted by atherosclerosis risk factors or coronary artery disease in women evaluated for suspected ischemia: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). *Clinical cardiology*. 2007; 30:69–74. DOI: 10.1002/clc.19 [PubMed: 17326061]

45. Chirinos JA, Akers SR, Trieu L, Ischiropoulos H, Doulias PT, Tariq A, Vassim I, Koppula MR, Syed AA, Soto-Calderon H, Townsend RR, Cappola TP, Margulies KB, Zamani P. Heart Failure, Left Ventricular Remodeling, and Circulating Nitric Oxide Metabolites. *Journal of the American Heart Association*. 2016; :5.doi: 10.1161/jaha.116.004133
46. Chen YZ, Qiao SB, Hu FH, Yuan JS, Yang WX, Cui JG, Zhang Y, Zhang CL. Left ventricular remodeling and fibrosis: Sex differences and relationship with diastolic function in hypertrophic cardiomyopathy. *European journal of radiology*. 2015; 84:1487–92. DOI: 10.1016/j.ejrad.2015.04.026 [PubMed: 26001434]

Figure 1.

Scatter plot with correlation coefficients of functional parameters and LVEDP presented. End-diastolic volume and end-systolic volume are indexed to body surface area. Mass-to-volume ratio is the ratio of cardiac mass to end-diastolic left ventricular volume.

Abbreviations: LVEDP, left-ventricular end-diastolic pressure.

Table 1

Clinical Findings in Women without CMD with Normal and Elevated Left Ventricular End-Diastolic Pressure (n=43)

Variable	LVEDP <15 mmHg (n = 19) [mean ± (SD)]	LVEDP ≥ 15 mmHg (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 (mmHg)	121 (18)	135 (20)	0.02
Diastolic blood pressure (mmHg)	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
<u>Any anti-hypertensive medication (%)</u>	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.

Table 2

CMR and CRT Findings in Women without CMD

Variable	LVEDP <15 mmHg (n = 19) [mean $\pm$ (SD)]	LVEDP $\geq$ 15 mmHg (n = 24) [mean $\pm$ (SD)]	P-value
End-diastolic volume index (mL/m ²)	74 (10)	67 (10)	0.03
End-systolic volume index (mL/m ²)	25 (9)	21 (6)	0.06
Left ventricular mass (g)	89 (10)	91 (17)	0.63
Mass-to-volume ratio (g/mL)	0.7 (0.08)	0.81 (0.1)	0.0003
Ejection fraction (%)	67 (8)	70 (6)	0.22
Stroke volume (mL)	82 (10)	81.4 (15.6)	0.99
Peak filling rate (mL/sec)	370 (84)	359 (67)	0.65
Time to peak filling rate (msec)	186 (37)	183 (27)	0.80
<u>Coronary reactivity testing:</u>			
Coronary flow reserve to adenosine	3 (0.5)	3.1 (0.5)	0.54
Coronary blood flow response to acetylcholine (%)	174 (102)	156 (108)	0.57
Coronary diameter response to acetylcholine (%)	11.2 (9.3)	10.3 (8.1)	0.74
Coronary diameter response to nitroglycerine (%)	22.1 (15.2)	19.1 (10.7)	0.46
LVEDP (mmHg)	10.9 (2.8)	18.1 (3.1)	by design

Abbreviations: LVEDP, left-ventricular end-diastolic pressure.