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Diastolic Dysfunction Measured by Cardiac Magnetic Resonance Imaging in Women with Signs and Symptoms of Ischemia but No Obstructive Coronary Artery Disease

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Abstract

Background: Women with chest pain and no obstructive coronary artery disease often have coronary microvascular dysfunction (CMD), diagnosed by invasive coronary reactivity testing (CRT). The relationship between CMD and diastolic function measured by cardiac magnetic resonance imaging (CMR) is not well described.

Methods: 41 women with suspected CMD underwent CRT and CMR. Left ventricular end-diastolic pressure (LVEDP), coronary flow reserve (CFR) and coronary blood flow (CBF) were measured invasively. Resting CMR of these women and 20 reference controls was assessed for LV mass, septal wall thickness, ejection fraction (LVEF), end-diastolic volume (EDV), peak filling rate (PFR) and time-to-peak-filling rate (tPFR). Pearson correlations and linear regression models were made.

Results: Mean age was 55±9, all had LVEF≥50%, and 16/41(40%) had LVEDP>15 mmHg. CMD (CFR<2.5 or CBF<50%) was present in 34/41(83%) women. tPFR (mean 178±110 msec) and PFR (mean 3.2±0.64 EDV/sec) were not significantly different in women with or without CMD. tPFR increased with age (r=0.37, p=0.017) and septal wall thickness (r=0.47, p=0.002),

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while PFR decreased with age (r=−0.45, p=0.003). There was an inverse relationship between CFR and tPFR (r=−0.3, p=0.058). Increasing mass was associated with decreasing CBF (p=0.02). Compared to controls, cases had lower LVEF (p=0.049) and lower EDV (p=0.0002).

Conclusion: In women with signs and symptoms of ischemia but no obstructive coronary artery disease, CMD and elevated LVEDP are prevalent. While non-endothelial dependent CMD may be related to diastolic dysfunction, further investigation is needed regarding links between CMD, diastolic dysfunction and the development of heart failure with preserved LVEF.

Keywords

microvascular coronary dysfunction; diastolic dysfunction; women's heart disease

Introduction

Sex-specific differences in ischemic heart disease presentation and pathophysiology are increasingly described. Ischemic heart disease is the leading cause of mortality among women in the United States and the world[1,2]. Chest pain and acute coronary syndromes are less likely to be associated with obstructive epicardial coronary artery disease (CAD) in women than in men[3]. Approximately 50% of women with signs and symptoms of ischemia but no obstructive CAD have evidence of coronary microvascular dysfunction (CMD)[4,5]. CMD is diagnosed by invasive coronary reactivity testing (CRT) using vasoactive substances to test endothelial and non-endothelial vascular function[6,7].

Diastolic dysfunction appears to be a primary mechanism in approximately 40% of all patients with heart failure[8] and is an independent predictor of mortality[9]. Women are more likely to be diagnosed with heart failure with preserved LV ejection fraction (HFpEF)[10-12] than men. Diastolic heart failure, which is associated with an annual mortality rate of 5-8% comparable to systolic heart failure, has been the focus of recent heart failure investigations[9,13-16]. While diastolic dysfunction does not always lead to HFpEF, the relationship between diastolic dysfunction and CMD has been uncertain and may offer therapeutic implications. Invasive measurement of left ventricular (LV) end-diastolic pressure is a marker of LV function and compliance. Elevated LV end-diastolic pressure (LVEDP) has been shown to be an independent predictor of mortality in ischemic heart disease, independent of LV systolic function[17,18].

There is little known regarding the relationship between CMD, LVEDP, and parameters of diastolic function in women. Cardiac magnetic resonance imaging (CMR) is an emerging modality for not only non-invasive evaluation of myocardial ischemia secondary obstructive CAD but also evaluation of ischemia from CMD, which is a more diffuse pattern of hypoperfusion with an abnormal myocardial perfusion reserve index[19,20]. Furthermore, myocardial systolic and diastolic function can also be assessed via CMR[21,22]. Diastolic function has recently been found to be impaired in women with signs and symptoms of ischemia in the absence of obstructive CAD, but there was no assessment of the potential relationship between invasive measures of CMD and the diastolic parameters[23].

The objective of this study is to examine the association between CMD, LVEDP, and diastolic dysfunction measured by invasive CRT and noninvasive CMR in women with signs and symptoms of ischemia but no obstructive CAD.

Methods

Patient Population:

Women with signs and symptoms of myocardial ischemia but no obstructive CAD at diagnostic invasive coronary angiography who underwent clinically indicated CRT and CMR as part of ongoing care related to persistent signs and symptoms of ischemia were enrolled into a registry at the Cedars-Sinai Women's Heart Center. Inclusion criteria included patients with signs and symptoms of myocardial ischemia (chest pain, abnormal stress testing, abnormal noninvasive testing) in the absence of obstructive CAD (<50% luminal obstruction in one or more epicardial coronary arteries on angiography) and preserved ejection fraction. Patients were excluded from the registry if they had life expectancy less than 6 months, age<21 years, valvular heart disease, history of congestive heart failure, and structural heart disease (such as LV hypertrophy). All study participants gave written informed consent before undergoing evaluation and the study protocol was approved by the Institutional Review Board at Cedars-Sinai Medical Center (CSMC). Demographic data were recorded with standardized questionnaires. CRT and CMR data were read on-site at the CSMC Core Laboratories.

A reference control group of 20 asymptomatic healthy women were recruited at CSMC based on their age and hormone use-status to match the cases in the registry. Inclusion criteria included the absence of signs or symptoms of myocardial ischemia and absence of cardiac risk factors by Framingham/NCEP criteria. Exclusion criteria included contraindications to CMR and inability to perform treadmill exercise. All women underwent maximum symptom-limited exercise treadmill testing and stress-rest CMR as previously published[24]. All women had no evidence of ischemia by exercise treadmill testing and CMR perfusion. This reference control group did not undergo any invasive coronary angiography or CRT.

Coronary Reactivity Testing:

Coronary angiography was performed to confirm the absence of obstructive CAD. LVEDP was measured, and diastolic dysfunction was defined as LVEDP > 15 mm Hg. Coronary microvascular and macrovascular endothelial and non-endothelial dependent function were then measured, using a standard protocol[25]. Using a Doppler flow wire (FloWire Volcano, San Diego, CA) in the proximal left anterior descending artery, coronary flow reserve (CFR) was measured by graded intracoronary adenosine injections of 18 mcg and 36 mcg, to create maximal hyperemia. Graded doses of intracoronary acetylcholine (0.182 and 18.2 mcg/ml) were infused for 2 minutes to measure average peak velocity and calculate coronary blood flow (CBF) as previously described[25]. Adenosine tests non-endothelial-dependent microvascular function, while acetylcholine tests endothelial dependent function. Non-endothelial-dependent CMD was defined as CFR < 2.5. Endothelial-dependent CMD was defined as CBF change < 50%.

CMR:

CMR scans were performed in a supine position on a 1.5 Tesla magnet (Siemens Sonata, Erlangen, Germany) with ECG-gating and a phase-array surface coil (CP Body Array Flex, Siemens Medical Systems, Erlangen, Germany). Resting cine CMR images were obtained in consecutive short-axis planes to encompass the entire left ventricle from the base to the apex. Standard Siemens Medical Imaging sequence was used for the studies: retrospectively ECG-gated steady-state free-precession cine, with repetition time 1 x RR interval [60 msec, dependent on heart rate], echo time 1.4 msec, slice thickness 8 mm, FOV 300x206 mm, image matrix 132 x 256, number of phases=25, bandwidth 830 Hz . All CMR scans were performed by the same operator.

Endocardial contours were traced manually from end-systole to end-diastole using Argus software (Siemens Medical) and used to measure end-systolic volume (ESV) and end-diastolic volume (EDV). Contours were applied by a single experienced observer. Frame-by-frame and slice-by-slice evaluation of cine images from end-systole to end-diastole was performed to ensure exclusion of epicardial fat, as well as the quality of endocardial and epicardial contours. Papillary muscles were included in the LV blood volume measurement and not included in the myocardial mass measurement; since papillary muscle volume is constant throughout the cardiac cycle, inclusion of papillary muscle volume would not significantly affect filling rates, which is the principal parameter determined in this study[26], although they will affect stroke volume and EDV used to normalize filling data[27]. Septal wall thickness and LV mass were calculated from the end-diastolic frames. Stroke volume was calculated as the difference between EDV and ESV, and ejection fraction was calculated as stroke volume divided by EDV. Heart rate and blood pressure were measured and recorded.

Volume-time curves were used to derive indices of diastolic dysfunction, including early peak filling rate (PFR) and time-to-peak-filling rate (tPFR) (Figure 1). Similar to peak early mitral inflow velocity (E) by echocardiography, PFR decreases during the progression from normal diastolic function to grade 1 diastolic dysfunction, and PFR normalized for EDV has been demonstrated to be a useful index for evaluation diastolic function[28,29]. Similar to deceleration time by echocardiography, tPFR is expected to prolong with grade 1 diastolic dysfunction[30]. From grade 1 diastolic dysfunction to grade 3 diastolic dysfunction, PFR increases while tPFR shortens[30]. Means, standard deviation and 95% confidence intervals have been reported for functional and geometric parameters of the normal LV in both men and women[24,31].

Statistical Methods:

Values of the continuous variables are presented as mean and standard deviations, unless otherwise specified. The relationships among demographic variables and measurements from CRT and CMR were examined using the Pearson product moment correlation. Fisher’s z transformation was applied to test correlation coefficients significantly different from zero, and Fisher’s exact test was used to evaluate categorical data. Linear regression models used logarithmic transformation on CFR and on CBF+100 to adjusted for skewed distributions. A standard stepwise procedure was used for model building with the CMR variables as

explanatory covariates. SAS 9.1.3 was used for all statistical analyses. All probabilities were two-tailed and a p value of less than 0.05 was considered statistically significant.

Results:

Demographics

Baseline demographics are depicted in Table 1. Almost all women were Caucasian, and many of the cases had risk factors for coronary artery disease, however, less than a third of the cases were taking antihypertensive or anti-anginal agents. Five cases were taking loop or thiazide diuretics. All cases had normal LV ejection fraction and no evidence of obstructive coronary artery disease on angiography. Angina symptoms (location, duration, and triggering/alleviating factors) did not differ between cases with and without CMD, although there was a trend towards lower frequency of chest pain episodes in the cases with CMD vs the cases without CMD (p=0.08). Mean time difference between the CRT and CMRICMR in 95% of women was 40 ± 13 days. Two women had their CRT and CMRICMR one year apart.

CRT measures of CMD

Mean LVEDP was mildly elevated at 15 ± 4.5 (range 5-24) mmHg (Table 2). 53% of cases had an LVEDP > 12 mm Hg, and 40% of cases had an LVEDP > 15 mm Hg. Mean CFR (2.8 ± 0.8) and CBF (53 ± 92%) were normal, but CMD (CFR<2.5 and/or CBF<50%) was present in 34/41 (83%) women. LVEDP did not correlate with CFR or CBF. CFR correlated with increasing age (r −0.45, p=0.0028)

CMR measures of LV structure and function

For all cases, LV mass index and septal wall thickness index were within normal range (Table 3). Overall case group mean tPFR was 178±110 msec and PFR was 3.2±0.64 end-diastolic volume/sec, with no significant differences between cases with CMD and cases without CMD. There were also no significant differences in tPFR and PFR in the cases with abnormal CFR vs abnormal CBF (Table 4).

Compared to the reference control group, the case group had lower LV ejection fraction (64±13% vs 70±3.9%, p= 0.049), lower EDV indexed to body surface area (59±12 vs 73±14 mL/m^2, p= 0.0002), and higher PFR indexed to EDV (3.2±0.6 vs 2.9±0.4, p=0.048). LV mass index was not quite statistically significant (44±9.2 vs 48±6.4, p= 0.086). Septal wall thickness and tPFR were not significantly different (p=0.38, p=1.0; respectively).

A trend for an inverse relationship was seen between CFR and tPFR (r= −0.3, p= 0.058) and between CBF and PFR (r= −0.28, p= 0.08). tPFR increased with age (r= 0.37, p= 0.017) and septal wall thickness (r= 0.47, p= 0.002) (Figure 2). We also found that PFR decreased with age (r= −0.45, p= 0.003). There was no statistically significant relationship noted between elevated LVEDP and CMR diastolic parameters.

Regression models were also made using the CMD parameters as continuous outcome to evaluate their relationship to CMR and clinical variables. BMI and LV mass were in a multiple linear regression with the transformed CBF as the outcome (model F test p=0.04,

R-squared=0.20). LV mass had a significant negative association (increasing LV mass was associated with decreasing CBF) with transformed CBF (p=0.02), and BMI had a positive association that was not quite significant (p=0.08). The model with log CFR used all 41 subjects and time to peak filling as the only explanatory factor (model F test p=0.01, R-squared=0.15). TPFR had a negative association with log CFR (p=0.01).

Discussion:

We report that a high percentage of women with signs and symptoms of ischemia but no obstructive CAD have an elevated invasively measured LVEDP. These women have lower LV ejection fraction and smaller EDV compared to reference controls. We found that these women had higher PFR than the age-matched reference controls, suggesting that the women may be progressing towards grade 2 diastolic dysfunction as opposed to grade 1 diastolic dysfunction[30]. Interestingly, diastolic function as measured by TPFR appears to be inversely related to adenosine CFR, a non-endothelial dependent pathway of CMD both in our correlation and regression analyses. However, CMR indices of diastolic dysfunction defined by tPFR and PFR were not significantly different between our patients with and without CMD. To our knowledge, this is the first study reporting abnormal filling pressures in women with a definitive diagnosis of CMD by invasive CRT, many of whom have resting diastolic dysfunction despite normal ventricular size and mass[23,32,33].

There appeared to be a trend for an inverse relationship between change in CBF to acetylcholine (a function of endothelial dependent pathways) and PFR in this study, which suggests that worsening CBF may be related to higher PFR. CBF also appeared to have an inverse relationship with LV mass, ie increasing LV mass was associated with worsening CBF. These observations have not been previously reported in CMR literature in women with CMD. Mendoza et al have reported that PFR measured by CMRICMR decreases during the progression from normal diastolic function to grade 1 diastolic dysfunction, and then increases during the progression from grade 1 diastolic dysfunction to grade 3 diastolic dysfunction[30]. However, this is consistent with echocardiography literature, as Lerman et al[34] found that abnormal CBF change to acetylcholine was associated with diastolic dysfunction by tissue Doppler echocardiography assessment.

Diastolic heart failure, increasingly termed HFpEF, is a prevalent and a significant problem in women[10]. Ischemic heart disease without obstructive CAD may be a mechanistic pathway in the pathogenesis of HFpEF. Our current data demonstrate that low CFR may be related to early evidence of diastolic dysfunction based on CMR indices. Although LVEDP was only modestly elevated in these women, we may be identifying preclinical diastolic dysfunction, which has been shown to progress to symptomatic HFpEF[35]. Diastolic dysfunction can be determined by CMR[21,36,37], and PFR and tPFR can be simply evaluated at the time of a routine CMR, and although they may not be as accurate in defining diastolic function as tagged imaging CMR[38,39], they are less time consuming to analyze. Automated processing of CMR can now generate LV filling curves within minutes, can measure PFR and tPFR with high reproducibility, and can be used to recognize graded severity of diastolic dysfunction similar to echocardiography[30].

The women in our study all had normal LV ejection fraction; 53% had an LVEDP >12 mm Hg and 40% had an LVEDP > 15 mm Hg. Mildy elevated LVEDP in the setting of preserved ejection fraction may contribute to exertional dyspnea and chest pain in women with CMD. Prior reports have demonstrated that increased LV stiffness impairs exercise tolerance in patients with HFpEF [40]. Our findings are consistent with a study by Elhabyan et al[41] who found a strong association between elevated LVEDP at cardiac catheterization and ischemia noted by perfusion defect on nuclear scan in 210 patients with no obstructive CAD at angiography. They concluded that elevated LVEDP may be considered one of the factors contributing to the pathogenesis of signs and symptoms of ischemia in this group of patients[41]. These findings are consistent with other myocardial perfusion studies that show that diastolic filling parameters with PFR and tPFR may correlate with LVEDP[42].

Several factors and clinical conditions are known to influence LVEDP. Impairment of myocardial contractility due to concentric hypertrophy from hypertension or valvular stenosis, restrictive or infiltrative cardiomyopathy, as well as myocardial ischemia due to obstructive CAD all lead to rise in compensatory preload as the left ventricle tries to maintain stroke volume[43]. CMD may lead to a compensatory elevated filling pressure because increased microvascular resistance causes worsening myocardial tissue perfusion and leads to an ischemic left ventricle[44,45]. CMD may also lead to progressive heart failure through oxidative stress and reduction in nitric oxide bioavailability[16]. Our results demonstrating normal LV mass and absence of LV hypertrophy using CMR suggest that the elevated LVEDP in our patients was not secondary to these known causes.

An elevated LVEDP is one of the first hemodynamic abnormalities seen in diastolic dysfunction[46]. Accordingly, our results suggest that CMD may be mechanistic pathway and pathophysiologic explanation of elevated filling pressures. Chronic pressure overload may lead to structural microvascular abnormalities which lead to myocardial hypoperfusion, which becomes obvious at times of increased demand, manifesting as exercise intolerance[47]. A relationship between arterial stiffness and diastolic dysfunction has been described, and women differ from men in central arterial stiffness[48]. A recent study reports that LV diastolic function measured by doppler echocardiography correlates significantly to arterial stiffness in women[49]. Since older women tend to develop HFpEF, it is interesting that in our cohort of symptomatic middle-aged women, we already find borderline elevations of LVEDP; we may be detecting an early form of cardiomyopathy, which if left untreated over the next several decades of a woman’s life, may lead to the syndrome of overt diastolic heart failure.

Study Limitations:

Absolute values for PFR and tPFR at one time-point in this cross-sectional study do not always accurately indicate the stage of diastolic function, similar to echo-derived early mitral inflow velocity (E) and deceleration time. Our study excluded patients with clinically diagnosed heart failure, however both PFR and tPFR have wide confidence intervals and thus are far from perfect for sensitivity to detect diastolic dysfunction as confirmed by echocardiographic or invasive methods. Given that loading conditions may vary and affect diastolic measurements, we obtained CMR on average within 2 months of the invasive CRT.

We cannot make any conclusions regarding causality of diastolic dysfunction in this study. CMD may be a consequence of diastolic dysfunction or vice versa. Invasive diastolic measurements of impaired relaxation (i.e. peak –dP/dt or measurement of passive stiffness) was not assessed. Research based techniques such as CMR tissue tagging to evaluate diastolic function was not used in this study, since this study evaluated clinically ordered CMR.

Another limitation of this study is the lack of adjustment for heart rate, which influences the loading condition of the heart. We performed averaging of the volume-time curves without adjustment for different cycle lengths, because the period of early diastole varies within a narrow range[50]. Despite not adjusting for heart rate, we were able to show that tPFR increases with age and increasing wall thickness, which is consistent with prior studies showing that worsening diastolic function with age and LV hypertrophy and helps to validate the methods[46,51,52]. Our measurements of both LVEDP and diastolic dysfunction by CMR were conducted at rest and therefore may be an underestimate of functional diastolic dysfunction. Our exclusion of papillary muscles from the LV mass and inclusion in the LV volumes also must be considered, as we adjusted the PFR for EDV, although our methods were consistent with our published reference control values. Finally, our high rate of CMD determined by clinically indicated invasive testing limits study specificity. Future work in larger sample sizes in more heterogenous populations is needed.

Conclusions:

There is a high prevalence of elevated filling pressures in symptomatic women with no obstructive CAD, who are suspected to have CMD. Prior investigation has demonstrated that these women also have diastolic dysfunction by CMR[23]. We now report that abnormal non-endothelial dependent CMD appears to be related to abnormal diastolic function. Further investigation is needed regarding links between CMD, diastolic dysfunction and the development of HFpEF.

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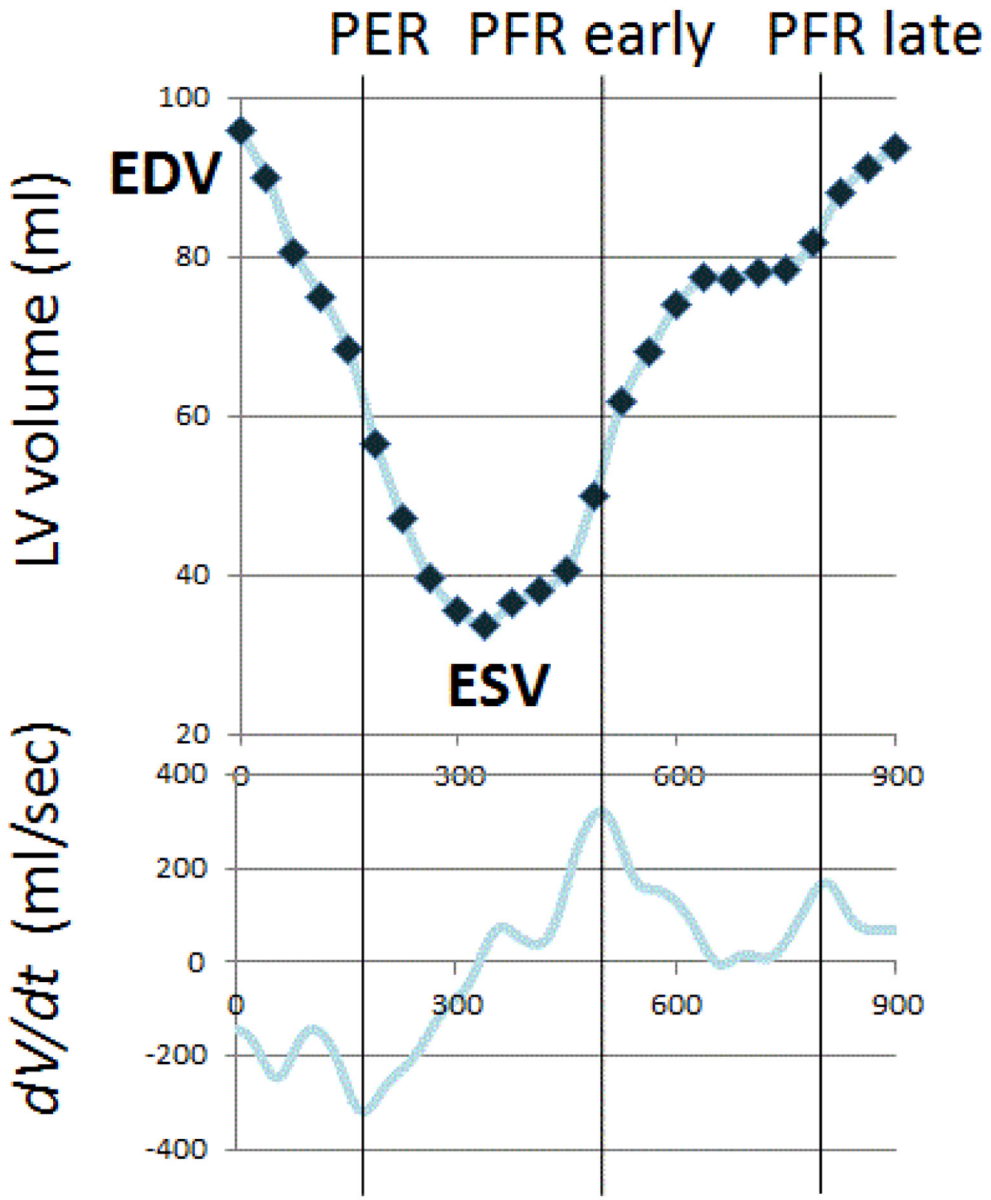

Figure 1: Time-Volume Curve.

The LV time-volume curve and its first derivative were used to determine the peak filling rate and the time to peak filling rate from end systole. LV=left ventricular, dV/dt= filling rate curve, EDV= end-diastolic volume, ESV=end-systolic volume, PER=peak ejection rate, PFR=peak filling rate

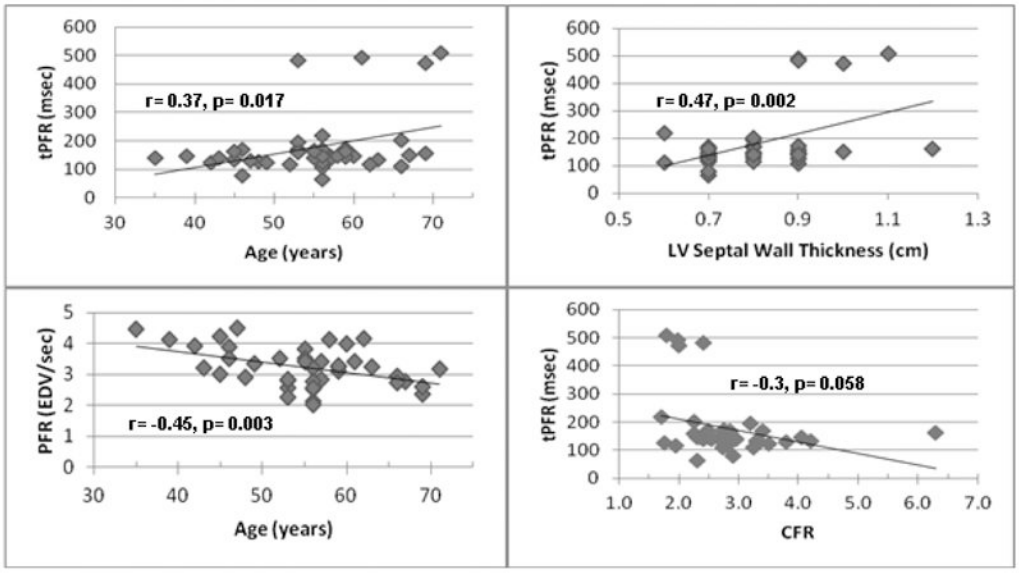

Figure 2: Correlation Graphs.

Relationships between age, time to peak filling rate (tPFR), peak filling rate (PFR), left ventricular (LV) septal wall thickness, and coronary flow reserve (CFR) were evaluated. TOP: tPFR increased with age and septal wall thickness. BOTTOM: There was an inverse relationship between PFR and age and between CFR and tPFR.

Table 1.

Baseline Demographics and Clinical Variables

Variables	Total Cases N=41	With CMD N=34	Without CMD N=7	Reference Controls N=20	p-Value*
Age	55 ± 9	55 ± 8	53 ± 8	54 ± 9	0.41
Body Mass Index	26 ± 4.3	26 ± 4.7	27 ± 3.9	25 ± 4	0.62
Race (non-Caucasian)	2 (4.9%)	2	0	2 (10%)	1.00
Hypertension	20 (49%)	15	3	0	1.00
Hyperlipidemia	20 (49%)	18	2	0	0.41
History of Smoking	18 (44%)	15	3	8 (40%)	1.00
Diabetes	1 (2%)	0	1	0	0.17
Systolic BP (mmHg)	138 ± 20	138 ± 21	134 ± 16	121 ± 24	0.58
Diastolic BP (mmHg)	71 ± 9.5	70 ± 9.1	77 ± 10	73 ± 11	0.13
Beta – Blockers	12 (29%)	12	0	0	0.08
Calcium Channel Blocker	9 (22%)	8	1	0	1.00
ACE Inhibitors	7 (17%)	7	0	0	0.32
Angiotensin receptor blocker	5 (12%)	4	1	0	1.00
Diuretics	5 (12%)	4	1	0	1.00
Nitrates	7 (17%)	6	1	0	1.00
Statins	19 (46%)	17	2	0	0.42

Values expressed as mean ± SD, or N (%).

ACE= Angiotensin converting enzyme, BP= blood pressure, CMD = coronary microvascular dysfunction defined by abnormal coronary flow reserve to adenosine and/or abnormal coronary blood flow change to acetylcholine

*cases with CMD vs cases without CMD

Table 2.

Coronary Reactivity Testing Results

Variables	Total Cases N=41	With CMD N=34	No CMD N=7	Controls N=20	p-Value*
LV End Diastolic Pressure	15 ± 4.5	15 ± 4.5	14 ± 6.1	n/a	0.62
Coronary Flow Reserve	2.8 ± 0.8	2.7 ± 0.9	3.1 ± 0.5	n/a	0.37
Δ Coronary Blood Flow	53 ± 92	29 ± 72	168 ± 94	n/a	<0.0001

Values expressed as mean ± SD.

CMD= coronary microvascular dysfunction defined by abnormal coronary flow reserve to adenosine and/or abnormal coronary blood flow change to acetylcholine, LV= left ventricular, **Δ** = change in coronary blood flow compared to baseline

*cases with CMD vs cases without CMD

Table 3.

CMR measures of left ventricular structure and function

Variables	Total Cases N=41	With CMD N=34	No CMD N=7	Controls N=20	p-Value*
LV Ejection Fraction (%)	64 ± 13%	67 ± 7.6%	62 ± 6.8	70 ± 3.9	0.15
LV Mass, index ** **(g/m²)**	44 ± 9.2	43 ± 8.1	38 ± 2.6	48 ± 6.4	0.17
Septal WT, index ** **(mm/m²)**	4.6 ± 0.7	4.6 ± 0.7	4.3 ± 0.5	4.6 ± 0.6	0.27
EDV, index ** **(mL/m²)**	59 ± 12	58 ± 11	56 ± 6.5	73 ± 14.5	0.64
PFR (EDV/sec)	3.2 ± 0.6	3.2 ± 0.6	3.1 ± 0.7	2.9 ± 0.4	0.68
Time to PFR (msec)	178 ± 110	186 ± 116	137 ± 32	200 ± 20	0.27

Values expressed as mean ± SD.

CMD = coronary microvascular dysfunction defined by abnormal coronary flow reserve to adenosine and/or abnormal coronary blood flow change to acetylcholine, EDV= end-diastolic volume, LV =left ventricle, PFR= peak filling rate, WT= wall thickness.

* cases with CMD vs cases without CMD

** indexed to body surface area

Table 4.

Diastolic Function in women with CMD

	Abnormal Coronary Flow Reserve (<2.5) (n=15)	Abnormal Δ Coronary Blood Flow (<50%) (n=27)	p-Value
PFR (EDV/sec)	3.1±0.7	2.9±0.9	0.46
Time to PFR (msec)	238±160	187±112	0.23

PFR= peak filling rate, EDV= end-diastolic volume, **Δ** = change in coronary blood flow compared to baseline