

Left ventricular concentric remodelling and functional impairment in women with ischaemia with no obstructive coronary artery disease and intermediate coronary flow reserve: a report from the WISE-CVD study

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Aims

Women with evidence of ischaemia but no obstructive coronary artery disease (INOCA) often have coronary microvascular dysfunction (CMD). Although invasively measured coronary flow reserve (CFR) is useful for the diagnosis of CMD, intermediate CFR values are often found of uncertain significance. We investigated myocardial flow reserve and left ventricular (LV) structural and functional remodelling in women with suspected INOCA and intermediate CFR.

Methods and results

Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study participants who had invasively measured intermediate CFR of $2.0 \leq \text{CFR} \leq 3.0$ ($n = 125$) were included for this analysis. LV strain, peak filling rate (PFR) and myocardial perfusion reserve index (MPRI) were obtained by cardiac magnetic resonance imaging. Participants were divided: (i) Group 1 ($n = 66$) high MPRI ≥ 1.8 , and (ii) Group 2 ($n = 59$) low MPRI < 1.8 . The mean age was 54 ± 12 years and CFR was 2.46 ± 0.27 . MPRI was significantly different but CFR did not differ between groups. LV relative wall thickness (RWT) trended higher in Group 2 and circumferential peak systolic strain and early diastolic strain rate were lower ($P = 0.039$ and $P = 0.035$, respectively), despite a similar LV ejection fraction and LV mass. PFR was higher in Group 1 and LV RWT was negatively related to PFR ($r = -0.296$, $P = 0.001$).

Conclusions

In women with suspected INOCA and intermediate CFR, those with lower MPRI had a trend towards more adverse remodelling and impaired diastolic LV function compared with those with higher MPRI. CFR was similar between the two groups. These findings provide evidence that both coronary microvessel vasomotion and structural and functional myocardial remodelling contribute to CMD.

Keywords

coronary microvascular dysfunction • women • coronary flow reserve • cardiac magnetic resonance • remodelling

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Introduction

More than half of women with evidence of ischaemia but no obstructive coronary artery disease (INOCA).^{1,2} Studies have shown that these patients often have coronary microvascular dysfunction (CMD) indicated by a reduced coronary flow reserve (CFR) of <2.5 in response to adenosine, which is the lower limit of normal flow reserve in coronary arteries without obstructive coronary artery disease (CAD).^{3,4} Although invasively measured CFR is useful for the diagnosis of CMD, this can provide intermediate values of uncertain significance in women with objective evidence of ischaemia. In these cases, additional information to inform clinical decision-making is needed; however, it remains unclear what additional information should be gathered. Moreover, CMD may result from not only functional coronary microvessel vasomotion but also the microvasculature structure which includes the stroma and myocardium. We have previously demonstrated that left ventricular (LV) diastolic function is impaired in women with signs and symptoms of ischaemia in the absence of obstructive CAD.⁵

Cardiac magnetic resonance imaging (CMRI) is a powerful, non-invasive tool, capable of providing objective, quantitative evaluation of LV morphology, function,⁶⁻⁸ and myocardial perfusion abnormalities.⁹⁻¹¹ Therefore, CMRI would provide the additional insight necessary to differentiate women with suspected INOCA and intermediate CFR.

We investigated myocardial flow reserve and LV structural and functional remodelling assessed by CMRI in women with suspected INOCA and intermediate CFR to understand the potential contribution of myocardial remodelling to CMD.

Methods

This analysis includes women enrolled in the National Heart, Lung, and Blood Institute-sponsored prospective multicenter Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction (WISE-CVD) study. All studies were performed at Cedars-Sinai Medical Center or the University of Florida, Gainesville, between January 2009 and June 2012 where institutional review boards approved the project and all participants provided written informed consent. Exclusion criteria were acute myocardial infarction within 30 days, percutaneous coronary intervention, coronary artery bypass grafting, or valve surgery subsequent to baseline qualifying coronary angiogram and any conditions that precluded accurate or safe testing or follow-up, specifically: obstructive CAD $\geq 50\%$ luminal diameter stenosis in ≥ 1 epicardial coronary artery, acute coronary syndrome, primary valvular heart disease with need for valve repair or replacement, concurrent cardiogenic shock, prior non-cardiac illness with estimated life expectancy <4 years, chest pain with known non-ischaemic pathogenesis (e.g. pericarditis, pneumonia, oesophageal spasm), contraindications to CMRI (pacemaker, other electronic device, severe claustrophobia), severe asthma (vasodilator stress contraindicated), severe renal impairment (gadolinium contrast contraindicated).

Stress CMRI was performed in 373 women per protocol. A subset ($n = 204$) underwent clinically indicated invasive coronary reactivity testing (CRT). The mean time difference between the CRT and CMRI was 35 ± 28 days, with no changes in medications and testing conditions per protocol. Eleven women were excluded from this analysis due to suboptimal CMRI for the feature tracking, and an additional nine women were excluded due to presence of myocardial scar detected by CMRI

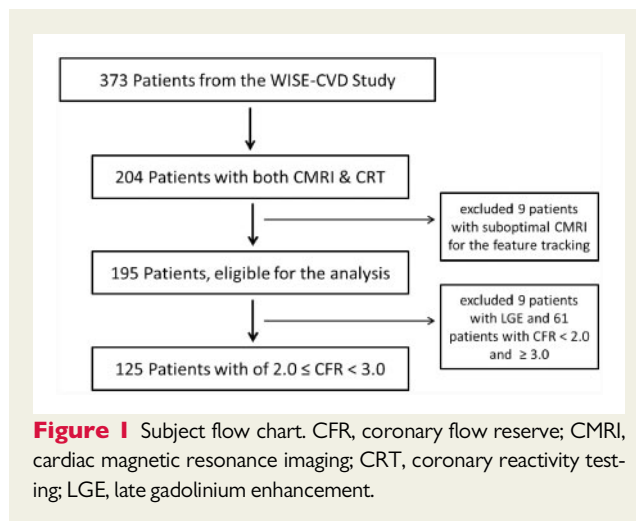


Figure 1 Subject flow chart. CFR, coronary flow reserve; CMRI, cardiac magnetic resonance imaging; CRT, coronary reactivity testing; LGE, late gadolinium enhancement.

late gadolinium enhancement. Finally, 125 women had an intermediate CFR of $2.0 \leq \text{CFR} < 3.0$ and were included in this analysis (Figure 1).

Long-acting nitrates, short-acting calcium-channel blockers, α -blockers, β -blockers, and angiotensin-converting enzyme-I/angiotensin-II receptor antagonists were withdrawn 24 h, and long-acting calcium-channel blockers were held for 48 h before CRT and CMRI testing. Sublingual nitroglycerine was not taken within 4 h before testing, and participants were caffeine-free and nicotine-free for 24 h before vasodilator stress.

Invasive coronary flow reserve measurement

CFR was measured using a standardized protocol.¹² A Doppler guidewire was placed in the proximal left anterior descending (LAD), and assessed coronary flow, with intracoronary adenosine (18 and 36 μg) used to achieve hyperaemia. CFR was derived from the ratio of the average peak velocity of blood flow at maximal hyperaemia and average peak velocity at rest as previously described. We have previously shown that this ratio closely approximates volumetric CFR in similar women enrolled in WISE.¹³ Graded doses of intracoronary acetylcholine (0.182 and 18.2 $\mu\text{g}/\text{mL}$) were infused to determine % epicardial coronary artery diameter change (ΔACh) and % coronary blood flow change (ΔCBF) in response to acetylcholine, as previously described.^{12,14}

Cardiac magnetic resonance imaging

A standardized CMRI protocol and equipment were used (1.5T Magnetom Avanto; Siemens Healthcare, Erlangen, Germany).¹¹ Stress and rest first-pass perfusion imaging were performed using gadolinium contrast of 0.05 mM/kg each (Gadodiamide, Omniscan, Amersham, Piscataway, NJ). For adenosine studies, the standard protocol of the WISE-CVD study was used with adenosine (140 mcg/kg/min). Regadenoson was employed as the coronary vasodilator if patients had a history of mild-moderate asthma or had prior intolerance to adenosine. LV function and delayed enhancement imaging were performed using a standardized approach, as previously described.⁵ LV mass and volumes were assessed by manually tracing the epicardial and endocardial borders of short-axis cine images using CAAS MRV 3.3 software (Pie Medical Imaging B.V., Netherlands). Volume–time curves were used to derive indices of diastolic dysfunction, including early peak filling rate (PFR) and time-to-peak-filling rate (tPFR). LV end-diastolic dimension, septal wall, and inferolateral wall thickness were measured in end-diastole from a short-axis frame immediately basal to the tip of papillary muscle tips.^{15,16}

Relative wall thickness (RWT) was calculated as [septal wall thickness + inferolateral wall thickness]/LV end-diastolic dimension.

Myocardial perfusion reserve index (MPRI), the CMRO-derived semi-quantitative index of CFR was defined as $MPRI = \text{Relative upslope}_{\text{stress}} / \text{Relative upslope}_{\text{rest}}$.¹¹ An American Heart Association 16-segment model was used (true apex not imaged); mean MPRI was the average of 16 segments. An A-MPRI was defined as the mean MPRI from nine LAD coronary artery territory segments to relate to the invasively CFR and CBF measures obtained in the LAD. Based on MPRI values,^{11,17} participants were divided into two groups for the analysis: (i) Group 1, MPRI ($n=66$), high MPRI ≥ 1.8 , and (ii) Group 2, MPRI ($n=59$), low MPRI < 1.8 .

CMRI myocardial strain analysis

Myocardial tissue tracking was performed on resting CMRI offline using previously acquired steady-state free precession cine images, and dedicated software (cvi42; Circle Cardiovascular Imaging, Inc., Calgary, AB, Canada).⁷ A series of short-axis CMRI images were chosen, spanning the left ventricle (base to apex). We obtained global circumferential strain (GCS), circumferential early diastolic strain rate (CSRe), global radial strain (GRS), and radial early diastolic strain rate (RSRe) from the strain analysis curves (Figure 2). Our in-lab intra-rater variability, expressed as a coefficient of variation, for each of the primary endpoints is as follows [mean \pm standard deviation (SD)]: GCS, 1% \pm 1%; GRS, 3% \pm 2%; CSRe, 6% \pm 5%; and RSRe, 7% \pm 5%.⁷

Statistical analysis

Values are expressed as mean \pm standard deviation or percentages as indicated. The t-test or chi-square test was used to evaluate differences in Group 1 vs. Group 2. The correlation between MPRI and other cardiac parameters assessed by CMRI was evaluated with the correlation analysis, and the significance of correlation between MPRI and PFR and other cardiac function was determined by multivariate linear regression analysis. After univariate screening, any candidate variable with a value of $P < 0.10$

was forced to enter a multivariate model. SPSS software (version 20.0) was used for statistical analysis. P -value < 0.05 was considered to be statistically significant.

Results

Baseline characteristics

Among the 373 WISE-CVD women who underwent stress CMRI, 204 women underwent clinically indicated invasive CRT and were included in this analysis. Nine women were identified as having presence of myocardial scar detected by CMRI late gadolinium enhancement. Because this was determined to be their likely primary aetiology, these women were not included in the remaining analysis. Of the women with clinically indicated CFR, 125 women had an intermediate CFR of $2.0 \leq \text{CFR} < 3.0$ and were included in this analysis (Figure 1).

Baseline characteristics are summarized in Table 1. Of 125 women, 66 (52.8%) subjects had MPRI ≥ 1.8 (Group 1) and 59 (47.2%) subjects had MPRI < 1.8 (Group 2). The mean age of study participants was 54 ± 12 years and CFR was 2.46 ± 0.27 . Group 2 participants were older ($P < 0.008$), but otherwise there were no significant group difference baseline demographics, clinical risk variables, or medication ($P = \text{NS}$ in all). Despite the older age in Group 2, CFR, ΔACh , and ΔCBF were not different between two groups (Table 1).

There was no significant difference of symptoms between chest pain and shortness of breath according to MPRI, CFR, and LV function. However, there was a trend towards higher frequency of chest pain episodes in low MPRI group vs. high MPRI group ($P = 0.065$), although angina symptoms (location, duration, triggering factors, and response to nitroglycerin) did not differ between two subgroups.

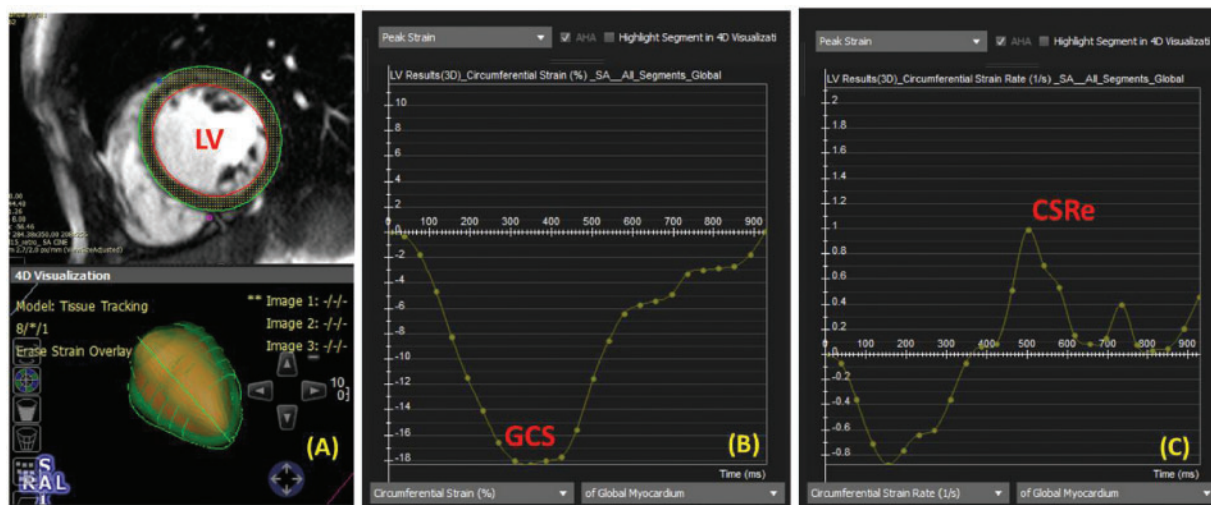


Figure 2 Myocardial tissue feature tracking in a representative ventricular short-axis cine image. (A) Contours are drawn on the endocardial and epicardial borders at a single phase of the cardiac cycle. (B) Global circumferential strain (GCS) curve from basal to apical all segments is shown throughout the cardiac cycle. (C) Circumferential early diastolic strain rate (CSRe) was automatically calculated as the time derivative of circumferential strain from (B).

Table 1 Baseline characteristics of women by MPRI

	Total subjects (n = 125)	Group 1 High MPRI (MPRI ≥ 1.8, n = 66)	Group 2 Low MPRI (MPRI < 1.8, n = 59)	P-value
Age, years	54.3 ± 11.7	51.3 ± 9.9	56.9 ± 12.6	0.008
Systolic BP, mmHg	127 ± 19	124 ± 20	130 ± 20	0.10
Diastolic BP, mmHg	70 ± 12	70 ± 11	70 ± 12	0.57
Heart rate, rpm	66 ± 10	66 ± 10	65 ± 10	0.66
Body mass index, kg/m ²	29.4 ± 7.2	29.2 ± 6.7	29.6 ± 7.6	0.74
Hypertension, n (%)	45 (38.5)	20 (37.0)	25 (39.7)	0.85
Diabetes mellitus, n (%)	13 (10.5)	7 (10.8)	6 (10.2)	0.77
Dyslipidaemia, n (%)	15 (12)	6 (9.1)	9 (15.3)	0.54
Current smoker, n (%)	6 (4.8)	4 (6.1)	2 (3.4)	0.34
Medication				
Beta blockers, n (%)	28 (22.4)	14 (21.2)	14 (23.7)	0.84
CCB, n (%)	23 (18.4)	9 (13.6)	14 (23.7)	0.33
Nitrate, n (%)	35 (28)	17 (25.6)	18 (30.5)	0.98
ACEI or ARB, n (%)	26 (20.8)	11 (16.7)	15 (25.4)	0.61
Aspirin, n (%)	3 (2.4)	3 (3.6)	0 (0)	0.66
Statins, n (%)	44 (35.2)	17 (25.8)	27 (45.8)	0.16
Coronary severity score	9.9 ± 4.4	9.8 ± 4.5	10.0 ± 4.3	0.67
Coronary reactivity test				
CFR	2.46 ± 0.27	2.43 ± 0.26	2.49 ± 0.27	0.16
ΔACh, %	0.2 ± 12.6	1.5 ± 13.1	-1.1 ± 12.1	0.29
ΔCBF	64.4 ± 70.8	64.0 ± 73.2	61.0 ± 68.3	0.83
LVEDP, mmHg	14.2 ± 4.9	14.8 ± 5.2	13.7 ± 4.6	0.21

ΔACh, change in epicardial coronary artery diameter in response to acetylcholine; ΔCBF, change in coronary blood flow (CBF) in response to acetylcholine; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CCB, calcium-channel blockers; CFR, coronary flow reserve; LVEDP, left ventricular end-diastolic pressure.

Assessment of left ventricular structural and functional remodelling by CMRI

Overall, MPRI was weakly related to age ($r = -0.173$, $P = 0.056$), but CFR was not ($r = 0.045$, $P = 0.624$). Comparison of LV myocardial function by MPRI group is shown in Table 2. By design, mean MPRI was significantly higher in Group 1. Furthermore, A-MPRI which specifically evaluated the same LAD coronary artery territory with that of invasive CFR, was also higher in Group 1. Among this subgroup of WISE-CVD, there was no significant correlation between CFR and MPRI ($r = -0.048$, $P = 0.603$, with adjusted by age). LV RWT trended higher in Group 2, despite a similar LV mass index, compared with Group 1. GCS and CSRe were lower ($P = 0.039$ and $P = 0.035$, respectively) in Group 2, but LV ejection fraction was not different between two groups. GRS was higher in Group 2, but RSRe was not different between the groups.

Univariate analysis of the relationship between groups to other cardiac parameters is depicted in Table 3. Low MPRI was related to older age, low PFR, GCS, GRS, and CSRe; however, age-adjusted analysis demonstrated that only low GCS remained negatively related to low MPRI ($r = -0.22$, $P = 0.02$). In multivariate analysis, GRS and GCS were related to MPRI group (Table 3).

PFR was related to LV RWT, GRS, RSRe, and CSRe. Systolic BP and LVMI were weakly related to PFR (Table 4). Regarding the relation to concentric remodelling, PFR was negatively related to LV

RWT ($r = -0.296$, $P = 0.001$) and this correlation was more apparent with adjusted by age ($r = -0.336$, $P < 0.001$, Table 4). By multivariate analysis, LV RWT was the most independent parameter related to PFR (Table 4).

Discussion

In women with suspected INOCA (evidence of ischaemia but no obstructive CAD) and intermediate CFR, those with lower MPRI had more LV concentric modelling and impaired diastolic LV function compared with those with higher MPRI, despite having similar CFR. Impaired LV circumferential strain values in women with lower MPRI may indicate greater subendocardial dysfunction. These results support the hypothesis that LV concentric remodelling and LV diastolic dysfunction may contribute to CMD, in addition to impairment of vasomotion, by progressive fibrosis from chronic repetitive coronary microvascular ischaemia,¹⁸ although causality cannot be inferred by our cross-sectional design.

The LV wall consists of endocardium, myocardium, and epicardium. The endocardium is the most vulnerable to the afterload or ischaemia and the function of endocardium is the most easily impaired in various cardiac diseases. Circumferential function is mainly determined by the endocardial layer, whereas radial function is an action of

Table 2 Comparison of LV myocardial structure and function by MPRI groups

	Group 1 High MPRI (MPRI \geq 1.8, n = 66)	Group 2 Low MPRI (MPRI < 1.8, n = 59)	P-value
MPRI	2.24 \pm 0.34	1.52 \pm 0.23	<0.001
A-MPRI	2.21 \pm 0.39	1.50 \pm 0.25	<0.001
LV mass index, g/m ²	51.8 \pm 5.8	51.3 \pm 8.1	0.66
LV RWT	0.33 \pm 0.06	0.36 \pm 0.09	0.08
LV ejection fraction, %	66 \pm 6	67 \pm 7	0.52
PFR, mL/s	374.1 \pm 104.4	335.1 \pm 99.5	0.035
Time to PFR, ms	199.6 \pm 75.0	198.5 \pm 51.3	0.92
GRS (%)	48.7 \pm 7.7	52.0 \pm 9.7	0.046
GCS (%)	-23.7 \pm 2.2	-22.7 \pm 3.1	0.039
RSRe (1/s)	-3.23 \pm 0.74	-3.28 \pm 0.98	0.75
CSRe (1/s)	1.47 \pm 0.35	1.34 \pm 0.32	0.037

A-MPRI, MPRI corresponding left anterior descending coronary artery; CSRe, circumferential early diastolic strain rate; GCS, global circumferential strain; GRS, global radial strain; LV, left ventricular; MPRI, myocardial perfusion reserve index; PFR, peak filling rate; RSRe, radial early diastolic strain rate; RWT, relative wall thickness.

Table 3 The relationship between MPRI group and other cardiac parameters

	Univariate analysis		Multivariate analysis		
	R	P-value	β	P-value	95% CI
Age	-0.237	0.008	-1.04	0.063	-0.998 to 1.082
Systolic blood pressure	-0.172	0.057			
LV mass index	0.040	0.658			
LV RWT	-0.155	0.096			
PFR	0.189	0.035			
GRS	-0.187	0.049	-1.19	0.024	-1.372 to 1.035
GCS	-0.196	0.039	-1.99	0.013	-3.448 to 1.153
CSRe	0.199	0.037			

CSRe, circumferential early diastolic strain rate; GCS, global circumferential strain; GRS, global radial strain; LV, left ventricle; MPRI, myocardial perfusion reserve index; PFR, peak filling rate; RWT, relative wall thickness.

Table 4 The relationship between PFR and other cardiac parameters

	Univariate analysis		Multivariate analysis		
	R	P-value	β	P-value	95% CI
Systolic blood pressure	0.159	0.089	0.126	0.17	-3.968 to 0.701
LV mass index	0.165	0.089	0.196	0.048	0.192 to 34.482
LV RWT	-0.336	<0.001	-0.307	<0.001	-0.005 to -0.001
MPRI	0.014	0.882			
GRS	0.256	0.008	-0.138	0.17	-0.267 to 1.531
GCS	-0.149	0.124			
RSRe	-0.418	<0.001	-0.455	0.001	-0.044 to -0.012
CSRe	0.262	0.006	0.104	0.39	-0.024 to 0.010

Regression analysis was performed with Low MPRI and other cardiac parameters, and adjusted for age. CSRe, circumferential early diastolic strain rate; GCS, global circumferential strain; GRS, global radial strain; LV, left ventricle; MPRI, myocardial perfusion reserve index; PFR, peak filling rate; RWT, relative wall thickness.

myocardial layer.¹⁹ In our study, GCS and CSRe were both lower in patients with low MPRI although LV ejection fraction was preserved. Our results combined with our prior work^{5,20} demonstrate that women with suspected INOCA have impaired LV endocardial function and diastolic dysfunction, which supports aetiological relations among endocardial impairment, LV diastolic dysfunction, and CMD, although directional causality cannot be not determined.

Notably, in our study of women with intermediate CFR, vasomotion represented by invasively determined CFR was similar in patients with high MPRI and with low MPRI, suggesting that MPRI may more accurately reflect CMD-related ischaemia due to contribution from the myocardium. Abnormalities in MPRI but without impairment in invasive CFR may reflect early or mild CMD.²¹ We previously demonstrated weak correlation between CFR and MPRI in women with suspected angina but no obstructive CAD.¹¹ Therefore, factors other than coronary vasomotion appear to be important in the physiology of microvascular ischaemia, such as LV concentric remodelling and dysfunction. Indeed, the low MPRI group demonstrated more LV concentric remodelling and impaired LV function than the high MPRI group.

MPRI was inversely related to LV concentric remodelling, with no increase in LV mass index in this population. LV concentric remodelling can occur due to an increase in afterload such as hypertension; however, in our study, the prevalence of hypertension was not different between the two groups, although systolic BP was slightly higher in the low MPRI group. Cardiovascular risk factors, such as hypertension, diabetes, and smoking contribute to a minority of CMD variance in WISE participants,²² thus it is not surprising that there were no significant differences in cardiovascular risk factor prevalence in the two MPRI groups.

Concentric remodelling can lead to extravascular compression of the coronary microvessels and coronary blood flow occurs predominantly during diastole, it is conceivable that LV diastolic changes also play a role in CMD. In INOCA patients with LV concentric remodelling, CFR reduction may initiate a process of abnormal coronary microvascular perfusion paralleling increased metabolic demand caused by pressure overload and increased wall thickness. Myocardial ischaemia occurs when there is an imbalance between myocardial oxygen (MVO₂) supply and demand; and the ischaemia is usually entirely or predominantly subendocardial. A previous WISE study showed that compared with the reference group, WISE participants with no obstructive CAD have changes in systolic wave reflections and diastolic timing that increase LV afterload and MVO₂ demand with the potential to reduce coronary artery perfusion.²³ They suggested that these alterations in cardiovascular function contribute to an undesirable mismatch in the MVO₂ supply/demand that promotes ischaemia and chest pain. In addition, wave-intensity analysis has shed light on the impact of LV hypertrophy on coronary microvascular flow, suggesting a disruption between systolic compression of the microcirculation and the resultant diastolic decompression.^{24,25}

The reduction in coronary microvascular perfusion can be also influenced by the increase in LV filling pressure, which enhances extravascular coronary resistance.²⁶ Because most of the coronary filling occurs during LV active relaxation,²⁷ the delay in LV relaxation can also contribute to reducing hyperaemic diastolic coronary flow.^{25,28} It is also possible that progressive subtle fibrosis caused by

chronic repetitive coronary microvascular impairment results in impairment of mid-wall LV function. In our result, RSRe represented as mid-wall LV diastolic function was significantly related to PFR.

Given that coronary blood flow mainly occurs in diastole, abnormalities in this phase of the cardiac cycle can have a strong effect on myocardial perfusion. Nevertheless, an increase in systolic intramyocardial and ventricular pressures, as typically occurs in primary and secondary LV hypertrophy, can also adversely affect myocardial perfusion.^{29–31} In contrast, myocardial ischaemia may produce LV diastolic alterations, even before the detection of wall motion and/or electrocardiographic ST segment changes. It is well known that LV diastolic dysfunction is detected in the early stage of reduced coronary blood flow to the myocardium. Specifically, elevations of LV end-diastolic pressure have long been recognized to occur during spontaneous or provoked ischaemia.^{32–34} Although we excluded participants with myocardial scar by CMRI late gadolinium enhancement, we cannot exclude subclinical uniform and focal perivascular fibrosis or interstitial fibrosis caused by chronic myocardial ischaemia and leading to increased microvascular resistance.^{26,35} Therefore, in CMD, while gross LV systolic dysfunction may not be apparent, LV diastolic function impairment may be both contributing to and a consequence of repeated bouts of subendocardial ischaemia.

These findings have prognostic significance in women with INOCA, as these women have worse diastolic function compared with normal controls.^{5,20} Low CFR and low myocardial perfusion reserve in patients with INOCA are related to worse prognosis.^{36–38} In addition, LV concentric remodelling itself also has adverse prognostic significance.^{39,40} Long-term follow-up of women with INOCA demonstrated a three-fold higher risk of cardiovascular events in comparison to asymptomatic healthy women, with the most frequent event being heart failure hospitalization,⁴¹ which we have documented to be heart failure with preserved ejection fraction (HFpEF).⁴² These findings have led to the hypothesis that CMD is a contributor to the development of HFpEF.⁴³ We propose that contributors to CMD are also known to favour hypertrophy and fibrosis contributing to diastolic dysfunction. Further long-term studies are needed to determine the prognostic role of LV concentric remodelling with diastolic impairment in patients with CMD, and to determine whether functional CMD has a similar or a different prognostic weight as compared with structural CMD.

Clinical implications

We have previously demonstrated that more than half of women with suspected INOCA have gold-standard evidence of myocardial ischaemia on magnetic resonance spectroscopy.⁴⁴ These women also have relatively high rates of heart failure hospitalizations, repeated coronary angiography, treatment costs, and adverse cardiovascular events compared with asymptomatic women.^{41,45} Despite these findings, knowledge gaps remain regarding pathophysiology which could lead to treatment targets. Our results demonstrating that both functional coronary microvessel vasomotion and structural microvasculature remodelling contribute to low MPRI provide additional pathophysiological insight and potential novel treatment targets. For example, these results may explain why standard pharmacological anti-anginal treatment can sometimes be disappointing in controlling angina symptoms. Further, why focused treatment on ventricular remodelling can improve angina,⁴⁶ and offers a putative

treatment target to reduce progression to HFpEF.⁴² Accordingly, CMRI MPRI and tissue tracking may provide additive information to assess suspected INOCA participants with intermediate CFR. Moreover, clinical trials of strategies to modulate myocardial substrate and function rather than functional coronary vasomotion should be considered.

Limitations

There are several limitations in this study. First, the invasive CFR and CMRI were performed on different days, potentially leading to day-to-day variability, although testing conditions were matched for the two measures. Secondly, we conducted this analysis from the WISE-CVD study which enrolled women only. While women are more likely to have no obstructive CAD on coronary angiography compared with men,⁴⁷ and women have relatively more CMD than men,⁴⁸ studies have been confounded by coronary angiography referral bias, and the relative prevalence of CMD in women and men is unknown. Thirdly, myocardial tissue feature tracking is a novel method to evaluate myocardial function by CMRI, is rapid and semi-automated, requires no additional scans and sequences, and reduces post-processing time compared with traditional myocardial tissue tagging.^{49,50} However, feature tracking imaging algorithms are dependent on image quality, frames, and endocardial border definition. The temporal resolution is lower than in echocardiography, which might be relevant for the assessment of strain rates for the diastolic function. Our feature tracking analyses were conducted on resting CMRI images, precluding our ability to understand direct links between CMD-related ischaemia and diastolic function.

Conclusions

In women with suspected INOCA and intermediate CFR, participants with lower MPRI had a trend towards more adverse concentric remodelling and impaired diastolic function compared with those with higher MPRI. Impaired LV strain values in women with lower MPRI may indicate greater subendocardial dysfunction despite similar CFR. These findings provide evidence that not only coronary microvessel vasomotion but also structural and functional myocardial remodelling may be contributors to CMD.

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