



# Evaluation of left ventricular diastolic function in patients with coronary microvascular dysfunction via cardiovascular magnetic resonance feature tracking

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**Background:** Coronary microvascular dysfunction (CMD) has been suggested to be one of the pathologic mechanisms contributing to heart failure with preserved left ventricular ejection fraction (LVEF) and left ventricular (LV) diastolic dysfunction. We therefore aimed to evaluate LV diastolic function in patients with CMD using cardiovascular magnetic resonance feature tracking (CMR-FT).

**Methods:** We prospectively enrolled 115 patients referred to cardiology clinics for chest pain assessment who subsequently underwent coronary computed tomography angiogram and stress perfusion CMR. CMD was defined as the presence of subendocardial inducible ischemia detected through visual assessment. LV diastolic function was evaluated using CMR-derived volume-time curves and CMR-FT parameters. The former included early peak filling rate (PFR) and time to PFR; the latter included LV global/regional peak longitudinal diastolic strain rate (LDSR), circumferential diastolic strain rate (CDSR), and radial diastolic strain rate (RDSR).

**Results:** A total of 92 patients with 1,312 segments were eventually included. Of these, 19 patients were classified as non-CMD (48.8±11.2 years; 63.2% male) and 73 as with CMD (52.3±11.9 years; 54.8% male). The LVEFs were similar and preserved in both groups (P=0.266). At the per-patient level, no differences were observed in PFR, time to PFR, or LV global diastolic strain rates between the two groups. At the per-segment level, 51% (665/1,312) of the myocardial segments were classified as CMD, whereas 49% (647/1,312) were classified as non-CMD. CMD segments showed significantly lower regional CDSR (P=0.019) and RDSR (P=0.006) compared with non-CMD segments.

**Conclusions:** Despite normal LV ejection fraction in CMD patients, decreased LV diastolic function in CMD myocardial segments indicates early diastolic impairment.

**Keywords:** Left ventricular diastolic function (LV diastolic function); cardiovascular magnetic resonance feature tracking (CMR-FT); coronary microvascular dysfunction (CMD)

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## Introduction

Symptoms of myocardial ischemia with no obstructive coronary artery disease (INOCA) are encountered frequently in clinical practice and thus constitute a diagnostic and therapeutic challenge (1-3). Up to two-thirds of patients with INOCA are believed to have coronary microvascular dysfunction (CMD) as the functional substrate of their ischemic symptoms (4-7). CMD is defined as the impaired vasodilation of arterioles leading to a diminished coronary flow reserve (CFR) or an insufficient increase in blood flow from rest to stress (1,5).

CMD is associated with increased mortality, even without macrovascular coronary artery disease (CAD) (8,9). Moreover, accumulating evidence suggests the presence of a correlation between CMD and left ventricular (LV) diastolic dysfunction, with CMD increasing the risk of developing heart failure with preserved ejection fraction (HFpEF) outcomes (10-12). A hypothesis is proposed that the diastolic dysfunction in CMD patients can eventually progress to HFpEF. It is worth noting that patients with CMD and diastolic dysfunction have been associated a poor prognosis, an increased rate of major adverse cardiovascular events (MACEs), and a more than 5-fold rate of HFpEF hospitalization (4,13-16).

Previous studies have reported changes in the echocardiographic indices of diastolic dysfunction in patients with CMD (17,18). Cardiac magnetic resonance (CMR) cine images are more accurate and comprehensive than is echocardiography in assessing LV morphology, LV function, and tissue characterization via CMR feature tracking (CMR-FT) (19-22). However, published research in this area is limited. Our study aimed to investigate whether patients with CMD had impaired LV diastolic function as assessed with CMR-FT.

## Methods

### Study population

The study participants comprised consecutive patients without a prior history of CAD who had undergone stress perfusion CMR (stress CMR) at Beijing Friendship Hospital between December 2019 and August 2021. They were referred to the cardiology department for suspected myocardial ischemia due to symptoms such as chest pain. Subsequently, they underwent diagnostic coronary computed tomography angiography (CCTA) which demonstrated no evidence of significant coronary

stenosis (main coronary stenosis >50% within 1 month). A final cohort of 115 patients with preserved LV ejection fraction (LVEF) was established. Patients with known CAD, including prior revascularization and/or myocardial infarction, primary cardiomyopathy (hypertrophic, dilated, and restrictive), or a prior history of heart failure, atrial fibrillation, or severe valvular disease were excluded from the final cohort. We collected baseline demographics and clinical variables of the study population, which are summarized in *Table 1*. This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Beijing Friendship Hospital Medical Ethics Committee (No. 2021-P2-418-01). All patients provided written informed consent. *Figure 1* depicts the study flowchart and exclusion criteria of patients.

### Acquisition of CMR parameters

CMR was performed using a MAGNETOM Prisma 3T magnetic resonance imaging scanner (Siemens Healthineers, Erlangen, Germany). All images were acquired using phased-array surface coils during mild expiration and electrocardiographic triggering. First, patients received adenosine triphosphate (ATP; 5 mg/mL) at an infusion rate of 0.16 mg/kg/min for approximately 4 minutes (heart rate increase  $\geq 10$  bpm or systolic blood pressure decrease  $\geq 10$  mmHg). This was followed by an intravenous administration of gadolinium (0.5 mmol/mL) at a rate of 3–4 mL/s and a subsequent 30-mL saline flush at the same flow rate to obtain the first-pass perfusion images using a T1-weighted fast gradient echo sequence for both scanners [repetition time/time to echo (TR/TE) = 2.1/1.03 ms, TI = 100 ms, temporal resolution = 155.7 ms, flip angle = 10°, voxel size = 1.9 × 1.9 × 8.0 mm<sup>3</sup>]. Three perfusion short-axis slice images (base, mid, and apex) of the left ventricle were acquired. Subsequently, balanced steady-state free-precession cine images were acquired in multiple short-axis locations (every centimeter from base to apex) and 3 long-axis locations (2-, 3-, and 4-chamber views; TR/TE = 3.3/1.43 ms, temporal resolution = 40 ms, flip angle = 50°, voxel size = 1.6 × 1.6 × 6.0 mm<sup>3</sup>). Rest perfusion images were acquired in the same 3 short-axis positions as those for the stress perfusion images at least 10 minutes after termination of the ATP infusion. Late gadolinium enhancement (LGE) images were acquired at least 10 minutes after gadolinium injection. The LGE parameters were as follows: TR/TE = 5.2/1.96 ms, TI = 300 ms, flip angle = 20°, voxel size = 1.8 × 1.8 × 8.0 mm<sup>3</sup>.

**Table 1** Baseline demographics and clinical variables of the study population

Variables	Non-CMD, N=19	CMD, N=73	P value
Demographic			
Age (years)	48.8±11.2	52.3±11.9	0.265
Sex (male)	12 (63.2)	40 (54.8)	0.512
BMI (kg/m <sup>2</sup> )	24.7±3.9	25.6±3.6	0.338
HR rest (beats/min)	65±11	69±9	0.052
HR stress (beats/min)	91±18	99±15	0.036*
HR increase (beats/min)	26±13	30±12	0.264
Systolic blood pressure (mmHg)	123±9	128±17	0.272
Diastolic blood pressure (mmHg)	73±12	77±10	0.211
CVD risk factor			
Hypertension	7 (36.8)	32(43.8)	0.583
Diabetes	4 (21.1)	17 (23.3)	0.836
Hypercholesterinemia	9 (47.4)	32 (43.8)	0.783
Smoker	6 (31.6)	20 (27.4)	0.718
Drinking	6 (31.6)	18 (24.7)	0.634
Laboratory and echocardiographic parameter			
NT-proBNP (pg/mL)	26.7±21.9	55.3±65.1	0.261
eGFR (mL/min/1.73 m <sup>2</sup> )	101.8±9.1	95.6±15.8	0.198
cTnl (ng/mL)	104.7 (96.6, 117.9)	98.9 (89.3, 104.8)	0.837
E velocity (cm/s)	80.3±15.2	76.1±18.4	0.462
A velocity (cm/s)	78.6±16.8	78.0±20.6	0.923
E/A ratio	1.1±0.2	1.0±0.4	0.947

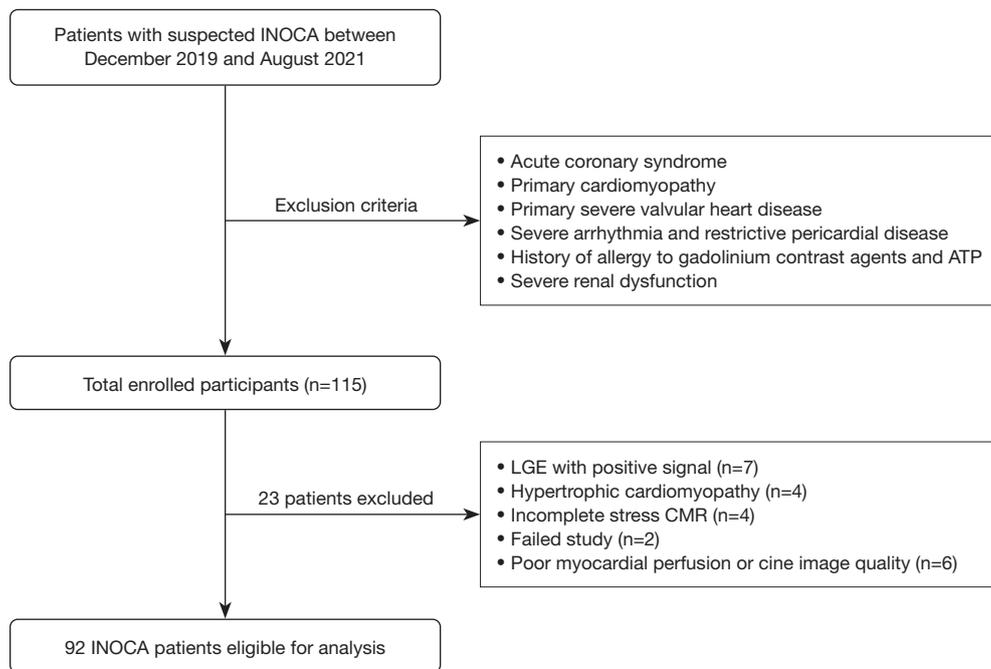
Data with a skewed distribution are expressed as median (maximum, minimum) values; otherwise, they are expressed as number (percentage) or mean ± SD. \*, significant result. CMD, coronary microvascular dysfunction; BMI, body mass index; HR, heart rate; CVD, cardiovascular disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; cTnl, cardiac troponin I; SD, standard deviation.

### LV diastolic function assessment

During image analysis, LV basic cardiac function parameters were measured. This was conducted by automatically tracing the epicardial and endocardial borders of the short-axis cine images at end diastole and end systole automatically using postprocessing software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). The automatically traced measurements were then manually adjusted as necessary. These parameters included LVEF, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), cardiac output (CO), stroke volume (SV), and cardiac index (CI).

LV diastolic function was evaluated using the time-

volume curve and CMR-FT strain analysis, which enabled the quantification of LV global and regional diastolic functions (19,23,24). The former was generated by continuous the automatic tracing of endocardial borders during complete cardiac cycles with manual adjustment; the first derivative curve used to obtain the LV peak filling rate (PFR) is illustrated in *Figure 2*. The PFR was defined as the maximal change in the LV volume per unit time ( $\Delta$  volume/ $\Delta$  phase), which was the LV maximum slope of the diastolic phase. Diastolic dysfunction was characterized as a decreased peak filling rate and prolonged time-to-peak-filling rate (T-PFR) (25,26). Finally, the myocardial



**Figure 1** Study flowchart and exclusion criteria of patients. INOCA, ischemia with no obstructive coronary artery disease; ATP, adenosine triphosphate; LGE, late gadolinium enhancement; CMR, cardiovascular magnetic resonance.

deformation was evaluated with CMR-FT of CMR cine images, as depicted in *Figure 2*. The indices reflecting LV diastolic function including LV peak longitudinal diastolic strain rate (LDSR), circumferential diastolic strain rate (CDSR), and radial diastolic strain rate (RDSR), were recorded (19,23).

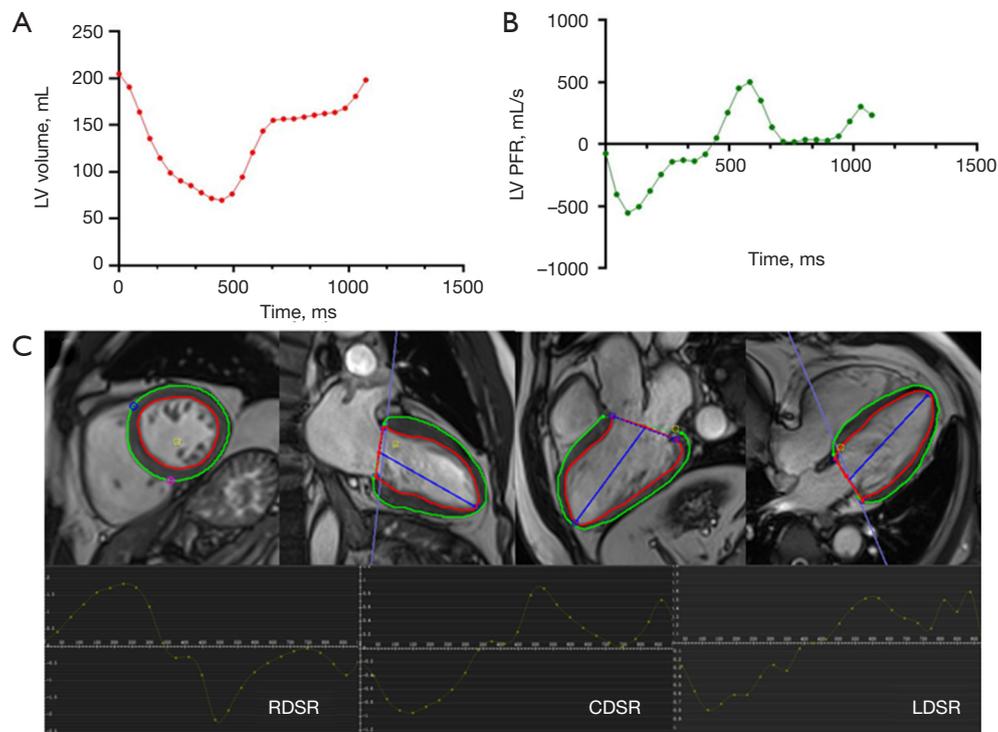
### Visual assessment of CMD

The noninvasive quantification of coronary microvascular function was performed using stress CMR. Poor-quality images or incomplete data were excluded from the analysis. The presence of ischemia was evaluated according to the segmental analysis of stress perfusion images, which were recorded in 16 segments (the apical segment is typically not in the field of view) based on the American Heart Association 17-segment model (27). CMD revealed the presence of inducible myocardial ischemia in the subendocardium. Inducible ischemia was defined as the presence of a stress perfusion defect and the absence of matching LGE in  $\geq 1$  segment that persisted for  $\geq 5$  dynamics (15,28,29), as illustrated in *Figure 3*. The presence of dark rim artifacts (DRAs) should be excluded during the visual assessment. The characteristics of DRA in this study

were considered to be the following: (I) artifacts are the most prominent when contrast arrives in the LV blood pool; (II) artifacts persist only transiently before the peak myocardial contrast enhancement; and (III) artifacts appear predominantly in the phase-encoding direction (30,31). All CMR perfusion images were analyzed by two skilled CMR readers (Cao J and He Y), with one of the readers (He Y) repeating the analyses at an interval of 1 month between analyses. Additionally, semiquantitative myocardial perfusion was analyzed using CVI42 software. This involved manually tracing contours surrounding the endocardium and epicardium to determine the LV myocardial signal intensity. The CMR-derived myocardial perfusion reserve index (MPRI), defined as the ratio of stress to rest upslope normalized to the upslope of the LV blood pool, was recorded (32,33).

### Statistical analysis

Continuous variables were assessed for normality and are presented as the mean  $\pm$  standard deviation (SD). The normally and nonnormally distributed variables between groups were compared using the independent samples *t*-test or nonparametric test (Mann-Whitney test



**Figure 2** Evaluation of LV diastolic function using CMR-derived time-volume curves and CMR-FT parameters. (A,B) LV time-volume curve and time-PFR. PFR was derived from the steepest gradient in the curve in the early diastolic phase. (C) Short axis and long axis (2-, 3-, and 4-chamber) cine images were selected to mark the endocardium (red lines) and epicardial contours (green lines) and obtain LV diastolic function indicators including RDSR, CDSR, and LDSR. The blue lines represent the LV boundary. The blue and pink circles represent the left and right ventricle intersection point. LV, left ventricular; PFR, peak filling rate; RDSR, radial diastolic strain rate; CDSR, circumferential diastolic strain rate; LDSR, longitudinal diastolic strain rate; CMR-FT, cardiovascular magnetic resonance feature tracking.

or Kolmogorov-Smirnov test). The categorical variables are presented as percentages and were compared using the chi-squared test. The intraclass correlation coefficient (ICC) was used to determine inter- and intraobserver reproducibility. Reproducibility was defined as poor (ICC <0.4), good (ICC 0.4–0.75), or excellent (ICC >0.75), and 95% confidence interval (95% CI) were determined in order to visualize inter- and intraobserver variability. A P value <0.05 indicated a statistically significant difference. All statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA).

## Results

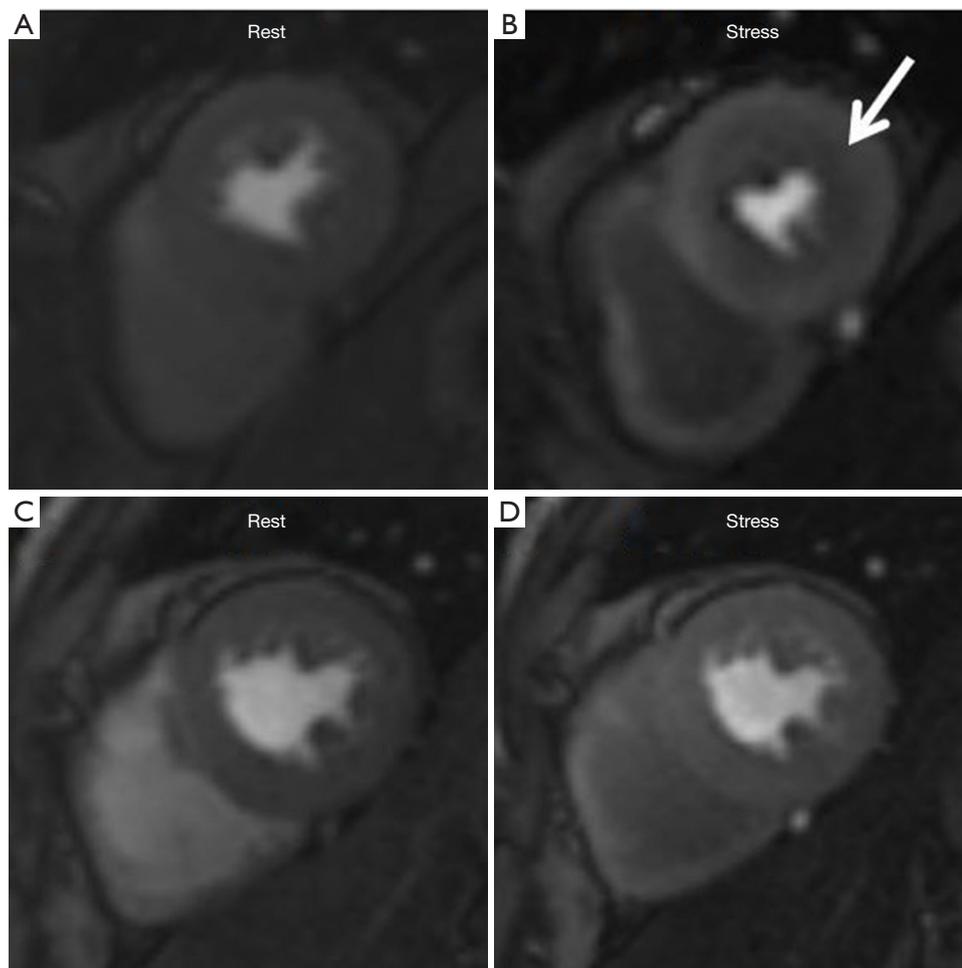
### Study demographics

A total of 80% (92/115) patients (52.5±11.8 years; 57% male) were included in the data analysis. Of the 115 patients, 23 patients were excluded for the following reasons:

7 patients had positive LGE, 4 patients had hypertrophic cardiomyopathy, 6 patients failed to complete the study, and 6 patients had poor image quality.

Of these, 73 (79%) patients (52.3±11.9 years; 54.8% male) had inducible myocardial ischemia in the subendocardium. The remaining 19 (21%) patients (48.8±11.2 years; 63.2% male) without myocardial ischemia were classified as non-CMD. Women (33/40, 82.5%) had a greater burden of CMD than did men (40/52, 77%).

At the per-segment level, 160 (11%) segments were excluded from the initial 1,472 myocardial segments due to various factors. These factors included the involvement of the outflow tract involved, scanning plane beyond the mitral valve, scanning plane of stress and rest perfusion mismatch, and inadequate image quality. Hence, the study finally included 1,312 (89%) myocardial segments. Among these segments, 665 (51%) segments were classified as CMD and 647 (49%) as non-CMD. The characteristics of the study



**Figure 3** Example of perfusion and rest first-pass perfusion images for visual assessment. (A,B) Patients with CMD and (C,D) and patients without CMD. (A,B) A patient with a visual assessment of CMD had inducible perfusion defects in the subendocardium, which were present only under stress (white arrow) and did not manifest during rest. (C,D) A patient with a visual assessment of non-CMD had no defects on stress or rest perfusion images. CMD, coronary microvascular dysfunction.

population are presented in *Table 1*.

For the reproducibility of CMD diagnosis by visual assessment, our study showed that the ICC for inter- and intraobserver agreement were 0.906 (95% CI: 0.861–0.937) and 0.874 (95% CI: 0.815–0.915), respectively.

#### *LV diastolic function evaluated using CMR*

The LV basic cardiac function parameters revealed a lower MPRI and SV in the CMD group compared with the non-CMD group (MPRI:  $1.49 \pm 0.3$  vs.  $1.86 \pm 0.6$ ,  $P < 0.005$ ; SV:  $71.21 \pm 15.4$  vs.  $76.96 \pm 9.3$  mL,  $P = 0.045$ ; *Table 2*). All patients had a preserved LVEF of  $\geq 50\%$ . No difference between the CMD and non-CMD groups was noted in terms of

LVEF ( $60.42 \pm 7.4$  vs.  $62.61 \pm 8.3\%$ ;  $P = 0.266$ ) and LVEDV ( $118.09 \pm 22.2$  vs.  $124.59 \pm 20.8$  mL;  $P = 0.253$ ). The PFR and T-PFR values were also not significantly different between the 2 groups (both  $P$  values  $> 0.05$ ; *Table 2*).

In addition, the LV global diastolic strain rates were not considerably distinct between the 2 groups (*Table 2*). However, when LV was divided into 16 segments for analysis and at the per-segment level, the ischemic segments revealed a remarkably lower regional CDSR [median 1.26 [interquartile range (IQR), 1.01–1.57] vs. median 1.32 (IQR, 1.00–1.65),  $P = 0.019$ ], and regional RDSR [median  $-2.28$  (IQR,  $-3.06$  to  $-1.65$ ) vs. median  $-2.45$  (IQR,  $-3.41$  to  $-1.64$ ),  $P = 0.006$ ] compared with the non-CMD segments. Furthermore, the regional LDSR was substantially higher

**Table 2** Basic cardiac function parameters and LV global diastolic function parameters

Variables	Non-CMD, N=19	CMD, N=73	P value
LV basic function			
MPRI	1.86±0.6	1.49±0.3	<0.005*
LVEF (%)	62.61±8.3	60.42±7.4	0.266
LVEDV (mL)	124.59±20.8	118.09±22.2	0.253
LVEDV/BSA	65.69±11.9	61.0±10.1	0.292
LVESV (mL)	47.63±17.3	46.88±13.7	0.842
LVESV/BSA	25.85±8.6	25.83±7.2	0.990
CO (L/min)	5.5±1.4	6.1±7.0	0.740
SV (mL)	76.96±9.3	71.21±15.4	0.045*
CI (L/min/m <sup>2</sup> )	3.11±0.9	3.15±0.8	0.832
LV global diastolic function			
PFR (mL/s)	372.03±107.1	382.41±127.6	0.757
T-PFR (s)	484.88±126.8	457.77±54.9	0.374
Global LDSR (s <sup>-1</sup> )	1.06±0.4	1.19±0.4	0.192
Global CDSR (s <sup>-1</sup> )	0.91±0.3	0.98±0.4	0.423
Global RDSR (s <sup>-1</sup> )	-1.69±0.9	-1.67±1.3	0.946

Data are expressed as mean ± SD. \*, significant result. LV, left ventricular; CMD, coronary microvascular dysfunction; MPRI, myocardial perfusion reserve index; LVEF, LV ejection fraction; LVEDV, LV end diastolic volume; BSA, body surface area; LVESV, LV end systolic volume; CO, cardiac output; SV, stroke volume; CI, cardiac index; PFR, peak filling rate; T-PFR, time-to-peak-filling rate; LDSR, longitudinal diastolic strain rate; CDSR, circumferential diastolic strain rate; RDSR, radial diastolic strain rate; SD, standard deviation.

in the CMD segments compared with the non-CMD segments [median 1.76 (IQR, 1.21–2.48) *vs.* median 1.55 (IQR, 1.18–2.26), P=0.003] (Table 3).

## Discussion

In this study, CMR parameters were used to verify the altered LV diastolic function in patients with CMD. First, the incidence of CMD was found to be higher in patients with signs and symptoms of ischemia but not in those with signs of obstructive CAD. Second, LV global diastolic function did not decrease in patients with CMD. Third, the regional LV diastolic function of CMD patients decreased.

Our findings are consistent with those of previous studies in terms of the clinical characteristics of CMD. Waheed *et al.* (34) reported that women typically had a greater burden of CMD, which was also reflected in our study. Of the female patients in this group, 82.5% (33/40) had CMD, whereas only 77% (40/52) of men had CMD. Moreover, all recruited patients with INOCA in both the CMD and non-

CMD groups exhibited cardiovascular (CV) risk factors (hypertension, diabetes, hypercholesterolemia, smoking, and drinking). Differences in LV diastolic parameters between the 2 groups could still be observed, suggesting that the impaired LV diastolic function in patients with CMD cannot be attributable to the CV risk factors. As for the incidence of CMD, several studies have reported CMD in a large proportion (one-half to two-thirds) of patients with INOCA (35,36). Interestingly, in Wei *et al.*'s study, CMD was present in 83% of women (25). The aforementioned CV risk factors eventually led to the development of CMD, indicating that the prevalence of CMD in this study population was relatively high.

Regarding regional CMD, previous studies (37,38) have confirmed that microcirculation abnormalities have a patchy distribution in the myocardial wall rather than a diffuse distribution, which is consistent with our visual evaluation. According to The European Society of Cardiology (ESC) Working Group on Coronary Pathophysiology and Microcirculation position paper (39), the mechanisms

**Table 3** LV regional diastolic function parameters evaluated using CMR-FT

Variables	Non-CMD	CMD	P value
Segments	647	665	
Regional LDSR (s <sup>-1</sup> )	1.55 (1.18–2.26)	1.76 (1.21–2.48)	0.003*
Regional CDSR (s <sup>-1</sup> )	1.32 (1.00–1.65)	1.26 (1.01–1.57)	0.019*
Regional RDSR (s <sup>-1</sup> )	-2.45 (-3.41 to -1.64)	-2.28 (-3.06 to -1.65)	0.006*

Data with a skewed distribution are expressed as median (IQR) values. \*, significant result. LV, left ventricular; CMR-FT, cardiovascular magnetic resonance feature tracking; CMD, coronary microvascular dysfunction; LDSR, longitudinal diastolic strain rate; CDSR, circumferential diastolic strain rate; RDSR, radial diastolic strain rate; IQR, inter-quartile range.

underlying CMD in patients nonobstructive CAD are still not completely understood, but they likely involve both functional and structural changes. Additionally, endothelial dysfunction is a key mediator in the pathogenesis of CMD, and it is believed that with advancement in medical technology, the future study of CMD will be more thorough and clearer.

#### ***Evaluation of LV global diastolic function using LV filling curves***

Notably, no PFR or T-PFR differences were observed between the patients with and without CMD in this study. In the study by Mendoza *et al.*, reduced PFR and prolonged T-PFR were found to reflect one aspect of LV global diastolic dysfunction, and LV filling curves could be used to discern the volumetric filling changes that occurred with graded severity of diastolic dysfunction. Moreover, the PFR decreased during the progression from normal diastolic function to grade 1 diastolic dysfunction and then increased during the progression from grade 1 diastolic dysfunction to grade 3 diastolic dysfunction (40). Therefore, even if PFR does not decrease, this does not necessarily mean that LV diastolic function is normal. In our study, the PFR in the CMD group did not decrease, which is in line with the findings of Wei *et al.*'s study (25). Moreover, the same results were obtained even in patients with HFpEF (26). In our study, the LV global diastolic function evaluated using LV filling curves did not decrease in patients with CMD, indicating that these parameters were not sufficiently sensitive to detect early LV diastolic dysfunction.

#### ***Evaluation of LV diastolic function using CMR-FT diastolic strain rates***

The CMR strain technique to assess LV diastolic function

was proposed several years ago (41) and has been used in a variety of diseases (17,19,24–26). The Women's Ischemia Syndrome Evaluation (WISE) study (42) demonstrated that diastolic function is impaired in women with signs and symptoms of ischemia without CAD, as assessed by CMR tissue tagging. Our study further stratified patients with INOCA into a CMD group and a non-CMD group, with decreased LV diastolic function being found to be more pronounced in CMD myocardial segments. Although our study demonstrated no reduction in CMR parameters indicating LV global diastolic function, this could be explained by the lack of ischemia in the myocardial segment during the early compensatory stage in patients with CMD.

In contrast to the studies by Taqueti *et al.* (16) and Shah *et al.* (10), in which stress myocardial perfusion positron emission tomography (PET) and adenosine stress transthoracic Doppler echocardiography were examined, respectively, our study used the CMR-FT technique to characterize cardiac morphology and diastolic function. The findings from the studies that patients with CMD have more impaired LV diastolic dysfunction than do non-CMD individuals were in concordance with our results. The aforementioned studies reported that the patients with impaired CFR or CMD a worse diastolic function, including both a lower  $e'$  and higher  $E/e'$ , as compared with the patients with preserved CFR or an absence of CMD. The LV ejection fractions in both groups were preserved, and there were no statistically significant differences in this regard. However, the pathophysiological mechanism underlying this phenomenon is still unclear (43).

CMD leading to increased LV diastolic stiffening has recently been proposed as the mechanism underlying the pathogenesis of HFpEF (44–47) due to the fact that the prevalence of CMD is high in both patients with HFpEF and patients with INOCA (10,12,16). We found that the prevalence of CMD assessed using stress CMR was

79% in the population of patients with INOCA. Thus, coronary microvascular ischemia caused by CMD may lead to myocardial injury, worsen LV global mechanics, and result in LV dysfunction. In particular, microvascular endothelial dysfunction and increased profibrotic cytokine may contribute to reduced coronary microvascular density and increased myocardial fibrosis, eventually progressing to HFpEF (16,44,48). Meanwhile, a recent PET study (16) reported a link between CMD and diastolic dysfunction in patients with angina and no obstructive CAD. Our study also demonstrated that CMD segments had a slightly impaired LV diastolic function compared with non-CMD segments. These findings thus suggest that one of the pathophysiological mechanisms underlying HFpEF is LV diastolic dysfunction and stiffness due to coronary microvascular ischemia.

Our study also a few limitations that should be noted. First, a single-center study design was employed with relatively small cohorts. Thus, future multicenter studies with larger cohorts are needed to confirm our findings. Second, we did not include a normal healthy population as a control group. Third, strain indicators, such as global longitudinal strain (GLS), which can serve as the marker of subclinical LV dysfunction, were not included in this article (49). This issue was addressed in our other studies in which CMD myocardial segments exhibited remarkably lower longitudinal strain (LS) and circumferential strain (CS). Moreover, biomarkers such as brain natriuretic peptide and cardiac troponin can serve as markers of LV dysfunction. However, heart failure biomarkers were not examined in this study, which limits scope of clinical applicability. However, we will collect this patient information in later studies. Finally, in this study we did not employ CFR, the gold standard for CMD. However, the technology is invasive and complex to operate, so our study did not examine this technology. Moreover, as confirmed by several studies (50-54), the sensitivity and specificity of stress CMR for the diagnosis of CMD are comparable to those of the invasive or noninvasive gold standard, but with CMR involving less pain, radiation dose, and cost to patients.

## Conclusions

Our study found CMD myocardial segments to have decreased LV diastolic function but normal LVEF. These findings point to the early diastolic impairment in CMD and establish a link between CMD and HFpEF. However, LV global diastolic function did not decrease in patients

with CMD in the early compensatory phase. Further studies are warranted to confirm whether there is an association between CMD and LV diastolic function in those patients with INOCA.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-47/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Beijing Friendship Hospital Medical Ethics Committee (No. 2021-P2-418-01). Written informed consent was obtained from all patients in this study.

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