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Microvascular Myocardial Ischemia in Patients With Diabetes Without Obstructive Coronary Stenosis and Its Association With Angina

Yarong Yu[1]*, Wenli Yang[1]*, Xu Dai[2], Lihua Yu[1], Ziting Lan[1], Xiaoying Ding[3], Jiayin Zhang[1]

[1]Department of Radiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]Institute of Diagnostic and Interventional Radiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Department of Endocrinology and Metabolism, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Objective: To investigate the incidence of microvascular myocardial ischemia in diabetic patients without obstructive coronary artery disease (CAD) and its relationship with angina.

Materials and Methods: Diabetic patients and an intermediate-to-high pretest probability of CAD were prospectively enrolled. Non-diabetic patients but with an intermediate-to-high pretest probability of CAD were retrospectively included as controls. The patients underwent dynamic computed tomography-myocardial perfusion imaging (CT-MPI) and coronary computed tomography angiography (CCTA) to quantify coronary stenosis, myocardial blood flow (MBF), and extracellular volume (ECV). The proportion of patients with microvascular myocardial ischemia, defined as any myocardial segment with a mean MBF ≤ of 100 mL/min/100 mL, in patients without obstructive CAD (Coronary Artery Disease–Reporting and Data System [CAD-RADS] grade 0–2 on CCTA) was determined. Various quantitative parameters of the patients with and without diabetes without obstructive CAD were compared. Multivariable analysis was used to determine the association between microvascular myocardial ischemia and angina symptoms in diabetic patients without obstructive CAD.

Results: One hundred and fifty-two diabetic patients (mean age: 59.7 ± 10.7; 77 males) and 266 non-diabetic patients (62.0 ± 12.3; 167 males) were enrolled; CCTA revealed 113 and 155 patients without obstructive CAD, respectively. For patients without obstructive CAD, the mean global MBF was significantly lower for those with diabetes than for those without (152.8 mL/min/100 mL vs. 170.4 mL/min/100 mL, $P < 0.001$). The mean ECV was significantly higher for diabetic patients (27.2% vs. 25.8%, $P = 0.009$). Among the patients without obstructive CAD, the incidence of microvascular myocardial ischemia (36.3% [41/113] vs. 10.3% [16/155], $P < 0.001$) and interstitial fibrosis (69.9% [79/113] vs. 33.3% [8/24], $P = 0.001$) were significantly higher in diabetic patients than in the controls. The presence of microvascular myocardial ischemia was independently associated with angina symptoms (adjusted odds ratio = 3.439, $P = 0.037$) in diabetic patients but without obstructive CAD.

Conclusion: Dynamic CT-MPI + CCTA revealed a high incidence of microvascular myocardial ischemia in diabetic patients without obstructive CAD. Microvascular myocardial ischemia is strongly associated with angina.

Keywords: Diabetes mellitus; Computed tomography angiography; Myocardial perfusion imaging; Myocardial ischemia

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*These authors contributed equally to this work.
Corresponding author: Jiayin Zhang, MD, Department of Radiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, #85 Wujin Rd, Shanghai 200080, China
• E-mail: andrewssmu@msn.com
Corresponding author: Xiaoying Ding, MD, Department of Endocrinology and Metabolism, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, #85 Wujin Rd, Shanghai 200080, China
• E-mail: dingxiaoying@sjtu.edu.cn

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INTRODUCTION

The prevalence of diabetes mellitus has progressively increased over the last two decades [1]. Type 2 diabetes mellitus (T2D) is a strong independent risk factor for coronary atherosclerosis and heart failure and has a poor prognosis [2]. Diabetic heart disease comprises a series of pathological changes ranging from macrovascular complications to impaired cardiac microstructure and function [3].

Coronary computed tomography angiography (CCTA) is widely used and valuable for accurately ruling out obstructive coronary stenosis in epicardial artery disease [4]. The initial CCTA strategy in patients with suspected coronary artery disease (CAD) results in better prognoses than the standard care strategy [5]. The diagnostic value of CCTA for diabetic coronary atherosclerosis lies in its non-invasive plaque characterization [6], usefulness in monitoring treatment outcomes [7], and risk stratification [8]. Moreover, with the technical advances in computational fluid dynamics [9], computed tomography (CT) fractional flow reserve (CT-FFR) has become useful in identifying hemodynamically significant stenosis in patients with diabetes [10].

Microvascular myocardial ischemia and myocardial fibrosis are the two major pathological features of diabetic cardiomyopathy. An autopsy study of patients with diabetes revealed a decrease in the number of capillaries and arterioles and increased arteriolar wall thickness [11]. A biopsy study also confirmed increased deposition of interstitial collagen types I and III in diabetic hearts [12]. Microvascular myocardial ischemia and myocardial fibrosis are strongly associated with unfavorable clinical outcomes [13], and it is clinically important to accurately detect them in patients with diabetes. However, neither CCTA nor CT-FFR can assess microvascular function, leading to an underestimation of diabetic microvascular ischemia.

CT myocardial perfusion imaging (CT-MPI) combined with CCTA has recently been introduced for the comprehensive quantitative assessment of coronary anatomy, myocardial perfusion, and myocardial fibrosis [14]. Dynamic CT-MPI offers absolute quantification of myocardial blood flow (MBF), and its diagnostic performance has been validated against invasive FFR [15]. However, it remains unclear whether this technique is useful for delineating the underlying impairment of the myocardial microvasculature in diabetes.

In this study, we hypothesized that the stress MBF quantified using dynamic CT-MPI may capture diabetic microvascular myocardial ischemia. Therefore, we aimed to investigate the usefulness of the combination of dynamic CT-MPI and CCTA in the diagnosis of microvascular myocardial ischemia in patients with diabetes without obstructive CAD and the relationship between microvascular myocardial ischemia and angina symptoms.

MATERIALS AND METHODS

Patient Population

The hospital ethics committee of Shanghai General Hospital approved this prospective study (approval number: 2021-049), and all patients provided informed consent. We consecutively enrolled T2D patients with intermediate-to-high pretest probability of CAD between April 2021 and January 2022. The inclusion criteria were: 1) patients with clinically confirmed T2D (defined as treatment with oral hypoglycemic agents or insulin; or fasting glucose ≥ 7.0 mmol/L) [16]; 2) patients with intermediate-to-high pretest probability of CAD according to the updated Diamond-Forrester score. The exclusion criteria were as follows: 1) patients with known obstructive CAD; 2) patients with a history of myocardial infarction or revascularization; 3) patients with cardiac devices, such as pacemakers, implantable cardioverter, and defibrillators or receiving cardiac resynchronization therapy; 4) patients with impaired renal function; 5) age of < 18 years; and 6) patients with concomitant cardiomyopathies. All enrolled patients were referred for combined dynamic CT-MPI and CCTA, and their angina symptoms were evaluated using the Canadian Cardiovascular Society grading system.

We also retrospectively included patients without diabetes who underwent dynamic CT-MPI with CCTA as controls. Part of the retrospective cohort has been previously reported [17]. Between January 2018 and December 2020, 1937 patients without diabetes but with an intermediate-to-high pretest probability of CAD were evaluated at an outpatient clinic. Of them, 310 patients referred for dynamic CT-MPI with CCTA were retrospectively included. The exclusion criteria were as follows: 1) history of myocardial infarction or revascularization, 2) concomitant cardiomyopathies, and 3) severely impaired CT image quality.

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Acquisition Protocol for Dynamic CT-MPI with CCTA

All patients underwent third-generation dual-source CT (SOMATOM Force; Siemens Healthineers). For the prospective diabetic cohort, the dynamic CT-MPI with CCTA strategy used a comprehensive protocol combining the calcium score, pre-contrast scan, dynamic stress CT-MPI, CCTA, and a 5-minute delayed post-contrast scan (Supplementary Fig. 1). Adenosine triphosphate was used as the stressor, with continuous intravenous infusion at 160 g/kg/min for 3 min before dynamic CT-MPI was triggered. A fixed volume of 50 mL of contrast medium was used for CT-MPI, whereas a dosage of 1.4 mL/kg was used for CCTA [18]. Details of the CT acquisition and reconstruction settings are provided in the Supplementary Material. For the retrospective non-diabetic control group, 43 patients underwent CT examination using the same protocol for the diabetic group, whereas 223 patients underwent CT-MPI with CCTA without pre-contrast and delayed post-contrast scans.

Image Analysis of CCTA

The CCTA data were reconstructed using a smooth kernel (BV40) and an iterative reconstruction technique (strength 3, ADMIRE, Siemens Healthineers). The reconstructed images with the best image quality for either of the systolic or diastolic phases were transferred to a dedicated plaque analysis software (Coronary Plaque Analysis, version 4.3, Siemens Healthineers) for further analysis.

Diameter stenosis was manually measured, and the Coronary Artery Disease–Reporting and Data System (CAD-RADS) [19] was recorded for patient-based analysis of the extent of stenosis. CAD-RADS grades 0–2 were considered non-obstructive, whereas CAD-RADS grades 3–5 were regarded as obstructive. Conventional high-risk plaque (HRP) features, including low-attenuation plaque, spotty calcification (SC), positive remodeling (PR), and napkin ring sign (NRS), were also recorded as previously defined [20]. Any lesion with at least two HRP features was considered an HRP [19,21].

All the above parameters were independently analyzed by two cardiovascular radiologists (with 14 and 4 years of experience in cardiac imaging) who were blinded to the clinical history and CT-MPI results. Disagreements were resolved by consensus.

Image Analysis of Dynamic CT-MPI

The CT-MPI images were reconstructed using a dedicated kernel (Qr36) to reduce iodine beam-hardening artifacts. All images were transferred to a CT-MPI software package (SyngoVia, version VB20A, VPCT, Siemens Healthineers) to quantify the MBF using a previously reported hybrid deconvolution model [22].

MBF was measured using a short-axis view of the left ventricle. A region of interest was placed at each segment of the left ventricle, excluding the apical segment, while avoiding the endocardial and epicardial interface according to the 17-segment model [23]. Previous studies have reported a cutoff value of 100 mL/min/100 mL to diagnose myocardial ischemia with reference to the invasive FFR [15] and 105 mL/min/100 mL as the lower limit of the normal range [24]. Therefore, the current study used 100 mL/min/100 mL as the cutoff value to differentiate ischemic from normal myocardium. In patients with CAD-RADS grades 0–2, microvascular ischemia was considered present if at least one myocardial segment had a mean MBF of ≤ 100 mL/min/100 mL. Other quantitative perfusion parameters, including myocardial blood volume (MBV), time to peak (TTP), and tissue transit time (TTT) were measured similarly.

The four image stacks of late iodine enhancement (LIE) were averaged to one final image stack using non-rigid registration to reduce image noise [25]. This was displayed as the short-axis view of the left ventricle for further analysis. The LIE was visually assessed and all segments with positive enhancement were recorded.

The extracellular volume (ECV) was evaluated using a previously reported method [26]. The pre-contrast, CCTA, and post-contrast dataset was loaded into a research software (Cardiac Function Analysis, version 2.0.7, Siemens Healthineers) for ECV quantification according to the following formula: $ECV_{CT} = (1 - \text{hematocrit}) \times (\Delta HU_{myo} / \Delta HU_{blood})$, where ΔHU is the change in Hounsfield unit attenuation between the pre and post-contrast scans [27]. The ECV results were displayed as a 17-segment polar map, which also showed a segment-based ECV and global ECV. A previous study of CT-quantified ECV in non-diseased patients revealed a normal mean value of 26.1 ± 2.0%, ranging from 22.6% to 30% [25]. Therefore, we used 30% as the cut-off value for the definite detection of segments with increased ECV.

The MBF, LIE, and ECV were independently analyzed by two cardiovascular radiologists (with 14 and 4 years of experience in cardiac imaging) who were blinded to the clinical history and CCTA results. All perfusion data were evaluated separately from the CCTA data at a minimum interval of 2 weeks. Disagreements were resolved by consensus.

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Sample Size Calculation

The sample size for the prospective diabetes cohort was calculated based on our preliminary data. We retrospectively reviewed the dynamic CCTA with CT-MPI results of 30 patients with diabetes and 30 without (not included in the current study) before enrollment in the current study. The incidence of microvascular myocardial ischemia was 20.0% in patients with diabetes and 6.6% in those without diabetes. Given the above findings, 260 patients were required to achieve 90% power to observe a significant difference in the incidence of microvascular ischemia between diabetic and non-diabetic patients at a two-sided significance level of 0.05. Ultimately, 418 patients were enrolled, providing more than 90% of the power to meet the primary endpoint.

Statistical Analysis

A one-sample Kolmogorov–Smirnov test was used to determine the normality of the data distribution. Continuous variables with normal distribution were expressed as mean ± standard deviation, while median and interquartile range were used otherwise. Student's *t*-test or the Mann-Whitney U test was used to compare continuous variables, and chi-squared or Fisher's exact test for categorical data was used as appropriate. Univariable and multivariable analyses were performed using binary logistic regression, with angina symptoms as the dependent variable. Variables for the multivariable analysis were selected based on the statistical significance of the univariable analysis and clinical relevance, while avoiding multicollinearity. Intra- and interobserver agreements for all parameters were measured using intraclass correlation coefficients (ICCs). Statistical significance was denoted by two-sided *P*-values of < 0.05. Statistical analyses were performed using SPSS statistical software (version 26.0; IBM Corp.).

RESULTS

Clinical Characteristics

Between April 2021 and January 2022, 190 patients with T2D and intermediate-to-high pretest probabilities of CAD were initially screened. Of these, 38 were excluded for various reasons (Fig. 1). One hundred and fifty-two patients (mean age: 59.7 ± 10.7, 77 males) were referred for dynamic CT-MPI with CCTA and enrolled in the diabetes group. In addition, 310 patients without diabetes but with an intermediate-to-high pre-test probability of CAD who underwent dynamic CT-MPI with CCTA were retrospectively reviewed. Forty-four patients were excluded based on the exclusion criteria (Fig. 1). Finally, 266 (mean age: 62.0 ± 12.3, 167 males) patients without diabetes were included as controls. The detailed demographic data of the two groups are presented in Supplementary Table 1.

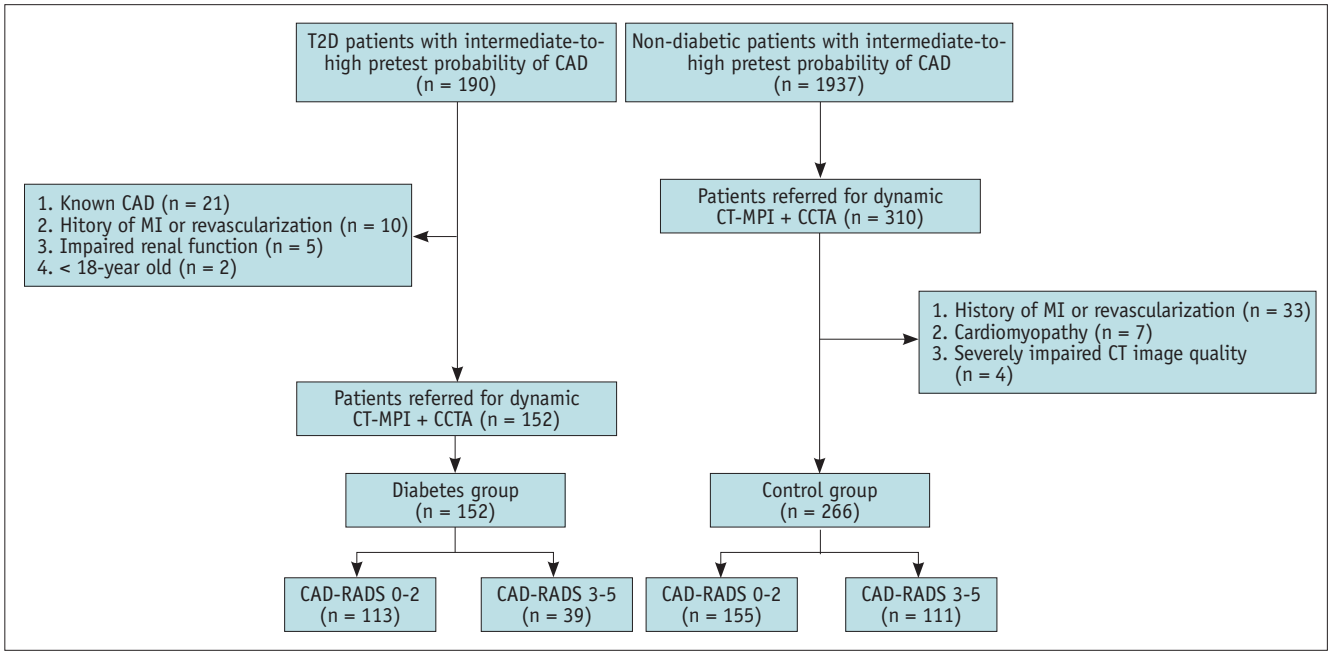

Fig. 1. Flow chart for the inclusion and exclusion of diabetic patients and non-diabetic controls of the present study. T2D = type 2 diabetes, CAD = coronary artery disease, MI = myocardial infarction, CT-MPI = CT myocardial perfusion imaging, CCTA = coronary computed tomography angiography, CT = computed tomography, CAD-RADS = Coronary Artery Disease–Reporting and Data System

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The median dose of contrast agent used was 100 mL (range, 80–100 mL) for all the patients. The mean effective radiation dose for CT examination was 7.41 (5.71–9.71) mSv when using 0.014 as the conversion factor. All CT-derived parameters had high inter- and intra-observer reproducibility (ICC > 0.75, P < 0.001 for all) (Supplementary Tables 2, 3).

CCTA Findings in Patients with and without Diabetes

CCTA revealed 39 patients with (CAD-RADS 3-5) and 113 patients without (CAD-RADS 0-2) obstructive CAD in the diabetes group (Fig. 1). For the non-diabetic cohort, 111 and 155 patients had and did not have obstructive CAD, respectively (Fig. 1). The clinical characteristics of the patients without obstructive CAD are shown in Table 1. Overall, HRP was not frequent in the diabetic (14.5%, 22/152) or non-diabetic (20.3%, 54/266, P = 0.137) group. Subgroup analysis of the patients without obstructive stenosis showed that the incidence of HRP, NRS, SC, and PR among the patients with and without microvascular ischemia were not statistically different (Supplementary Table 4).

Table 1. Characteristics of patients without obstructive CAD

	DM (n = 113)	Non-DM (n = 155)	P
Age, yr	58.3 ± 10.3	59.4 ± 12.7	0.449
Sex, male	54 (47.8)	89 (57.4)	0.119
Other risk factors			
Hypertension	58 (51.3)	69 (44.5)	0.270
Dyslipidemia	68 (60.2)	51 (32.9)	< 0.001
Current smoker	31 (27.4)	28 (18.1)	0.068
BMI, kg/m^2	24.3 ± 3.8	24.5 ± 3.1	0.551
Symptom			0.432
Asymptomatic	87 (77.0)	128 (82.6)	
CCS I	24 (21.2)	26 (16.8)	
CCS II	2 (1.8)	1 (0.7)	
Dyspnea	28 (24.8)	29 (18.7)	0.231
Pretest probability			0.720
15–85	110 (97.3)	153 (98.7)	
≥ 85	3 (2.7)	2 (1.3)	
CACS			0.165
0	67 (59.3)	104 (67.1)	
1–100	37 (32.7)	33 (21.3)	
100–400	7 (6.2)	12 (7.7)	
> 400	2 (1.8)	6 (3.9)	
CAD-RADS category			0.003
CAD-RADS 0	24 (21.2)	26 (16.8)	
CAD-RADS 1	35 (31.0)	80 (51.6)	
CAD-RADS 2	54 (47.8)	49 (31.6)	
HR increment, beats/min	12.8 ± 6.5	14.0 ± 9.9	0.249

Values are presented as mean ± standard deviation or n (%) unless otherwise indicated.
CAD = coronary artery disease, DM = diabetes mellitus, BMI = body mass index, CCS = Canadian Cardiovascular Society, CACS = Coronary Artery Calcium Scoring, CAD-RADS = Coronary Artery Disease–Reporting and Data System, HR = heart rate

Microvascular Myocardial Ischemia without Obstructive CAD in Patients with and without Diabetes

For patients without obstructive stenosis, the mean MBFs of the apical, middle, and basal segments were significantly lower for the patients with diabetes than for those without (Table 2, Figs. 2, 3). In addition, the mean TTP of the apical, middle, and basal segments of the patients with diabetes was markedly greater than that of the controls (Table 2). However, there were no differences between the two groups related to other perfusion parameters, such as MBV and TTT (P > 0.05 for all).

Using 100 mL/min/100 mL as the cutoff value, microvascular myocardial ischemia was observed in 41 (36.3%) of the 113 patients with diabetes without obstructive stenosis. In contrast, the incidence of microvascular ischemia was significantly lower for the participants with diabetes (10.3%, 16/155, P < 0.001). Among the patients with microvascular ischemia, there was no significant difference between those with and without diabetes relative to the number of ischemic segments per patient (Table 2).

In addition, various clinical and imaging parameters of the microvascular ischemia (+) and (-) subgroups of diabetes were compared. Anginal symptoms were more frequently observed in patients with ischemia, along with decreased MBV and prolonged TTP (Supplementary Table 5).

Interstitial Fibrosis in Patients with and without Diabetes without Obstructive CAD

LIE and CT-quantified ECV were performed for all 113 patients with diabetes without obstructive stenosis and 24 patients without diabetes and obstructive stenosis. According to the visual analysis, only nine patients in the diabetes group had a positive LIE (Supplementary Table 6). In contrast, focal or diffuse ECV increase (increased ECV in at least one myocardial segment) was more commonly observed in the patients with diabetes than in those without (69.9% [79/113] vs. 33.3% [8/24], P = 0.001), indicating a high prevalence of subtle interstitial fibrosis in diabetes. The mean global ECV measured using CT was also higher for the patients with diabetes (27.2 ± 2.6%) than for the controls (25.8 ±

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Table 2. Comparison of CT-MPI parameters for evaluating myocardial perfusion between DM and control patients without obstructive CAD

Characteristics	DM (n = 113)	Non-DM (n = 155)	*P*
MBF_{apex}, mL/min/100 mL	153.1 ± 30.9	168.4 ± 36.7	< 0.001
MBF_{middle}, mL/min/100 mL	156.4 ± 30.6	174.8 ± 35.2	< 0.001
MBF_{base}, mL/min/100 mL	149.0 ± 26.1	167.9 ± 33.8	< 0.001
MBV_{apex}, mL/100 mL	19.9 ± 3.9	19.3 ± 3.3	0.173
MBV_{middle}, mL/100 mL	20.3 ± 3.8	19.9 ± 3.2	0.359
MBV_{base}, mL/100 mL	19.5 ± 3.3	19.3 ± 3.0	0.606
TTT_{apex}, sec	15.4 ± 1.7	15.3 ± 1.7	0.804
TTT_{middle}, sec	15.3 ± 1.6	15.1 ± 1.7	0.436
TTT_{base}, sec	15.6 ± 1.5	15.3 ± 1.5	0.212
TTP_{apex}, sec	11.2 ± 2.6	9.9 ± 1.9	< 0.001
TTP_{middle}, sec	11.0 ± 2.4	9.7 ± 1.8	< 0.001
TTP_{base}, sec	11.0 ± 2.4	9.7 ± 1.8	< 0.001
Microvascular ischemia, n (%)*	41 (36.3)	16 (10.3)	< 0.001
Number of ischemic segments†	4.6 ± 4.2	4.2 ± 4.1	0.749

Values are presented as mean ± standard deviation unless otherwise indicated. All quantitative parameters were given in the mean values of basal (segment #1 to #6), middle (segment #7 to #12), and apical (segment #13 to #16) segments according to 17-segment model. *Microvascular ischemia was diagnosed if at least one myocardial segment had mean MBF ≤ 100 mL/min/100 mL in patients without obstructive stenosis, †Number of ischemic segments in patients with myocardial ischemia.
CT-MPI = computed tomography myocardial perfusion imaging, DM = diabetes mellitus, CAD = coronary artery disease, MBF = myocardial blood flow, MBV = myocardial blood volume, TTT = tissue transit time, TTP = time to peak

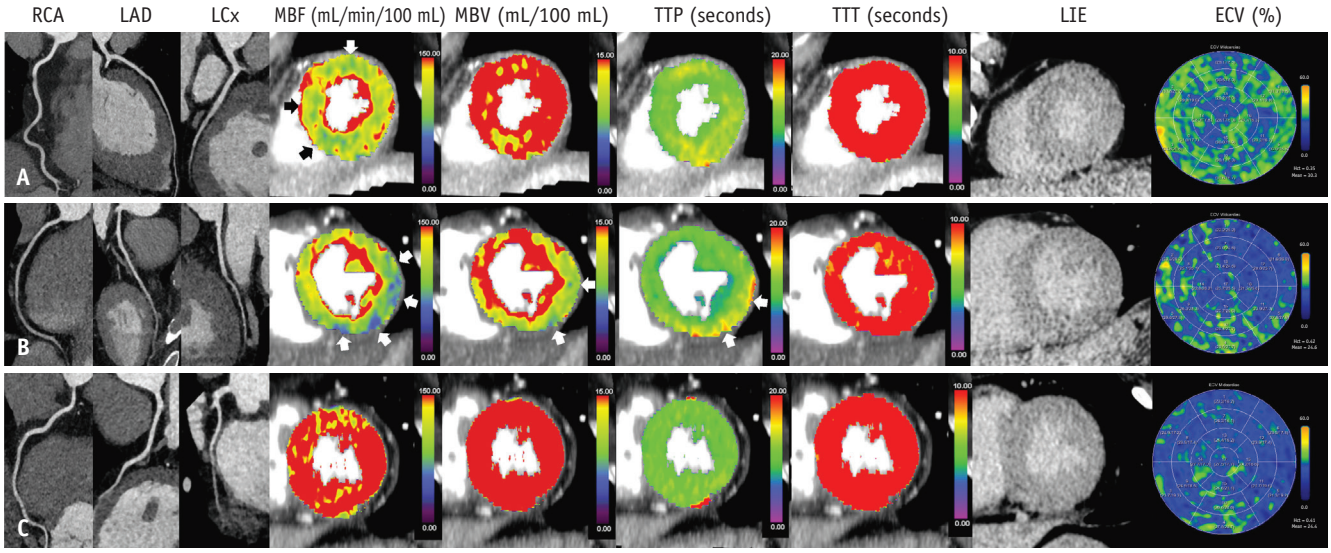

Fig. 2. Quantitative analysis of myocardial perfusion and interstitial fibrosis in patients with and without diabetes without obstructive stenosis. **A:** Representative case of a 65-year-old diabetic female with exertional chest pain. CCTA revealed mild atherosclerosis of the coronary arteries without obstructive stenosis. MBF diffusely decreased (ranging from 77.6 mL/min/100 mL to 95.9 mL/min/100 mL) (white and black arrows) whereas ECV diffusely increased (global ECV = 30.3%), indicating the presence of microvascular ischemia and interstitial fibrosis. LIE did not show evident enhancement. **B:** Representative case of a 63-year-old male patient with diabetes and exertional chest pain. CCTA revealed normal coronary vasculature. MBF of the basal lateral and inferior segments was significantly reduced (ranging from 69.0 mL/min/100 mL to 75.3 mL/min/100 mL) (white arrows) whereas ECV was within the normal range (global ECV = 24.6%), indicating the presence of microvascular ischemia and absence of interstitial fibrosis. LIE did not show evident enhancement. **C:** Representative case of a 60-year-old male patient with diabetes but without angina symptoms. MBF (mean MBF = 175.7 mL/min/100 mL) and ECV (global ECV = 24.4%) were within the normal range, indicating the absence of microvascular ischemia and interstitial fibrosis. LIE did not show evident enhancement. RCA = right coronary artery, LAD = left anterior descending artery, LCx = left circumflex artery, MBF = myocardial blood flow, MBV = myocardial blood volume, TTP = time to peak, TTT = tissue transit time, LIE = late iodine enhancement, ECV = extracellular volume, CCTA = coronary computed tomography angiography, Hct = hematocrit

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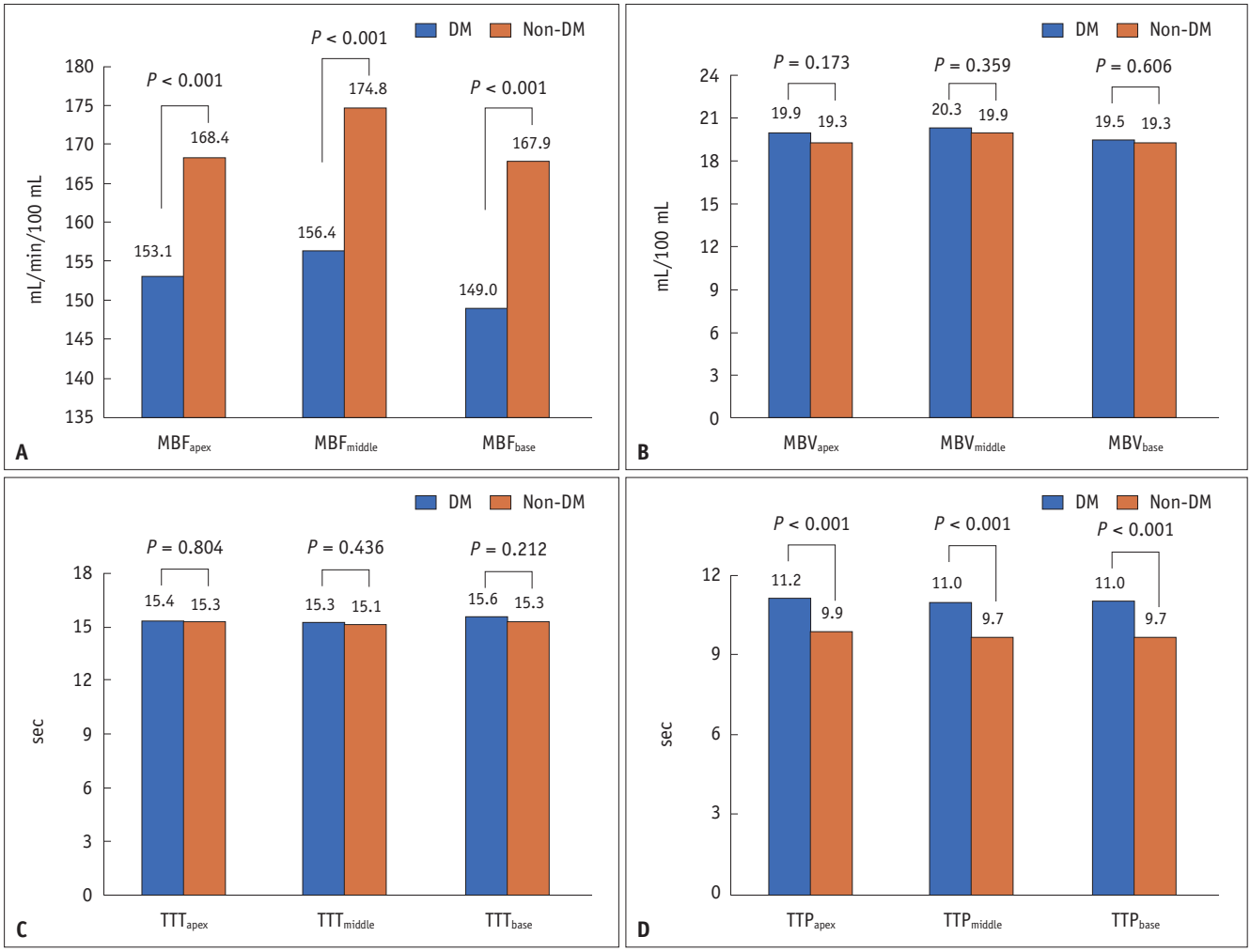

Fig. 3. Comparison of the CT-MPI parameters for evaluating myocardial perfusion stratified by DM in patients without obstructive stenosis. **A-D:** Differences in MBF, MBV, TTT, and TTP of the apex, middle, and base segments in the patients with and without diabetes and without obstructive stenosis. CT-MPI = CT myocardial perfusion imaging, DM = diabetes mellitus, MBF = myocardial blood flow, MBV = myocardial blood volume, TTT = tissue transit time, TTP = time to peak, CT = computed tomography

1.7%, $P = 0.009$). Moreover, the patients with diabetes had more involved segments with CT-ECV of ≥ 30% (5.1 ± 4.2 vs. 2.1 ± 0.6, Supplementary Table 6).

In addition, interstitial fibrosis is more prevalent in patients with diabetes than microvascular ischemia. In the present cohort without obstructive stenosis, 28 patients with diabetes had microvascular ischemia and segment-based ECV elevation, 51 had segment-based ECV elevation without ischemia, and 13 had microvascular ischemia and normal ECV.

Association of Microvascular Myocardial Ischemia and Interstitial Fibrosis with Angina Symptoms in Diabetes without Obstructive CAD

Among the patients with diabetes but without obstructive stenosis, microvascular angina was considered in 26 patients with symptoms. Stratified by the presence of microvascular angina, the incidence of microvascular ischemia, number of ischemic segments, global MBF, and global MBV were significantly higher for patients with diabetes than for those without. Further details are presented in Table 3.

Univariable logistic regression analysis revealed that microvascular myocardial ischemia, global MBF, and MBV were significantly associated with angina. Multivariable logistic regression analysis showed that the presence of microvascular ischemia was the only parameter strongly associated with microvascular angina (adjusted odds ratio = 3.439, $P = 0.037$). Details of the logistic regression analysis are presented in Table 4.

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Table 3. Characteristics of patients with diabetes without obstructive CAD stratified by angina symptom

	Angina (+) (n = 26)	Angina (-) (n = 87)	*P*
Age, yr	61.5 ± 9.8	57.3 ± 10.3	0.063
Sex, male	15 (57.7)	39 (44.8)	0.249
Hypertension	14 (53.8)	44 (50.6)	0.770
Dyslipidemia	18 (69.2)	50 (57.5)	0.282
Current smoker	8 (30.8)	23 (26.4)	0.562
CACS	0.00 (0.00–16.65)	0.00 (0.00–9.80)	0.359
DM duration, yr	10.7 ± 8.3	8.2 ± 6.6	0.103
BMI, kg/m^2	24.70 ± 4.09	24.16 ± 3.75	0.533
HbA1c, %	8.10 (6.98–9.80)	8.10 (7.10–10.00)	0.705
Fast glucose, mmol/L	6.36 (5.67–8.31)	6.80 (5.42–8.94)	0.637
With insulin treatment	15 (57.7)	56 (64.4)	0.537
Presence of microvascular myocardial ischemia	18 (64.3)	23 (27.1)	< 0.001
Number of ischemia segments*	6.6 ± 5.5	3.0 ± 1.8	0.006
Global MBF, mL/min/100 mL	134.2 ± 27.6	158.4 ± 26.7	< 0.001
Global MBV, mL/100 mL	18.5 ± 3.5	20.3 ± 3.5	0.019
Global TTT, sec	15.3 ± 1.7	15.4 ± 1.5	0.760
Global TTP, sec	11.5 ± 2.3	10.9 ± 2.5	0.290
Any HRP	1 (3.8)	4 (4.6)	> 0.999
Any LAP	1 (3.8)	5 (5.7)	> 0.999
Any NRS	1 (3.8)	0 (0.0)	0.519
Any SC	0 (0.0)	2 (2.3)	> 0.999
Any PR	5 (19.2)	22 (25.3)	0.525
CT-ECV, %	27.0 ± 2.3	27.3 ± 2.6	0.578
Number of segments of CT-ECV ≥ 30%†	4.7 ± 4.1	5.2 ± 4.3	0.630
Presence of elevated ECV	17 (68.0)	62 (70.5)	0.813

Values are presented as mean ± standard deviation, n (%), median (interquartile range) unless otherwise indicated.
*Number of ischemic segments in patients with myocardial ischemia, †Number of segments with CT-ECV ≥ 30% in patients with elevated ECV.
CAD = coronary artery disease, CACS = Coronary Artery Calcium Scoring, DM = diabetes mellitus, BMI = body mass index, HbA1c = hemoglobin A1c, MBF = myocardial blood flow, MBV = myocardial blood volume, TTT = tissue transit time, TTP = time to peak, HRP = high-risk plaque, LAP = low attenuation plaque, NRS = napkin-ring sign, SC = spotty calcification, PR = positive remodeling, CT = computed tomography, ECV = extracellular volume

DISCUSSION

This study had two major findings. First, the incidence of microvascular myocardial ischemia without obstructive CAD was significantly higher among patients with diabetes than among the controls. In addition, microvascular myocardial ischemia was strongly associated with angina in patients with diabetes without obstructive CAD.

Growing evidence suggests that diabetes and prediabetic states contribute considerably to important alterations in coronary microvascular regulation. Rats with T2D exhibit deteriorating coronary circulation, which is directly correlated with the severity of coronary arteriolar structural remodeling during the development of early diabetic microangiopathy [28]. Reduced cardiac expression of proangiogenic vascular endothelial growth factor and its receptors leads to reduced angiogenesis, which, together with impaired coronary endothelial function and increased microvascular stiffness, results in microvascular ischemia and sustained diabetes [29].

Positron emission tomography (PET) and cardiac magnetic resonance (CMR) are two noninvasive imaging modalities used to quantify MBF and myocardial perfusion reserve [30]. However, their clinical values in the evaluation of diabetic microvascular ischemia are limited due to the sheer functional assessment and inability to rule out obstructive stenosis. Dynamic CT-MPI with CCTA has emerged as an ideal method for the anatomical and functional evaluation of CAD [17], indicating its potential role in the diagnosis of diabetic microvascular ischemia. A previous study revealed reduced

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Table 4. Analysis of the association of various variables with angina symptom in DM patients without obstructive CAD

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*P*	Adjusted odds ratio	95% CI	*P*
Age (per + 1 year)	1.046	0.999–1.101	0.067	1.039	0.987–1.100	0.157
Sex, male	1.678	0.697–4.150	0.252			
DM duration (per + 1 year)	1.051	0.989–1.117	0.107			
Hypertension	1.140	0.473–2.779	0.770			
Dyslipidemia	1.665	0.670–4.438	0.285			
Current smoking	1.237	0.455–3.164	0.664			
BMI (per + 1 kg/m^2)	1.037	0.923–1.160	0.529			
Fast glucose (per + 1 mmol/L)	0.661	0.796–1.139	0.961			
HbA1c (per + 1%)	0.965	0.778–1.173	0.729			
Any HRP	0.830	0.041–5.934	0.870			
With insulin treatment	0.755	0.310–1.876	0.537			
Presence of microvascular myocardial ischemia	6.261	2.471–17.140	< 0.001	3.439	1.090–11.438	0.037
MBF (per + 1 mL/100 mL/min)	0.965	0.944–0.983	< 0.001	0.981	0.957–1.005	0.137
MBV (per + 1 mL/100 mL)	0.832	0.704–0.963	0.021	0.963	0.802–1.135	0.671
TTT (per + 1 sec)	0.956	0.719–1.279	0.758			
TTP (per + 1 sec)	1.092	0.919–1.287	0.293			
CT-ECV (per + 1%)	0.951	0.794–1.130	0.574			

DM = diabetes mellitus, CAD = coronary artery disease, CI = confidence interval, BMI = body mass index, HbA1c = hemoglobin A1c, HRP = high-risk plaque, MBF = myocardial blood flow, MBV = myocardial blood volume, TTT = tissue transit time, TTP = time to peak, CT = computed tomography, ECV = extracellular volume

global MBF in patients with diabetes, as demonstrated by dynamic CT-MPI [31]. Nevertheless, ECV analysis was not performed in this study with a small sample size, and no specific criteria were used to identify microvascular ischemia.

In this study, we compared various segment-based perfusion parameters of patients with and without diabetes. The mean MBFs of the apical, middle, and basal segments were significantly lower for the group with diabetes than for the controls. In addition, using 100 mL/min/100 mL as the cutoff value to differentiate between ischemic and normal myocardium [15,24], the incidence of myocardial ischemia without obstructive stenosis was markedly higher among the patients with diabetes than among the controls (36.3% vs. 10.3%, $P < 0.001$). These suggest that diabetes has a significant impact on the development of microvascular ischemia, which is commonly present before progression to obstructive CAD. Moreover, the presence of myocardial ischemia was the only parameter that was strongly associated with angina pectoris in patients with diabetes without obstructive stenosis. Thus, these findings highlight the clinical significance of using dynamic CT-MPI with CCTA to identify this important pathology and target a specific diabetic population that may benefit from anti-anginal and anti-ischemic medication [24]. In addition to microvascular ischemia, interstitial fibrosis is an important pathological feature of diabetic heart disease [32]. In the present study, diabetes was associated with a more frequent occurrence of LIE and a higher mean global ECV, indicating that this metabolic disorder leads to more severe and diffuse fibrosis. Nevertheless, this finding needs to be validated in further prospective studies due to the limited number of cases in the control group.

Advanced coronary atherosclerosis is another hallmark of diabetes-related heart disease, and HRP is commonly encountered in asymptomatic patients with T2D [33]. The current study also investigated coronary anatomy and plaque characteristics in diabetes. According to the present findings, the majority of the patients with T2D had CAD-RADS grades 0–2 with an intermediate-to-high pretest probability of CAD. HRP was only sporadically observed in the non-obstructive group, and its incidence was significantly lower than that of microvascular ischemia. This suggests that myocardial ischemia may develop earlier than advanced atherosclerosis.

Based on these results, the clinical implications of the present study are as follows. Microvascular ischemia and interstitial fibrosis are two early pathological changes that

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precede advanced coronary atherosclerosis. Myocardial ischemia without obstructive stenosis is closely related to angina pectoris, which occurs in a large proportion of patients with T2D. Accurate diagnosis of this etiology helps target a specific cohort that may benefit from anti-anginal and anti-ischemic treatments. In addition, dynamic CT-MPI with CCTA may be a valuable alternative for the assessment of microvascular ischemia and myocardial fibrosis in patients with diabetes. It allows the comprehensive evaluation of epicardial vessel anatomy, myocardial perfusion, and ECV quantification, especially in patients with diabetes with contradictions for other functional imaging modalities.

Despite these valuable findings, this study had several limitations. First, this was a cross-sectional observational study without long-term follow-up. It remains unclear whether CT-quantified MBF and ECV can predict the prognosis of patients with diabetes without obstructive CAD. Therefore, future longitudinal studies are required to determine the prognostic value of these quantitative CT parameters in a diabetic cohort. In addition, there were no imaging data on cardiac function; therefore, we were unable to assess the impact of left ventricular remodeling on MBF as quantified by CT-MPI. Moreover, despite the prospective enrollment of patients with diabetes, the controls were included from an existing retrospective cohort in the current study. This resulted in discrepancies in clinical characteristics between the two groups. Finally, myocardial perfusion reserve quantified by PET or CMR, which is the reference standard for diagnosing microvascular dysfunction [34], was not available in the current study. Stress in MBF may be insufficient to depict microvascular dysfunction. Therefore, further studies incorporating PET or CMR are warranted for precise evaluation of microvascular dysfunction.

In conclusion, dynamic CT-MPI with CCTA revealed a higher incidence of microvascular myocardial ischemia in patients with diabetes without obstructive CAD than in those without. In addition, microvascular myocardial ischemia is strongly associated with angina in patients with diabetes without obstructive CAD.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.0297.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jiayin Zhang, Xiaoying Ding. Data curation: Yarong Yu, Wenli Yang. Formal analysis: Yarong Yu, Wenli Yang, Xu Dai, Ziting Lan. Funding acquisition: Jiayin Zhang. Investigation: Yarong Yu, Wenli Yang, Xu Dai, Ziting Lan, Jiayin Zhang. Methodology: Yarong Yu, Wenli Yang. Project administration: Jiayin Zhang, Xiaoying Ding. Resources: Jiayin Zhang, Xiaoying Ding. Software: Yarong Yu, Wenli Yang. Supervision: Jiayin Zhang, Xiaoying Ding. Validation: Jiayin Zhang, Xiaoying Ding. Visualization: Lihua Yu, Ziting Lan. Writing—original draft: Yarong Yu, Jiayin Zhang. Writing—review & editing: Jiayin Zhang, Yarong Yu.

ORCID IDs

Yarong Yu
https://orcid.org/0000-0001-8070-0055
Wenli Yang
https://orcid.org/0009-0008-6555-8722
Xu Dai
https://orcid.org/0009-0007-3490-7152
Lihua Yu
https://orcid.org/0009-0005-2751-5594
Ziting Lan
https://orcid.org/0000-0002-1275-5537
Xiaoying Ding
https://orcid.org/0000-0001-6290-8485
Jiayin Zhang
https://orcid.org/0000-0001-7383-7571

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