

RESEARCH

Open Access



Incremental effect of coronary obstruction on myocardial microvascular dysfunction in type 2 diabetes mellitus patients evaluated by first-pass perfusion CMR study

Jin Wang¹, Zhi-Gang Yang¹, Ying-Kun Guo², Yu Jiang¹, Wei-Feng Yan¹, Wen-Lei Qian¹, Han Fang¹, Chen-Yan Min¹ and Yuan Li^{1*}

Abstract

Background Type 2 diabetes mellitus (T2DM) frequently coexists with obstructive coronary artery disease (OCAD), which are at increased risk for cardiovascular morbidity and mortality. This study aimed to investigate the impact of coronary obstruction on myocardial microcirculation function in T2DM patients, and explore independent predictors of reduced coronary microvascular perfusion.

Methods Cardiac magnetic resonance (CMR) scanning was performed on 297 T2DM patients {188 patients without OCAD [T2DM(OCAD -)] and 109 with [T2DM(OCAD +)]} and 89 control subjects. CMR-derived perfusion parameters, including upslope, max signal intensity (MaxSI), and time to maximum signal intensity (TTM) in global and segmental (basal, mid-ventricular, and apical slices) were measured and compared among observed groups. According to the median of Gensini score (64), T2DM(OCAD +) patients were subdivided into two groups. Univariable and multivariable linear regression analyses were performed to identify independent predictors of microcirculation dysfunction.

Results T2DM(OCAD -) patients, when compared to control subjects, had reduced upslope and prolonged TTM in global and all of three slices (all $P < 0.05$). T2DM(OCAD +) patients showed a significantly more severe impairment of microvascular perfusion than T2DM(OCAD -) patients and control subjects with a more marked decline upslope and prolongation TTM in global and three slices (all $P < 0.05$). From control subjects, through T2DM(OCAD +) patients with Gensini score ≤ 64 , to those patients with Gensini score > 64 group, the upslope declined and TTM prolonged progressively in global and mid-ventricular slice (all $P < 0.05$). The presence of OCAD was independently correlated with reduced global upslope ($\beta = -0.104$, $P < 0.05$) and global TTM ($\beta = 0.105$, $P < 0.05$) in patients with T2DM. Among T2DM(OCAD +) patients, Gensini score was associated with prolonged global TTM ($r = 0.34$, $P < 0.001$).

Conclusions Coronary artery obstruction in the context of T2DM exacerbated myocardial microcirculation damage. The presence of OCAD and Gensini score were independent predictors of decreased microvascular function.

Trial registration: Retrospectively registered.

Keywords Type 2 diabetes mellitus, Obstructive coronary artery disease, First-pass perfusion, Microvascular dysfunction, Magnetic resonance imaging

*Correspondence:

Yuan Li

dr.liyuan@163.com

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Type 2 diabetes mellitus (T2DM) is accompanied by multisystem micro- and macro-vascular complications [1, 2]. As one of the major risk factors for coronary artery, T2DM can affect coronary microvasculature as well as epicardial coronary arteries [3]. Growing evidence has underscored deleterious effects of coronary microvascular dysfunction (CMD) in T2DM patients, which might lead to adverse left ventricular (LV) remodeling, reduced myocardial function, and worse clinical outcomes [4, 5]. In addition, there is a markedly increased incidence of major adverse cardiovascular events (MACE) associated with coronary macrovascular complication, such as obstructive coronary artery disease (OCAD), in patients with T2DM [1, 2, 6]. Accumulating data have indicated that CMD is correlated with increased cardiovascular mortality and poor prognosis in T2DM patients with OCAD [7–9]. Thus, early identification of CMD among those patients might contribute to risk stratification and prognosis evaluation for optimal medical treatments [10, 11].

Several studies have demonstrated that microvascular resistance is influenced by the severity of epicardial artery stenosis [12–14]. Although structural, functional, and metabolism alterations of the microvasculature and extravascular changes might elucidate CMD [15–17], the pathophysiological mechanisms of CMD under the presence of coronary obstruction remain not fully understood. Since CMD is an independent predictor of MACE in T2DM patients [5], it is utmost significant to assess coronary microvascular function and understand the relationship between epicardial coronary obstruction and CMD among those patients.

First-pass cardiac magnetic resonance (CMR) perfusion has emerged as a sensitive, non-invasive and accurate imaging modality for monitoring myocardial microvascular function, which has been extensively validated in various diseases [18–20]. To the best of our knowledge, most studies have investigated effects of obesity or hypertension on myocardial perfusion in T2DM patients [21, 22], whereas the additive impact of epicardial coronary obstruction on myocardial microcirculation damage has rarely been studied in those patients [23]. Herein, we aimed to: 1) evaluate the impact of coronary obstruction on myocardial microcirculation function in T2DM patients, and 2) to investigate independent predictors of reduced coronary microvascular perfusion.

Methods

Study population

Patients with T2DM who underwent CMR examination at our institution were retrospectively enrolled in this study from January 2015 to April 2022. Invasive

coronary angiography (ICA) examination was performed to diagnose OCAD. OCAD was defined on condition that angiographic evidence of $\geq 50\%$ diameter stenosis showed in at least one major epicardial coronary artery [24]. According to the American Diabetes Association guidelines [25], T2DM was diagnosed and the diagnostic criteria were as follows: typical diabetes symptoms and random plasma glucose (PG) level ≥ 11.1 mmol/L, or fasting PG level ≥ 7.0 mmol/L, or 2-h PG level ≥ 11.1 mmol/L after a 75-g oral glucose tolerance test, or hemoglobin A_{1c} level ≥ 6.5 mmol/L. The Exclusion criteria included patients with type 1 diabetes mellitus, previous coronary artery bypass grafting or stenting, primary cardiomyopathy, valvular or congenital heart disease, severe renal dysfunction with an estimated glomerular filtration rate < 30 ml/min/1.73m², any contraindication to CMR examination, and CMR image quality is unsuitable for diagnosis.

Ultimately, 297 T2DM patients (mean age, 58.95 ± 11.61 years; 197 male) were enrolled into the study and were classified into two groups: T2DM without OCAD [T2DM(OCAD–), $n=188$] and T2DM with OCAD [T2DM(OCAD+), $n=109$]. Age- and sex-matched individuals were enrolled served as the control group. The exclusion criteria of the control group were as follows: history of systematic or cardiovascular disease, known diabetes mellitus or impaired glucose tolerance, and abnormalities detected by CMR, such as abnormal ventricular motion, perfusion defect, and decreased LV ejection fraction (LVEF), etc. Finally, a total of 89 individuals (mean age, 56.38 ± 8.63 years; 51 male) were included in this study. This study protocol was approved by the Biomedical Research Ethics Committee of our hospital. Written informed consent was waived because of the retrospective nature of the study.

Invasive coronary angiography

According to the standard Judkins technique, invasive coronary angiography was performed by experienced interventional cardiologists adopting radial or femoral artery approach. On the basis of the number of diseased coronary arteries with $\geq 50\%$ stenosis, T2DM(OCAD+) patients were categorized as a one-, two-, or three-vessel disease. Coronary artery stenosis of $\geq 50\%$ in left main coronary artery was regarded as three-vessel disease [26]. Based on the method described in the literature [27], Gensini coronary score was used for evaluating the severity of OCAD and was calculated by two independent experienced cardiologists.

CMR protocol

CMR examination was performed on a 3.0 T whole-body scanner Trio Tim or MAGNETOM Skyra (Siemens

Medical Solutions, Erlangen, Germany). All participants were examined in the supine position, and equipped with standard ECG-triggering device and 32-channel body phased array coils. During the end-inspiratory breath-holding period, continuous data acquisition was performed using a retrospective vector ECG gating technique. Cine imaging was performed in the short-axis slices, as well as the two-, three-, and four-chamber in the long-axis covering the whole LV from the base to the apex views using a balanced steady-state free precession (bSSFP) sequence. The following scanning parameters were used: repetition time [TR]: 2.8 ms or 3.4 ms, echo time [TE]: 1.2 ms, field of view [FOV]: $303 \times 360 \text{ mm}^2$ or $284 \times 340 \text{ mm}^2$, flip angle 50° or 38° , slice thickness 8 mm, and matrix size 162×192 or 174×208 .

Subsequently, gadolinium-based contrast agent was intravenously injected at a dose of 0.2 mL/kg body weight (injection rate: 2.5–3.0 mL/s), then a 20 mL saline flush was injected immediately following contrast at a rate of 3.0 mL/s. Rest first-pass perfusion images in three standard short-axis slices (basal, mid-ventricular, and apical) and in one slice of four-chamber view were acquired using an inversion recovery prepared echo-planar imaging sequence. The following scanning parameters were used: repetition time [TR]: 163.2 ms or 149.8 ms, echo time [TE]: 1.06 or 0.99 ms, field of view [FOV]: $240 \text{ mm} \times 320 \text{ mm}^2$ or $270 \times 360 \text{ mm}^2$, flip angle 10° , slice thickness 8 mm, and matrix size 132×176 or 144×192 .

CMR data analysis

CMR images analysis was evaluated offline using commercial software (cvi⁴², Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) by two experienced radiologists. For each participant, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV stroke volume (LVSV), LV myocardial mass, and LVEF were calculated using the above-mentioned software by manually outlined the epicardial and endocardial borders of the LV myocardium on a stack of short-axis cine images at the end-systolic and end-diastolic phases. LV papillary muscles and moderator bands were excluded from LV myocardial mass and included in LV cavity. LV volumes and mass were corrected for body surface area (BSA), which was calculated using the Mosteller equation [28].

For analyzing LV myocardial perfusion, signal intensity-time curves, including each myocardial segment based on the 16-segment model (Bull's eye plot) and the blood pool, were generated by manually delineated epicardium, endocardium and blood pool counters in first-pass perfusion images of all three short-axis slices (the basal, middle, and apical) with exclusion of papillary muscles and moderator bands. Each myocardial segmental perfusion parameters, including upslope, time

to maximum signal intensity (TTM) and maximum signal intensity (MaxSI), were consequently obtained from myocardial signal intensity-time curves (Fig. 1, A2-C2, A4-C4, A6-C6). All LV global myocardial perfusion parameters were calculated by averaging values of the 16 myocardial segments.

Evaluation of reproducibility of LV myocardial perfusion parameters

Inter- and intra-observer variability for LV global and segments myocardial microcirculation perfusion measurements were determined in 60 random cases that included 43 T2DM patients and 17 control subjects. Intra-observer variability was obtained by comparison of perfusion parameters by the same observer with over 7 years of CMR experience in 2-month interval. To determine inter-observer variability, a second investigator with 7 years of CMR experience, who was unaware of the first observer's results, compared independent measurements in the same population.

Statistical analysis

All calculations were done with IBM SPSS Statistics for Windows version 24.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 7.0a (GraphPad Software, San Diego, California, USA). Continuous variables were expressed as means with standard deviations or medians with inter-quartile ranges. One-way analysis of variance (One-way ANOVA) followed by Bonferroni's post hoc-test or the Kruskal–Wallis rank test (when appropriate) were used to analyze differences among control subjects, T2DM(OCAD-) group, and T2DM(OCAD+) group, or among control subjects, T2DM(OCAD+) patients with Gensini score ≤ 64 group, and those patients with Gensini score > 64 group.

Univariable and multivariable linear regression analyses were used to investigate the independent and combined correlations of OCAD and T2DM with LV microvascular dysfunction, and evaluate independent predictors of impaired myocardial microcirculation perfusion among T2DM(OCAD+) patients. Candidate variables with *P* values of less than 0.1 in the univariable analysis were included in the final multivariable linear regression models with a stepwise selection procedure. Intra-class correlation coefficient (ICC) was used to assess intra- and inter-observer agreements. A two-tailed *P* value of < 0.05 was considered significant.

Results

Baseline characteristics of the study cohort

Table 1 summarizes baseline characteristics of the study cohort. T2DM(OCAD+) patients demonstrated longer disease duration [5 (0.75, 10) vs. 2 (0,

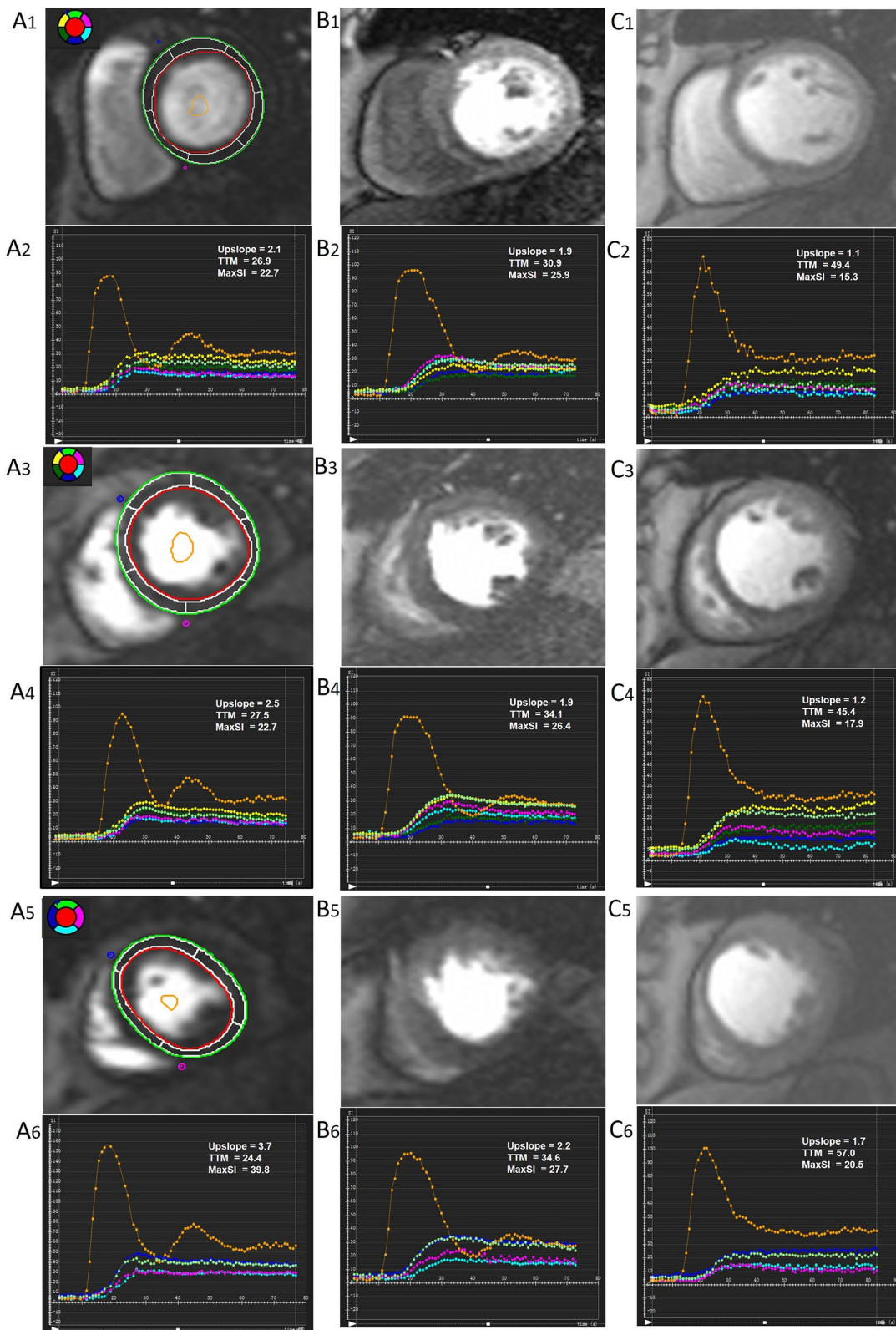


Fig. 1 Representative first-pass perfusion CMR images and signal intensity-time curves in a control subject (A1–A6), T2DM(OCAD–) patient (B1–B6), and T2DM(OCAD+) patient (C1–C6). Signal intensity-time curves were acquired from basal, mid-ventricular, and apical slices. T2DM type 2 diabetes mellitus; OCAD obstructive coronary artery disease. MaxSI max signal intensity, TTM time to maximum signal intensity

Table 1 Baseline characteristics of the study cohort

	Control subjects	T2DM	T2DM	
	(n = 89)	(n = 297)	T2DM (OCAD -) (n = 188)	T2DM (OCAD +) (n = 109)
Male, n (%)	51 (57.3%)	197 (66.3%)	109 (58%)	88 (80.7%) [§]
Age (years)	56.38 ± 8.63	58.95 ± 11.61	57.52 ± 12.34	61.42 ± 9.80 [§]
Systolic blood pressure (mmHg)	113.25 ± 11.17	132.51 ± 22.34 [#]	134.26 ± 22.04*	129.50 ± 22.64*
Diastolic blood pressure (mmHg)	74.45 ± 6.29	81.27 ± 13.95 [#]	82.11 ± 13.73*	79.83 ± 14.28*
Heart rate (beats/min)	72.45 ± 7.0	82.51 ± 15.31 [#]	83.69 ± 15.87*	80.46 ± 14.14*
BSA (m ²)	1.59 ± 0.16	1.73 ± 0.19 [#]	1.70 ± 0.19*	1.77 ± 0.19*
BMI (kg/m ²)	21.31 ± 3.31	25.39 ± 4.19 [#]	25.28 ± 4.17*	25.58 ± 4.23*
Smoking, n (%)	10 (11.24%)	121 (40.7%) [#]	66 (35.1%)*	55 (50.5%) [§]
Diabetes duration (years)	—	3 (0, 9.75)	2 (0,8)	5(0.75, 10) [§]
TC (mmol/L)	3.79 ± 0.89	4.01 ± 1.37	4.13 ± 1.51	3.82 ± 1.06
TG (mmol/L)	1.14 ± 0.80	1.91 ± 1.51 [#]	1.92 ± 1.51*	1.89 ± 1.53*
LDL (mmol/L)	2.16 ± 0.72	2.21 ± 1.03	2.25 ± 1.12	2.13 ± 0.85
HDL (mmol/L)	1.26 ± 0.30	1.12 ± 0.37 [#]	1.16 ± 0.40	1.05 ± 0.30*
Fasting plasma glucose (mmol/L)	4.75 ± 0.63	9.12 ± 4.20 [#]	8.53 ± 3.91*	10.14 ± 4.49 [§]
HbA _{1c} (%)	5.16 ± 0.30	7.43 ± 1.31 [#]	7.06 ± 1.20*	8.08 ± 1.22 [§]
eGFR(ml/min/1.73m ²)	90.08 ± 13.48	78.61 ± 22.38 [#]	79.18 ± 23.51*	77.66 ± 20.39*
Gensini score	—	64 (37, 101)	—	64 (37, 101)
Location of coronary artery occlusion (LAD/LCX/RCA)	—	100(91.7%)/54(49.5%) /70(64.2%)	—	100(91.7%)/54(49.5%) /70(64.2%)
Number of coronary arteries affected (One/Two/Three-vessel)	—	36(33%)/29(26.6%) /44(40.4%)	—	36(33%)/29(26.6%) /44(40.4%)
OCAD treatment				
PCI	—	70 (64.2%)	—	70 (64.2%)
CABG	—	4 (3.7%)	—	4 (3.7%)
Statins, n (%)	—	95 (87.2%)	—	95 (87.2%)
Anti-thrombotic agents, n (%)	—	98 (89.9%)	—	98 (89.9%)
Calcium antagonists, n (%)	—	28(25.7%)	—	28(25.7%)
ACEI/ARB, n (%)	—	36 (33.0%)	—	36 (33.0%)
Beta blockers, n (%)	—	40 (36.7%)	—	40 (36.7%)
T2DM treatment				
Diet controlled, n (%)	—	86 (29%)	61 (32.4%)	25 (22.9%)
Insulin, n (%)	—	82 (27.6%)	47 (25%)	35 (32.1%)
GLP-1/DPP-4 inhibitor, n (%)	—	16 (5.4%)	11 (5.9%)	5 (4.6%)
α-Glucosidase inhibitor, n (%)	—	83 (27.9%)	49 (26.1%)	34 (31.2%)
Biguanides, n (%)	—	114 (38.4%)	63 (33.5%)	51 (46.8%)
Sulfonylureas, n (%)	—	52 (17.5%)	33 (17.6%)	19 (17.4%)

All values are presented as mean ± SD or n (%) or median (Q1-Q3)

T2DM type 2 diabetes mellitus, OCAD obstructive coronary artery disease, BSA body surface area, BMI body mass index, HbA_{1c} glycated hemoglobin, TC total cholesterol, TG triglycerides, LDL low-density lipoprotein, HDL high-density lipoprotein, eGFR estimated glomerular filtration rate, LAD left descending artery, LCX left circumflex artery, RCA right coronary artery; PCI percutaneous coronary intervention, CABG coronary artery bypass grafting; ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker; GLP-1/DPP-4 inhibitor glucagon-like peptide-1/dipeptidyl peptidase 4 inhibitor

P < 0.05 T2DM patients vs. control subjects; **P* < 0.05 vs. control subjects; §*P* < 0.05 vs. T2DM(OCAD -) group

8) years, *P* < 0.05], more likely to be older (61.42 ± 9.8 vs. 57.52 ± 12.34, *P* < 0.05), and more often men (80.7% vs. 58%, *P* < 0.05), as well as more smokers (50.5% vs. 35.1%, *P* < 0.05) than those T2DM(OCAD -) patients.

Among T2DM(OCAD +) patients, 36(33%) patients had one-vessel disease, 29(26.6%) had two- vessel disease, and 44(40.4%) had three-vessel disease. In addition, the left ascending artery, left circumflex artery, and right coronary stenosis rate were 91.7%, 49.5%, and

64.2%, respectively. The median of Gensini score was 64 (37, 101) in those T2DM patients with OCAD.

CMR-derived parameters analysis in T2DM patients with and without OCAD and control subjects

CMR-derived parameters for observed groups are listed in Table 2. LVS_{VI} and LVEF exhibited gradually decrease, while LVES_{VI} showed a significant progressive increase from control subjects, through T2DM(OCAD⁻), to T2DM(OCAD⁺) patients (all $P < 0.05$). Compared with control subjects, T2DM patients both with and without OCAD had increased LVED_{VI} and LVMI (both $P < 0.05$).

With regard to the LV myocardial first-pass perfusion, T2DM patients even without OCAD had worse microvascular function, which was supported by decreased upslope and increased TTM in global and all of three short-axis segments (basal, mid-ventricular, and apical) compared to the control subjects (all $P < 0.05$). Microcirculation dysfunction also existed and were exhibited a more marked impairment in the T2DM(OCAD⁺) patients than those T2DM(OCAD⁻) and control

subjects, which was evident by a more reduced upslope and longer TTM in global and those above slices (all $P < 0.05$) (Figs. 1 and 2).

First-pass CMR perfusion indices evaluation in T2DM(OCAD⁺) patients with different Gensini score group and control subjects

T2DM (OCAD⁺) patients were categorized into two subgroups based on the median value (64) of the Gensini score: T2DM (OCAD⁺) patients with Gensini score ≤ 64 group ($n = 53$) and those with Gensini score > 64 group ($n = 56$). The LV global and segmental myocardial perfusion parameters for observed groups are exhibited in Fig. 3. In middle-ventricular segment, the upslope declined and the TTM prolonged progressively from control subjects, through T2DM (OCAD⁺) patients with Gensini score ≤ 64 , to those with Gensini score > 64 (all $P < 0.05$). The same trends were observed in the global upslope and TTM among those above three groups (all $P < 0.05$). The upslope in basal and apical segments were

Table 2 Differences of CMR-derived parameters among T2DM(OCAD⁻) patients, T2DM(OCAD⁺) patients, and control subjects

	Control subjects	T2DM	
	(n = 89)	T2DM (OCAD ⁻) (n = 188)	T2DM (OCAD ⁺) (n = 109)
LV geometry and function			
LVEF (%)	63.6 (58.2, 67.6)	54.5 (38.1, 63.3)*	36.8 (27.0, 53.8) [§]
Indexed LV mass (g/m ²)	42.4 (36.1, 49.0)	51.5 (42.8, 67.5)*	60.4 (48.1, 66.6)*
Indexed LVEDV (mL/m ²)	79.7 (68.8, 87.7)	90.0 (74.1, 116.7)*	106.6 (78.4, 140.7)*
Indexed LVESV (mL/m ²)	28.2 (23.9, 33.4)	40.0 (27.3, 72.9)*	59.5 (35.8, 101.8) [§]
Indexed LVS _{VI} (mL/m ²)	49.9 (42.8, 54.4)	44.4 (32.8, 54.6)*	41.4 (32.0, 49.6) [§]
First-pass perfusion parameters			
Basal			
Upslope	2.26 ± 0.91	1.85 ± 0.87*	1.52 ± 0.88 [§]
MaxSI	18.90 ± 5.86	18.55 ± 6.98	16.48 ± 6.62
TTM (s)	27.42 ± 10.39	33.86 ± 14.78*	39.08 ± 17.55 [§]
Mid-ventricular			
Upslope	2.69 ± 1.03	2.16 ± 0.93*	1.76 ± 0.96 [§]
MaxSI	23.01 ± 7.05	21.88 ± 7.28	19.91 ± 7.65*
TTM (s)	27.34 ± 10.52	33.72 ± 15.02*	40.14 ± 16.91 [§]
Apical			
Upslope	3.25 ± 1.23	2.69 ± 1.16*	2.26 ± 1.22 [§]
MaxSI	28.92 ± 8.41	27.42 ± 9.01	25.45 ± 9.44
TTM (s)	29.68 ± 10.82	35.12 ± 14.48*	41.88 ± 18.60 [§]
Global			
Upslope	2.66 ± 1.00	2.18 ± 0.92*	1.80 ± 0.96 [§]
MaxSI	22.80 ± 6.75	21.99 ± 7.18	19.97 ± 7.47*
TTM (s)	28.06 ± 10.31	34.21 ± 14.25*	40.18 ± 16.80 [§]

All values are presented as median (Q1-Q3) or mean ± SD. LV left ventricular, EF ejection fraction, EDV end-diastolic volume, ESV end-systolic volume, SV stroke-volume, MaxSI max signal intensity, TTM time to maximum signal intensity. * $P < 0.05$ vs. control group; [§] $P < 0.05$ vs. T2DM (OCAD⁻) group

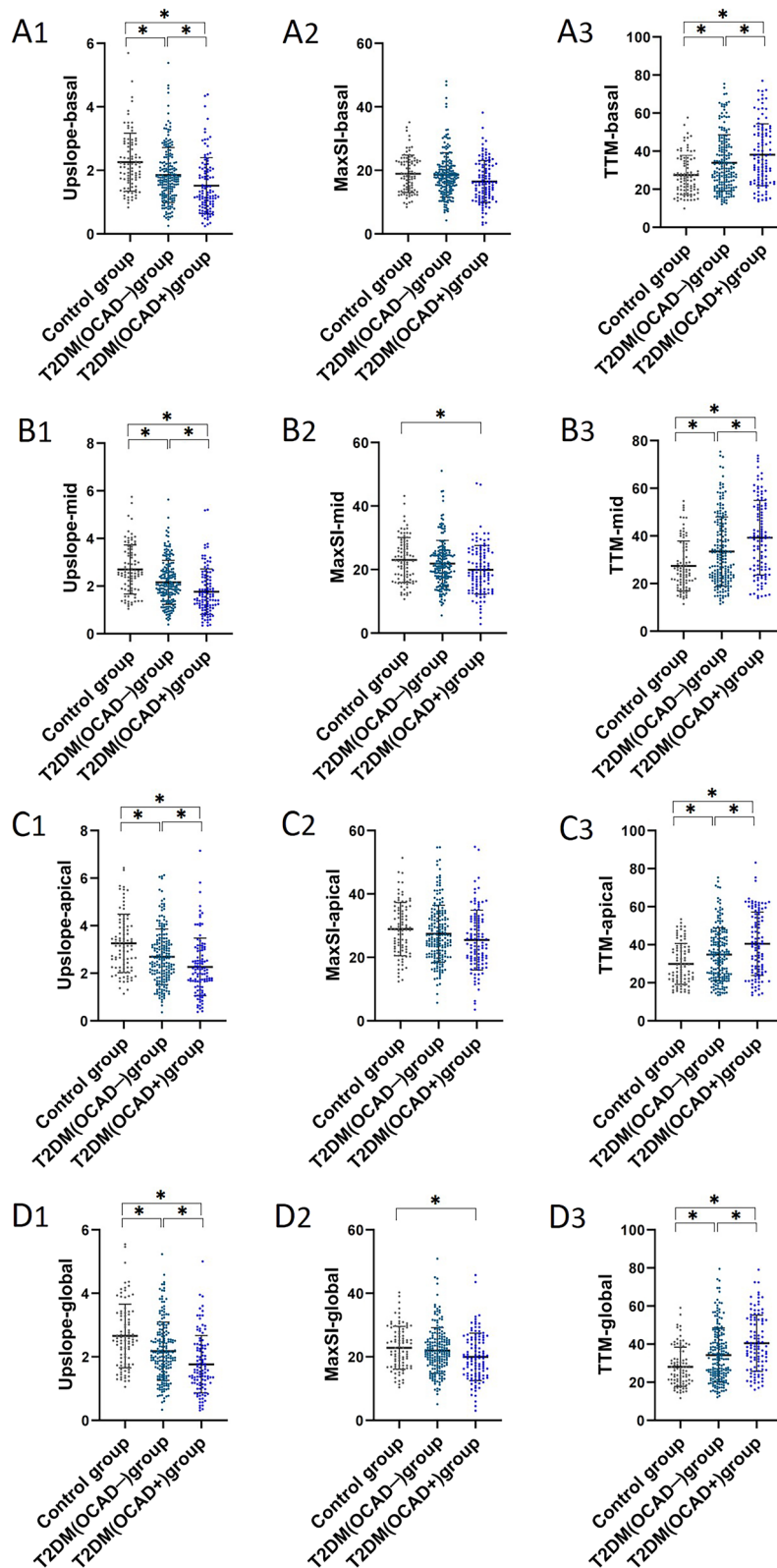


Fig. 2 Comparison of first-pass perfusion parameters among control subjects, T2DM(OCAD-) patients, and T2DM(OCAD+) patients in the basal slice (A1-A3), mid-ventricular slice (B1-B3) and apical slice (C1-C3), as well as in global (D1-D3). Abbreviations as in Fig. 1. * $P < 0.05$

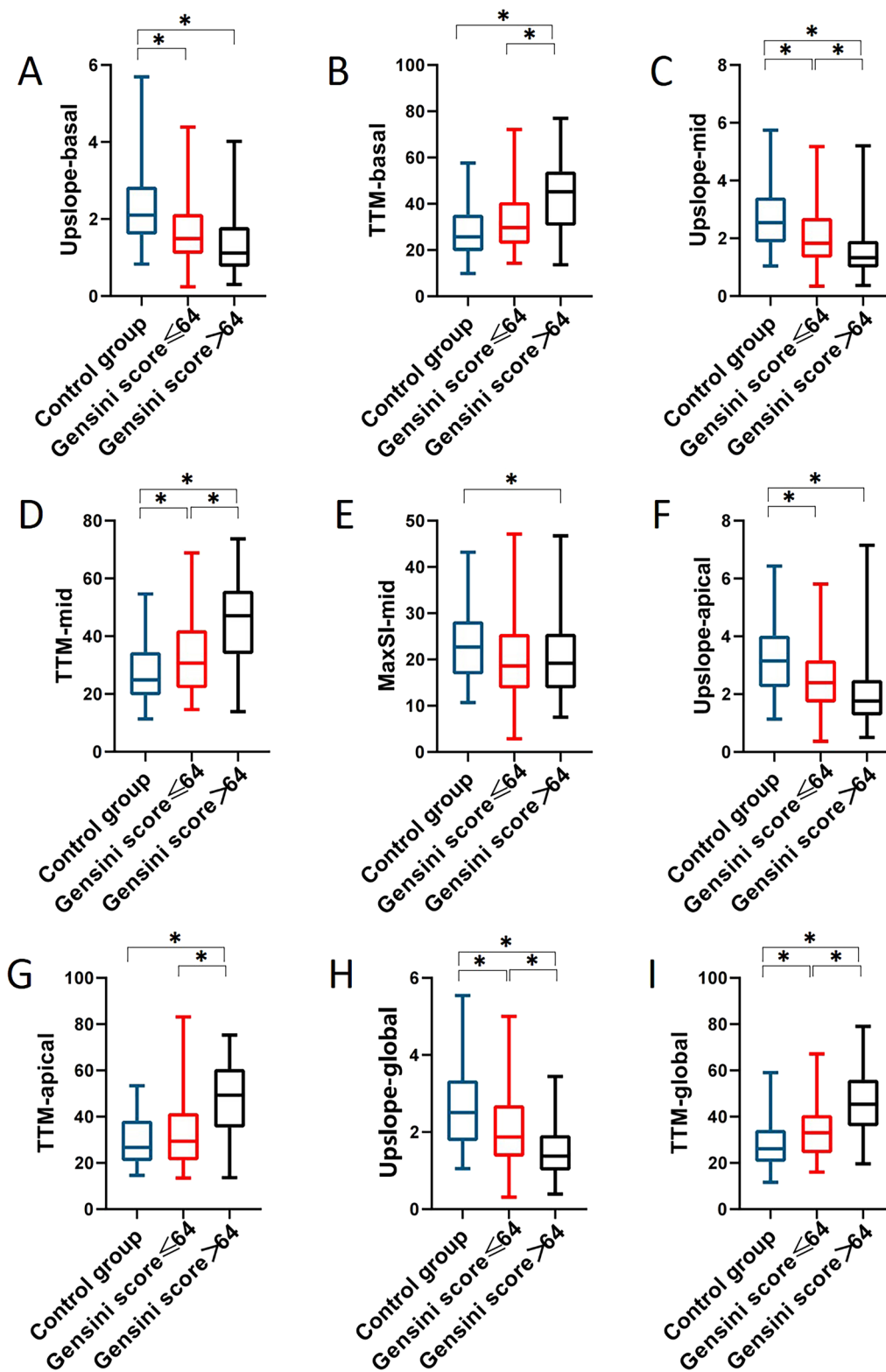


Fig. 3 Differences of myocardial microvascular perfusion indices among control subjects, T2DM(OCAD+) patients with Gensini score ≤ 64 , and those patients with Gensini score > 64 . Comparison of upslope and TTM in the basal slice (A, B), apical slice (F, G) and in global (H, I), as well as upslope, TTM, and MaxSI in the mid-ventricular slice (C, D, E) among above-mentioned three groups. Abbreviations as in Fig. 1. * $P < 0.05$

similar between subgroups of T2DM (OCAD+) patients with different Gensini score (all $P > 0.05$).

Incremental effect of OCAD on LV myocardial microvascular perfusion in T2DM patients

Multivariable linear regression analyses were performed to determine additive effect of OCAD on LV myocardial microvascular perfusion in T2DM patients using two models (Table 3). OCAD and T2DM were entered alone in model 1 with adjustment for sex, age, BMI, BSA, heart rate, systolic and diastolic blood pressure, smoking, and diabetes duration, demonstrating that the presence of OCAD or T2DM was independently associated with LV global upslope (OCAD: $\beta = -0.15$, $P = 0.003$, $R^2 = 0.19$; T2DM: $\beta = -0.23$, $P < 0.001$, $R^2 = 0.22$) and global TTM (OCAD: $\beta = 0.14$, $P = 0.005$, $R^2 = 0.23$; T2DM: $\beta = 0.19$, $P = 0.001$, $R^2 = 0.23$). With adjusted for those above demographic factors, OCAD and T2DM were entered together in model 2 showed that OCAD in the context of T2DM was significantly correlated with global upslope ($R^2 = 0.22$) and global TTM ($R^2 = 0.24$).

Associations between global TTM and Gensini score, as well as clinical factors

As shown in Table 4, the univariable analysis in T2DM(OCAD+) patients exhibited that global TTM was positively associated with the Gensini score ($r = 0.34$, $P < 0.001$) (Fig. 4), and male sex ($r = 0.398$, $P < 0.001$), as well as smoking ($r = 0.282$, $P = 0.003$). In addition, there was a negative correlation between systolic blood pressure and global TTM ($r = -0.35$, $P < 0.001$). After controlling for confounding factors, including age, sex, BMI, BSA, heart rate, systolic and diastolic blood pressure, smoking, and diabetes duration, Gensini score remained

Table 4 Associations between global TTM and Gensini score, as well as clinical factors in T2DM(OCAD+) patients

	TTM-global (s)				
	Univariable		Multivariable		
	r	p	β	p-value	R2
Gensini score	0.34	<0.001	0.182	0.042	0.226
Sex	0.398	<0.001	0.315	<0.001	
Age	-0.138	0.153	N/A	N/A	
BMI	-0.097	0.317	N/A	N/A	
BSA	0.151	0.117	N/A	N/A	
SBP	-0.353	<0.001	-0.226	0.013	
DBP	-0.194	0.043	N/A	N/A	
Heart rate	-0.034	0.729	N/A	N/A	
Smoking	0.282	0.003	N/A	N/A	
Diabetes duration	0.051	0.600	N/A	N/A	

β is adjusted regression coefficient

Factors with $P < 0.1$ in the univariable analyses were included in the stepwise multiple liner regression model

Abbreviations as in Tables 1 and 2

the independent predictor of increased global TTM ($\beta = 0.182$, $P = 0.042$, $R^2 = 0.226$).

Inter- and intra-observer variabilities of first-pass perfusion parameters

The inter- and intra-observer agreements of LV myocardial first-pass perfusion parameters were demonstrated in Table 5 and were considered excellent. The ICCs for inter-observer variability of LV myocardial perfusion in basal, mid-ventricular, apical segments, and global were 0.899–0.914, 0.909–0.951, 0.881–0.969, and 0.902–0.933, respectively. The ICCs for intra-observer variability of those above LV perfusion indices were

Table 3 Uni- and multi-variable linear regression analyses correlations of T2DM and OCAD with global coronary microvascular dysfunction

	Upslope-global					TTM-global (s)				
	Univariable		Multivariable			Univariable		Multivariable		
	r	p	β	p-value	R2	r	p	β	p-value	R2
Model 1: adjusted for demographic factors										
T2DM	-0.26	<0.001	-0.23	<0.001	0.22	0.25	<0.001	0.19	0.001	0.23
OCAD	-0.27	<0.001	-0.15	0.003	0.19	0.26	<0.001	0.14	0.005	0.23
Model 2: adjusted for demographic factors										
T2DM	-0.26	<0.001	-0.17	0.002	0.22	0.25	<0.001	0.16	0.004	0.24
OCAD	-0.27	<0.001	-0.10	0.037		0.26	<0.001	0.11	0.037	

β is adjusted regression coefficient

Factors with $P < 0.1$ in the univariable analyses were included in the stepwise multiple liner regression model

T2DM type 2 diabetes mellitus, OCAD obstructive coronary artery disease, TTM time to maximum signal intensity

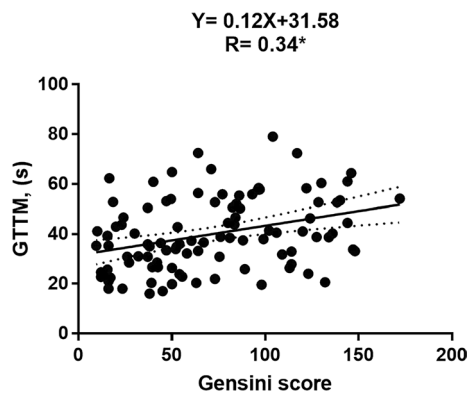


Fig. 4 Association between global TTM and Gensini score in T2DM(OCAD+) patients. T2DM type 2 diabetes mellitus, OCAD obstructive coronary artery disease, TTM time to maximum signal intensity. * $P < 0.001$

Table 5 Intra- and inter-observer variabilities of first-pass perfusion parameters

	Intra-observer (n = 60)		Inter-observer (n = 60)	
	ICC	95% CI	ICC	95% CI
Basel				
Upslope	0.924	0.874–0.955	0.914	0.858–0.949
MaxSI	0.900	0.835–0.940	0.899	0.833–0.939
TTM (s)	0.913	0.857–0.948	0.908	0.848–0.945
Mid-ventricular				
Upslope	0.942	0.903–0.965	0.940	0.900–0.964
MaxSI	0.910	0.851–0.946	0.909	0.850–0.946
TTM (s)	0.968	0.946–0.981	0.951	0.917–0.971
Apical				
Upslope	0.936	0.893–0.962	0.924	0.869–0.956
MaxSI	0.972	0.952–0.983	0.969	0.948–0.982
TTM (s)	0.908	0.847–0.945	0.881	0.803–0.929
Global				
Upslope	0.905	0.844–0.943	0.904	0.842–0.942
MaxSI	0.931	0.885–0.959	0.933	0.888–0.960
TTM (s)	0.911	0.852–0.947	0.902	0.839–0.941

ICC intraclass correlation coefficient, CI confidence interval, MaxSI max signal intensity, TTM time to maximum signal intensity

0.900–0.924, 0.910–0.968, 0.908–0.972, and 0.905–0.931, respectively.

Discussion

The present study investigated impact of coronary obstruction on coronary microcirculation function in the context of T2DM assessed by first-pass perfusion CMR imaging. The following main findings were obtained: (1) T2DM was linked with impairment of myocardial microcirculation perfusion. (2) coronary obstruction, in the

context of T2DM, might exacerbate myocardial microvascular dysfunction. (3) the presence of OCAD and the Gensini score were independent predictors of damaged microcirculation function.

Effect of T2DM on microcirculation abnormalities

Multiple randomized clinical trials using different techniques have confirmed marked reduction of coronary flow reserve reflecting coronary microvascular function in diabetes patients, even in the absence of OCAD [8, 29, 30]. The present study using fist-pass perfusion CMR imaging supported the findings of those above investigations by demonstrating impaired LV myocardial microvascular perfusion with reduced upslope and prolonged TTM in global and all of three segments in T2DM(OCAD–) patients despite with preserved LVEF. In addition, our results were also in line with previous evidence that impaired microvascular function affected the left ventricle globally in addition to regionally in patients with T2DM [31].

Coronary microvascular abnormalities in T2DM involves multiple complex pathophysiological mechanisms including hyperglycemia, insulin resistance, and systemic inflammation, as well as autonomic dysfunction [29, 32, 33]. Furthermore, these abnormalities precede the onset of contractile dysfunction and clinically overt OCAD [34], and are also associated with poor cardiovascular prognosis [8]. Hence, early detection of coronary microvascular dysfunction in patients with T2DM might be helpful for early intervention to avoid adverse cardiovascular events [11].

Incremental effect of coronary obstruction on microcirculation dysfunction in the context of T2DM

Several researches have founded patients with known coronary artery disease had impaired hyperemic flow and coronary flow reserve [9, 35, 36]. This present study extended these findings to patients with both OCAD and T2DM, a population that previously has rarely been explored, which exhibited that T2DM(OCAD+) patients had a more reduction in upslope and prolongation in TTM in global and all of three segments than those T2DM(OCAD–) patients and control subjects, suggesting that OCAD might exacerbate microcirculation damage in T2DM. Together, those above findings indicated that it is imperative to actively treat OCAD in patients with T2DM. Current therapies for diabetes patients with multi-vessel OCAD include percutaneous coronary intervention and coronary artery bypass graft (CABG), both of which have improved the prognosis among those patients [37, 38].

The pathophysiologic mechanisms of epicardial coronary artery obstruction on myocardial microcirculation

dysfunction are poorly established, although several potential mechanisms have been proposed, including prearteriolar and arteriolar constriction and improper subepicardial prearteriolar dilatation in the existence of multiplied myocardial oxygen consumption [15, 16]. In addition, enhanced sympathetic activation is also likely to contribute to microvascular dysfunction under the coronary obstruction [16, 39]. Further researches in the context of T2DM are warranted on the underlying mechanisms of OCAD affecting coronary microcirculation function.

First-pass perfusion CMR for evaluation of myocardial microvascular function

Currently, nuclear imaging and myocardial contrast echocardiography can be used to evaluate myocardial microcirculation function. However, both of these modalities are subject to certain limitations [15, 40]. First-pass perfusion CMR is a non-invasive and radiation-free modality for detecting myocardial ischemia with high diagnostic accuracy and spatial resolution [18–20, 40]. First-pass perfusion CMR parameters are derived from myocardial signal intensity-time curve including upslope, MaxSI, and TTM, which have been applied as semi-quantitative markers of tissue perfusion and associated with coronary microvascular function [18–20, 41].

In current study, there were excellent intra- and inter-observer agreements of the first-pass CMR perfusion technique for measuring upslope, MaxSI, and TTM among patients with T2DM. Previous studies have indicated that coronary microcirculation function, as evaluated by first-pass CMR myocardial perfusion, might serve as an additional marker for prognosis evaluation and therapeutic response [18, 20, 42]. As coronary microvascular dysfunction is an independent and strong risk factor of clinical deterioration and death in patients with T2DM and OCAD [9], future studies will focus on using this technique to evaluate the prognosis among those patients.

Independent predictors of microvascular dysfunction

Much less is known about the interrelationship between the coronary microcirculation and the epicardial coronary arteries [12–14]. In our data, the presence of OCAD was an independent predictor of myocardial microcirculation dysfunction in the context of T2DM. A better comprehension of the relationship between the epicardial coronary artery obstruction and microvascular disorder would be beneficial to effectively diagnose and treat microvascular dysfunction in patients with T2DM. Current researches show that multi-lineage cell therapy is a

novel, translatable approach and is expected to improve microvascular disease in diabetic patients [43, 44].

Our results suggested that T2DM(OCAD+) patients with Gensini score > 64 might had a more severe microvascular dysfunction than those patients with Gensini score \leq 64 and control subjects. Increasing evidence has demonstrated that the extent and severity of coronary artery stenosis are associated with decreased myocardial microcirculation perfusion among patients with known or suspected coronary artery disease [45–47].

Data from experimental study in pig model conducted by Fearon et al. [48] have found that microvascular resistance is not affected by the epicardial coronary artery stenosis severity. Conversely, by analyzing the correlation between the Gensini score and microcirculation function, the current study demonstrated that global TTM prolonged progressively along with the increase of the Gensini score which is widely used for quantifying the severity of OCAD [27]. Possible reason for this discrepancy might be explained by the differences between animal models and humans. Taken together, our observations implied that the severity of the OCAD was also a predictor of coronary microcirculation dysfunction. Consequently, early prevention and active intervention of OCAD are expected to improve coronary microvascular function [15, 16] in patients with T2DM (OCAD+).

Limitations

Our study has several limitations. Firstly, this was a mono-centric study, which carries inherent bias in terms of selection. A multicenter study is desirable to generalize our observations. Secondly, as a cross-sectional analysis, we cannot know the evolution of cardiac microcirculation damage in patients with T2DM(OCAD+) overtime with the progression of OCAD. Further follow-up studies will be performed to address this question. Thirdly, stress CMR perfusion imaging has been reported to prospectively evaluate myocardial ischemia in some cardiovascular diseases [19, 20, 42]. Due to the inherent limitations of retrospective design, future prospective trials will use this imaging modality to explore the incremental effect of OCAD on myocardial microcirculation function among T2DM patients. Finally, not all of our T2DM(OCAD–) patients were performed ICA examination or coronary computed tomography angiography to exclude OCAD, and control individuals were not performed those above examination to exclude no clinical symptoms coronary artery obstruction. According to comprehensive evaluation of the patients by clinical history, laboratory examination, electrocardiography, and

echocardiography, OCAD was deemed to be unlikely in those patients [21].

Conclusions

Coronary artery obstruction in the context of T2DM might exacerbate myocardial microcirculation damage. The presence of OCAD and Gensini score were independent predictors of myocardial microvascular dysfunction. Early detection myocardial microcirculation abnormalities using first-pass perfusion CMR in T2DM patients, especially when comorbid with OCAD, would be essential for timely therapeutic interventions.

Abbreviations

T2DM	Type 2 diabetes mellitus
OCAD	Obstructive coronary artery disease
CMR	Cardiac magnetic resonance
MaxSI	Max signal intensity
TTM	Time to maximum signal intensity
CMD	Coronary microvascular dysfunction
PG	Plasma glucose
LV	Left ventricular
ICA	Invasive coronary angiography
bSSFP	Balanced steady-state free precession
TR	Repetition time
TE	Echo time
FOV	Field of view
LVEDV	LV end-diastolic volume
LVESV	LV end-systolic volume
LVSV	LV stroke volume
LVEF	LV ejection fraction
BSA	Body surface area
ICC	Intra-class correlation coefficient

Acknowledgements

Not applicable.

Author contributions

JW, YL and ZGY participated in the study design. JW analyzed the data and drafted the manuscript. YKG and YL revised the manuscript. HF and CYM collected the data. YJ, WLQ and WFY analyzed the data and gave advice on data presentation. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (82120108015, 81971586, 81771887, 81471722), the 1-3-5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18013), Sichuan Province Science and Technology Support Program (2022NSFSC0828), and the Fellowship of China Postdoctoral Science Foundation (2021M692287).

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Biomedical Research Ethics Committee of our hospital. Written informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Radiology, West China Hospital, Sichuan University, 37# Guo Xue Xiang, Chengdu 610041, Sichuan, China. ²Department of Radiology, Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3, Renmin South Road, Chengdu 610041, Sichuan, China.

Received: 18 March 2023 Accepted: 30 May 2023

Published online: 28 June 2023

References

- Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *Lancet*. 2022;400(10365):1803–20.
- Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation*. 2022;145(9):e722–59.
- Erdogan D, Yucel H, Uysal BA, Ersoy IH, Icli A, Akcay S, et al. Effects of prediabetes and diabetes on left ventricular and coronary microvascular functions. *Metabolism*. 2013;62(8):1123–30.
- Yan WF, Xu HY, Jiang L, Zhang L, Guo YK, Li Y, et al. Early longitudinal changes in left ventricular function and morphology in diabetic pigs: evaluation by 3.0T magnetic resonance imaging. *Cardiovasc Diabetol*. 2023;22:6.
- Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation*. 2012;126(15):1858–68.
- Bax JJ, Inzucchi SE, Bonow RO, Schuijff JD, Freeman MR, Barrett EJ. Global dialogue group for the evaluation of cardiovascular risk in patients with diabetes cardiac imaging for risk stratification in diabetes. *Diabetes Care*. 2007;30:1295–304.
- Zhang W, Singh S, Liu L, Mohammed AQ, Yin G, Xu S, et al. Prognostic value of coronary microvascular dysfunction assessed by coronary angiography-derived index of microcirculatory resistance in diabetic patients with chronic coronary syndrome. *Cardiovasc Diabetol*. 2022;21(1):222.
- Kato S, Fukui K, Kodama S, Azuma M, Iwasawa T, Kimura K, et al. Incremental prognostic value of coronary flow reserve determined by phase-contrast cine cardiovascular magnetic resonance of the coronary sinus in patients with diabetes mellitus. *J Cardiovasc Magn Reson*. 2020;22(1):73.
- Marwick TH, Case C, Sawada S, Vasey C, Short L, Lauer M. Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. *Diabetes Care*. 2002;25(6):1042–8.
- Levelt E, Piechnik SK, Liu A, Wijesurendra RS, Mahmood M, Ariga R, et al. Adenosine stress CMR T1-mapping detects early microvascular dysfunction in patients with type 2 diabetes mellitus without obstructive coronary artery disease. *J Cardiovasc Magn Reson*. 2017;19(1):81.
- Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation*. 2010;121:2317–25.
- Sambuceti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical increase in microvascular resistance during tachycardia downstream from a severe stenosis in patients with coronary artery disease: reversal by angioplasty. *Circulation*. 2001;103(19):2352–60.
- Chamuleau SA, Siebes M, Meuwissen M, Koch KT, Spaan JA, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol*. 2003;285(5):H2194–200.
- Marzilli M, Sambuceti G, Fedele S, L'Abbate A. Coronary microcirculatory vasoconstriction during ischemia in patients with unstable angina. *J Am Coll Cardiol*. 2000;35(2):327–34.
- Leung DY, Leung M. Non-invasive/invasive imaging: significance and assessment of coronary microvascular dysfunction. *Heart*. 2011;97(7):587–95.

16. Camici PG, Filippo C. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–40.
17. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol*. 2015;12:48–62.
18. Yang MX, Li QL, Wang DQ, Ye L, Li KM, Lin XJ, et al. Myocardial microvascular function assessed by CMR first-pass perfusion in patients treated with chemotherapy for gynecologic malignancies. *Eur Radiol*. 2022;32:6850–8.
19. Jerosch-Herold M. Quantification of myocardial perfusion by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2010;12(1):57.
20. Ge Y, Antiochos P, Steel K, Bingham S, Abdullah S, Chen YY, et al. Prognostic Value of Stress CMR Perfusion Imaging in Patients With Reduced Left Ventricular Function. *JACC Cardiovasc Imaging*. 2020;13(10):2132–45.
21. Jiang L, Shi K, Guo YK, Ren Y, Li ZL, Xia CC, et al. The additive effects of obesity on myocardial microcirculation in diabetic individuals: a cardiac magnetic resonance first-pass perfusion study. *Cardiovasc Diabetol*. 2020;19(1):52.
22. Jiang L, Ren Y, Yu H, Guo YK, Liu X, Deng MY, et al. Additive effect of hypertension on left ventricular structure and function in patients with asymptomatic type 2 diabetes mellitus. *J Hypertens*. 2021;39(3):538–47.
23. Montone RA, Pitocco D, Gurgoglione FL, Rinaldi R, Del Buono MG, Camilli M, et al. Microvascular complications identify a specific coronary atherosclerotic phenotype in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2022;21(1):211.
24. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231–2264.
25. Chamberlain JJ, Rhinehart AS, Shaefer CF Jr, Neuman A. Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association Standards of medical care in diabetes. *Ann Intern Med*. 2016;164(8):542–52.
26. Wang XB, Cui NH, Liu X, Liu X. Mitochondrial 8-hydroxy-2'-deoxyguanosine and coronary artery disease in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2020;19:22.
27. Rampidis GP, Benetos G, Benz DC, Giannopoulos AA, Buechel RR. A guide for Gensini Score calculation. *Atherosclerosis*. 2019;287:181–3.
28. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance—2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson*. 2020;22:19.
29. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol*. 2003;41:1387–93.
30. Leccisotti L, Cinti F, Sorice GP, D'Amario D, Lorusso M, Guzzardi MA, et al. Dapagliflozin improves myocardial flow reserve in patients with type 2 diabetes: the DAPAHEART Trial: a preliminary report. *Cardiovasc Diabetol*. 2022;21(1):173.
31. L'Abbate A. Large and micro coronary vascular involvement in diabetes. *Pharmacol Rep*. 2005;57(suppl):3–9.
32. Sundell J, Rönnemaa T, Laine H, Raitakari OT, Luotolahti M, Nuutila P, et al. High-sensitivity C-reactive protein and impaired coronary vasoreactivity in young men with uncomplicated type 1 diabetes. *Diabetologia*. 2004;47:1888–94.
33. Quiñones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenez X, Hernandez G, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. *Ann Intern Med*. 2004;140:700–8.
34. Stevens SR, Segar MW, Pandey A, Lakhnygina Y, Green JB, McGuire DK, et al. Development and validation of a model to predict cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease. *Cardiovasc Diabetol*. 2022;21(1):166.
35. Werner GS, Ferrari M, Richartz BM, Gastmann O, Figulla HR. Microvascular dysfunction in chronic total coronary occlusions. *Circulation*. 2001;104(10):1129–34.
36. Tomai F, Ribichini F, Ghini AS, Ferrero V, Andò G, Vassanelli C, et al. Elevated C-reactive protein levels and coronary microvascular dysfunction in patients with coronary artery disease. *Eur Heart J*. 2005;26(20):2099–105.
37. Abdallah MS, Wang K, Magnuson EA, Spertus JA, Farkouh ME, Fuster V, et al. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA*. 2013;310(15):1581–90.
38. Ram E, Fisman EZ, Tenenbaum A, Iakobishvili Z, Peled Y, Raanani E, et al. Revascularization outcomes in diabetic patients presenting with acute coronary syndrome with non-ST elevation. *Cardiovasc Diabetol*. 2022;21(1):175.
39. Heusch G, Deussen A, Thamer V. Cardiac sympathetic nerve activity and progressive vasoconstriction distal to coronary stenoses: feed-back aggravation of myocardial ischemia. *J Auton Nerv Syst*. 1985;13:311–26.
40. Schindler TH, Dilsizian V. Coronary microvascular dysfunction: clinical considerations and noninvasive diagnosis. *JACC Cardiovasc Imaging*. 2020;13(1 Pt 1):140–55.
41. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation*. 2003;108(4):432–7.
42. Stuckey DJ, Carr CA, Meader SJ, Tyler DJ, Cole MA, Clarke K. First-pass perfusion CMR two days after infarction predicts severity of functional impairment six weeks later in the rat heart. *J Cardiovasc Magn Reson*. 2011;13(1):38.
43. Kawamura M, Paulsen MJ, Goldstone AB, Shudo Y, Wang H, Steele AN, et al. Tissue-engineered smooth muscle cell and endothelial progenitor cell bi-level cell sheets prevent progression of cardiac dysfunction, microvascular dysfunction, and interstitial fibrosis in a rodent model of type 1 diabetes-induced cardiomyopathy. *Cardiovasc Diabetol*. 2017;16(1):142.
44. Shudo Y, Cohen JE, Macarthur JW, Atluri P, Hsiao PF, Yang EC, et al. Spatially oriented, temporally sequential smooth muscle cell-endothelial progenitor cell bi-level cell sheet neovascularizes ischemic myocardium. *Circulation*. 2013;128(11 Suppl 1):S59–68.
45. Naya M, Murthy VL, Taqueti VR, Foster CR, Klein J, Garber M, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. *J Nucl Med*. 2014;55(2):248–55.
46. Driessen RS, de Waard GA, Stuijzand WJ, Rajmakers PG, Danad I, Bom MJ, et al. Adverse plaque characteristics relate more strongly with hyperemic fractional flow reserve and instantaneous wave-free ratio than with resting instantaneous wave-free ratio. *JACC Cardiovasc Imaging*. 2020;13(3):746–56.
47. Naya M, Murthy VL, Blankstein R, Sitek A, Hainer J, Foster C, et al. Quantitative relationship between the extent and morphology of coronary atherosclerotic plaque and downstream myocardial perfusion. *J Am Coll Cardiol*. 2011;58(17):1807–16.
48. Fearon WF, Aarnoudse W, Pijls NH, De Bruyne B, Balsam LB, Cooke DT, et al. Microvascular resistance is not influenced by epicardial coronary artery stenosis severity: experimental validation. *Circulation*. 2004;109(19):2269–72.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

