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ORIGINAL ARTICLE

Impact of diabetes on coronary physiology evaluated by quantitative flow ratio in patients who underwent percutaneous coronary intervention

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ABSTRACT

Aims/Introduction: There are mixed opinions on the influence of diabetes on the prognosis of patients receiving percutaneous coronary intervention (PCI). Therefore, in this study, the quantitative flow ratio (QFR), an emerging technology of functional evaluation, was used to explore the impact of diabetes on coronary physiology in patients who underwent PCI.

Materials and Methods: Patients who underwent successful PCI and a 1-year angiographic follow up were retrospectively screened and analyzed by the QFR. Based on the presence or absence of diabetes, 677 enrolled patients (794 vessels) were classified into a diabetes group (211 patients, 261 vessels) and a non-diabetes group (466 patients, 533 vessels). The results of QFR analysis and clinical outcomes were compared between the two groups.

Results: The two groups reached a similar level of post-PCI QFR (0.95 ± 0.09 vs 0.96 ± 0.06, $P = 0.292$). However, at the 1-year follow up, the QFR was lower (0.93 ± 0.11 vs 0.96 ± 0.07, $P < 0.001$), and the degree of QFR decline was more obvious (–0.024 ± 0.090 vs –0.008 ± 0.070, $P = 0.023$) in the diabetes group. Additionally, diabetes was independently associated with functional restenosis (odds ratio 2.164, 95% confidence interval 1.210–3.870, $P = 0.009$) and target vessel failure (odds ratio 2.654, 95% confidence interval 1.405–5.012, $P = 0.003$).

Conclusion: As evaluated by the QFR, patients with diabetes received less coronary physiological benefit from PCI, which was consistent with their clinical outcomes.

INTRODUCTION

It is well documented that diabetes promotes the formation and progression of coronary artery disease (CAD). Microvascular and macrovascular complications induced by diabetes increase the risk of adverse cardiovascular events in patients who are diagnosed with CAD[1–3]. Percutaneous coronary intervention (PCI) has been generally recognized as a standard therapy to treat anatomical stenosis of coronary arteries. Nevertheless, current studies hold mixed opinions on the influence of diabetes on the prognosis of PCI[4–9]. Therefore, the impact of diabetes on the prognosis of patients who have undergone PCI is in need of reassessment brought by new approaches.

Functional evaluation is of increasing significance in CAD patients, because not all coronary dysfunction is consistent with the degree of obstructive coronary disease, and the former might not be well reflected in conventional coronary angiography[10,11]. Fractional flow reserve (FFR) is currently recognized as the gold standard for making revascularization

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decisions and tracing the coronary physiology in follow up. However, the clinical application of the FFR is still limited by the use of dilatation drugs, pressure guide wires, long measurement times and high costs[12–14]. The quantitative flow ratio (QFR) is an emerging and less-invasive technology for conveniently computing the FFR value based on three-dimensional (3-D) coronary artery reconstruction and fluid dynamics[15]. The accuracy of QFR compared with the FFR was confirmed by previous landmark studies[15–19]; furthermore, the recent trial "Comparison of Quantitative **F**low Ratio Guided and **A**ngiography Guided Percutaneous Inter**V**ention in Patients with C**OR**onary Artery Disease : FAVOR III China" confirmed that the QFR-guided strategy of PCI can improve clinical outcomes[20]. Therefore, the QFR has gradually been recognized as an alternative measure in coronary functional evaluation.

Although relevant technologies have emerged rapidly, these functional evaluation methods are typically underutilized, especially in CAD patients with complications, such as diabetes. Research on tracking the coronary physiology after PCI is relatively rare, and the impact of diabetes on the prognosis of PCI still lacks the evidence from a perspective of functional assessment. Therefore, the present study aimed to explore the impact of diabetes on coronary physiology in patients who underwent PCI through QFR.

MATERIALS AND METHODS

Study design

Consecutive patients who underwent PCI were recruited from August 2015 to March 2017 at Fujian Medical University Union Hospital, Fuzhou, China. Patients who underwent PCI and were tracked by a 1-year angiographic follow up (scheduled by protocol) were eligible for enrollment when inclusion criteria were met. The indications for QFR computation were as follows: (i) diameter stenosis percentage (DS%) of at least one lesion between 50–90% (visual assessment); and (ii) reference vessel diameter size ≥2.5 mm (visual assessment). Patients with any of the following clinical characteristics were excluded: (i) acute ST segment elevation myocardial infarction within 7 days[21]; (ii) lack of follow-up data; and (iii) circumstances where QFR computation could not be carried out, including reference vessel diameter size <2 mm (visual assessment), lack of two optimal angiographic projections at least 25° apart, lesion involving a myocardial bridge or bypass graft and severe overlap or tortuosity of target blood vessels, and poor angiographic image quality.

All enrolled patients were computed retrospectively for QFR, and their clinical characteristics at the pre-PCI, post-PCI and 1-year follow-up evaluations were collected. During the first hospitalization, all patients underwent an oral glucose tolerance test, and according to previous medical history or diagnostic criteria of the World Health Organization[22], the patients were classified into a diabetes group and a non-diabetes group.

PCI procedure and QFR computation

The revascularization guidelines at that time were used as the principles of PCI[23]. Experienced cardiologists decided that the type and expansion of the stent relied on their own judgment. We routinely recommended that all treated patients accept the review of coronary angiography after 1 year.

QFR computations were carried out by two trained operators who were blinded to the clinical data through the AngioPlus system (Pulse Medical Imaging Technology Shanghai, Shanghai, China) according to standard procedures. The 3-D reconstruction of the target vessel was carried out based on automated contouring of two angiographic projections recorded at 15 frames/s and at least 25° apart. After 3-D reconstruction, the QFR and blood flow resistance (BFR) value of the target coronary artery were computed through contrast flow velocity models[15]. In addition, 3-D reconstruction of the vessel provides quantitative coronary angiography (QCA) information of the target vessel comprising the minimal lumen diameter, DS% and area stenosis percentage (AS%). Late lumen loss was defined as the difference in minimal lumen diameter between the post-PCI and follow-up evaluations. The QFR changes were chosen to present physiological changes.

Data collection and follow up

All patients received standard pharmacological management in accordance with the clinical guidelines[23]. An electronic medical record system was used to retrospectively collect relevant clinical data on the enrolled patients at the time of first hospitalization and at the 1-year follow up. Renal insufficiency was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 during the first hospitalization. The hospital clinical laboratory was responsible for measuring serum biochemical results, such as glucose, glycated hemoglobin, low-density lipoprotein cholesterol (LDL-C), creatinine, troponin I, N-terminal pro-brain natriuretic peptide and C-reactive protein. Echocardiography was used to determine the left ventricular ejection fraction and E/e′. E/e′ is the ratio of the mitral peak velocity of early filling (E) to the early diastolic mitral annular velocity (e′) as an indicator of cardiac diastolic function.

Functional restenosis was defined as QFR <0.8 at the 1-year follow up after successful PCI. The diagnosis of myocardial infarction (MI) was made according to the fourth universal definition of MI[24]. Target vessel failure (TVF) was defined as the composite of cardiovascular death, target vessel-related MI and target vessel revascularization[25]. If there was no clear non-cardiac cause, all deaths were considered cardiac. Any MI without a clearly identifiable culprit vessel was counted as target vessel related. Any segment of the target vessel including the target lesion that underwent repeat percutaneous or surgical revascularization was recorded as target vessel revascularization[25].

The functional restenosis data were derived from the results of QFR computation. The incidence of TVF within 1 year was recorded by telephoning patients or through medical record queries.

Statistical analysis

Data were analyzed at the vessel level for results of functional evaluation, and at the patient level for baseline characteristics and clinical outcomes. Continuous variables are presented as the mean and standard deviation for normally distributed data, or as the medians and interquartile range for non-normally distributed data. Categorical variables are presented as counts and percentages. Normality was tested with the Kolmogorov–Smirnov test or Shapiro–Wilk test. Comparisons between continuous variables were evaluated with Student's *t*-test, Welch's t test or the Mann–Whitney *U*-test. Comparisons between categorical variables were carried out with Pearson's χ^2-test or Fisher's exact test. Variables with a *P*-value <0.10 in univariable logistic regression analysis were entered into a multivariable model. A *P*-value <0.05 was considered statistically significant. All analyses were carried out with SPSS 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 1,016 patients (1,198 vessels) were recruited for the present study. After exclusion on the basis of predefined criteria, 677 patients (794 vessels) were included in the final analysis. All enrolled patients were divided into a diabetes group (211 patients, 261 vessels) and a non-diabetes group (466 patients, 533 vessels) based on the presence or absence of diabetes (Figure 1).

Baseline characteristics

Patients with diabetes accounted for 31.2% of all enrolled patients. The diabetes group had a higher rate of hypertension (72.0% vs 59.7%, $P = 0.002$), renal insufficiency (6.2% vs 2.4%, $P = 0.013$) and previous PCI history (22.3% vs 11.4%, $P < 0.001$). The non-diabetes group had relatively higher proportions of smoking history (60.3% vs 51.2%, $P = 0.026$) and ST segment elevation myocardial infarction (≥7 days; 21.5% vs 14.2%, $P = 0.027$). In addition, higher glucose levels (8.70 ± 3.47 vs 5.60 ± 1.14, $P < 0.001$) and E/e′ values (14.55 ± 5.86 vs 12.63 ± 12.94, $P < 0.001$), and lower LDL-C levels (2.82 ± 1.02 vs 3.01 ± 1.01, $P = 0.015$) were found in the diabetes group. No significant difference was found in age, sex, previous MI, creatinine, troponin I, N-terminal pro-brain natriuretic peptide, C-reactive protein, left ventricular ejection fraction or medications at discharge between the two groups (Table 1).

Variation of biochemical indicators and echo variables

The glycated hemoglobin level of the diabetes group and glucose levels of both groups were decreased at the 1-year follow

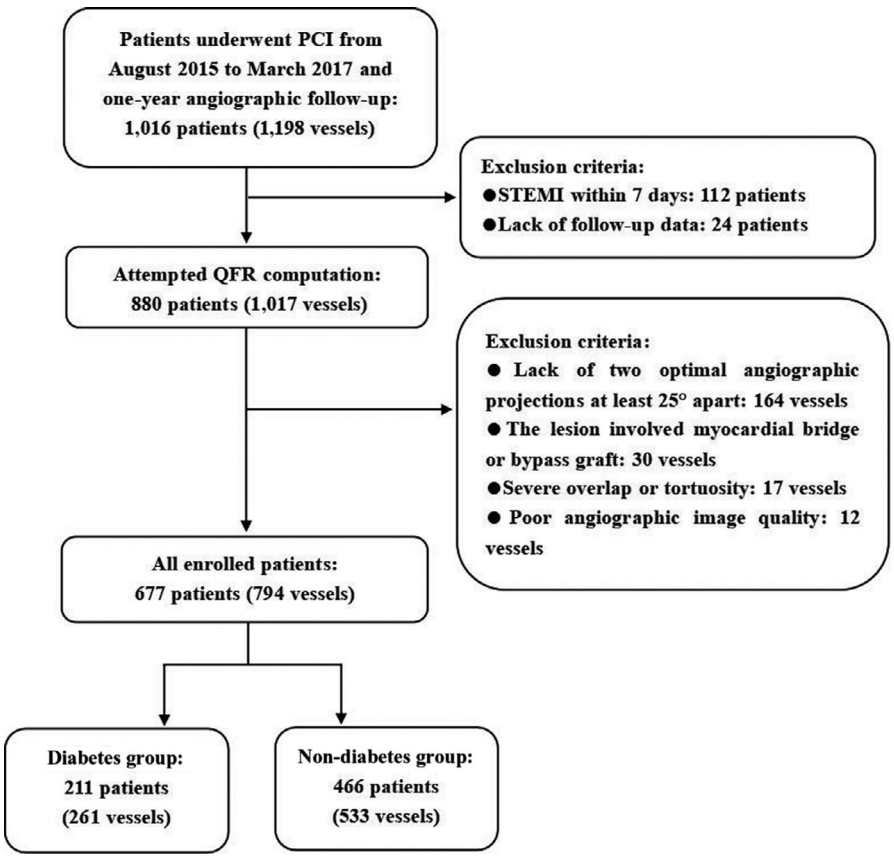

Figure 1 | Study flowchart. PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; STEMI, ST-segment elevation myocardial infarction.

Table 1 | Baseline characteristics

	Diabetes group (n = 211)	Non-diabetes group (n = 466)	P-value
Age (years)	63.57 ± 9.50	62.38 ± 10.38	0.250
Male, n (%)	168 (79.6)	387 (83.0)	0.283
Smoking history, n (%)	108 (51.2)	281 (60.3)	0.026
Hypertension, n (%)	152 (72.0)	278 (59.7)	0.002
Renal insufficiency, n (%)	13 (6.2)	11 (2.4)	0.013
Previous MI, n (%)	26 (12.3)	42 (9.0)	0.185
Previous PCI, n (%)	47 (22.3)	53 (11.4)	<0.001
Type of coronary artery disease			
Stable angina, n (%)	27 (12.8)	44 (9.4)	0.187
Unstable angina, n (%)	117 (55.5)	244 (52.4)	0.455
NSTEMI, n (%)	37 (17.5)	78 (16.7)	0.798
STEMI (≥7 days), n (%)	30 (14.2)	100 (21.5)	0.027
Medications at discharge			
Antiplatelet agent, n (%)	211 (100)	466 (100)	–
Statin, n (%)	211 (100)	466 (100)	–
ACEI/ARB, n (%)	169 (80.1)	344 (73.8)	0.078
Insulin, n (%)	53 (25.1)	–	–
OHA, n (%)	125 (59.2)	–	–
α-Glucosidase inhibitor, n (%)	98 (46.4)		
Insulin secretagogues, n (%)	88 (41.7)		
Metformin, n (%)	23 (10.9)		
DPP-4 inhibitor, n (%)	3 (1.4)		
Insulin sensitizer, n (%)	1 (0.5)		
Pre-PCI			
Glucose (mmol/L)	8.70 ± 3.47	5.60 ± 1.14	<0.001
HbA_{1c} (%)	7.90 ± 1.59	–	–
LDL-C (mmol/L)	2.82 ± 1.02	3.01 ± 1.01	0.015
Creatinine (μmol/L)	85.60 ± 53.29	78.97 ± 19.60	0.415
Troponin I (μg/L)	4.61 ± 12.25	6.75 ± 13.79	0.321
NT-proBNP (pg/mL)	146.00 (57.50, 631.50)	158.00 (58.00, 600.00)	0.893
CRP (mg/L)	2.27 (0.78, 7.48)	2.72 (0.86, 7.85)	0.411
LVEF (%)	60.11 ± 12.03	60.61 ± 10.88	0.853
E/e′	14.55 ± 5.86	12.63 ± 12.94	<0.001
1-year follow up			
Glucose (mmol/L)	7.39 ± 2.66	5.32 ± 0.92	<0.001
HbA_{1c} (%)	7.67 ± 1.43	/	/
LDL-C (mmol/L)	2.30 ± 1.07	2.24 ± 0.81	0.766
Creatinine (μmol/L)	85.92 ± 53.23	81.45 ± 22.90	0.777
Troponin I (μg/L)	0.01 ± 0.03	0.01 ± 0.01	0.503
NT-proBNP (pg/mL)	100.00 (46.25, 250.75)	75.00 (40.00, 173.25)	0.038
CRP (mg/L)	1.13 (0.50, 3.81)	0.88 (0.43, 2.47)	0.051
LVEF (%)	62.11 ± 10.46	62.09 ± 10.58	0.969
E/e′	14.72 ± 6.59	12.62 ± 5.03	<0.001
ΔE/e′†	0.17 ± 5.87	-0.01 ± 13.30	0.627

Values are presented as the mean ± standard deviation, median (interquartile range) or n (%). ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycated hemoglobin A_{1c}; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. †ΔE/e′ = follow-up E/e′ – Pre-PCI E/e′.

up, but the diabetes group still had a higher glucose level (7.39 ± 2.66 vs 5.32 ± 0.92, P < 0.001). At the 1-year follow up, the LDL-C levels of the two groups reached a similar level (2.30 ± 1.07 vs 2.24 ± 0.81, P = 0.766). Additionally, the diabetes group had higher levels of N-terminal pro-brain natriuretic peptide (100.00 [46.25–250.75] vs 75.00 [40.00–173.25], P = 0.038) and E/e′ values (14.72 ± 6.59 vs 12.62 ± 5.03, P < 0.001; Table 1).

Table 2 | Results of quantitative coronary angiography and functional evaluation

	Diabetes group (n = 261)	Non-diabetes group (n = 533)	P-value
Target vessel			
LM, n (%)	2 (0.8)	9 (1.7)	0.296
LAD, n (%)	130 (49.8)	290 (54.4)	0.222
LCX, n (%)	43 (16.5)	83 (15.6)	0.744
RCA, n (%)	84 (32.2)	136 (25.5)	0.049
Other branches, n (%)	2 (0.8)	15 (2.8)	0.061
Post-PCI			
MLD (mm)	1.88 ± 0.49	1.93 ± 0.55	0.386
DS (%)	28.38 ± 11.89	27.59 ± 11.22	0.527
AS (%)	37.44 ± 17.25	35.45 ± 16.35	0.168
BFR (mmHg × s/m)	3.77 (0.58, 24.08)	4.22 (0.61, 20.00)	0.871
QFR	0.95 ± 0.09	0.96 ± 0.06	0.292
1-year follow-up			
MLD (mm)	1.74 ± 0.50	1.83 ± 0.49	0.012
LLL[†] (mm)	0.14 ± 0.44	0.11 ± 0.53	0.362
DS (%)	32.82 ± 13.06	29.25 ± 11.16	<0.001
ΔDS[‡] (%)	4.44 ± 12.39	1.65 ± 12.21	0.007
AS (%)	43.95 ± 18.61	39.01 ± 16.85	0.001
ΔAS[‡] (%)	6.51 ± 17.68	3.56 ± 18.45	0.024
BFR (mmHg × s/m)	12.37 (1.69, 44.04)	6.15 (1.34, 27.09)	0.009
ΔBFR[‡] (mmHg × s/m)	2.09 (–0.67, 19.83)	0.65 (–3.60, 12.51)	0.004
QFR	0.93 ± 0.11	0.96 ± 0.07	<0.001
ΔQFR[‡]	–0.024 ± 0.090	–0.008 ± 0.070	0.023
Functional restenosis[§], n (%)	26 (10.0)	25 (4.7)	0.004

Values are presented as the mean ± standard deviation and median (interquartile range). AS, area stenosis; BFR, blood flow resistance; DS, diameter stenosis; LAD, left anterior descending artery; LCX, left circumflex artery; LLL, late lumen loss; LM, left main artery; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; QFR, quantitative flow ratio; RCA, right coronary artery. [†]LLL was defined as the difference in MLD between post-PCI and follow up. [‡]ΔDS = follow-up DS – post-PCI DS; ΔAS = follow-up AS – post-PCI AS; ΔBFR = follow-up BFR – post-PCI BFR; ΔQFR = follow-up QFR – post-PCI QFR. [§]Functional restenosis was defined as the 1-year follow-up QFR <0.8.

QCA and QFR analysis

There was no significant difference in the post-PCI QCA results between the two groups. However, at the 1-year follow up, the minimal lumen diameter (1.74 ± 0.50 vs 1.83 ± 0.49, P = 0.012), DS% (32.82 ± 13.06 vs 29.25 ± 11.16, P < 0.001) and AS% (43.95 ± 18.61 vs 39.01 ± 16.85, P = 0.001) of the diabetes group were significantly worsened. The increases in DS % (4.44 ± 12.39 vs 1.65 ± 12.21, P = 0.007) and AS% (6.51 ± 17.68 vs 3.56 ± 18.45, P = 0.024) were also more obvious in the diabetes group (Table 2).

After successful revascularization, the post-PCI BFR (3.77 [0.58–24.08] vs 4.22 [0.61–20.00], P = 0.871) and QFR (0.95 ± 0.09 vs 0.96 ± 0.06, P = 0.292) of the two groups reached similar levels (Figure 2a,b). Nevertheless, the increase in BFR (2.09 [–0.67, 19.83] vs 0.65 [–3.60, 12.51], P = 0.004) and the follow-up BFR (12.37 [1.69–44.04] vs 6.15 [1.34–27.09], P = 0.009) were higher in the diabetes group. The diabetes group suffered more severe damage to the QFR value after 1 year (–0.024 ± 0.090 vs –0.008 ± 0.070, P = 0.023; Figure 3), which led to a lower follow-up QFR (0.93 ± 0.11 vs 0.96 ± 0.07, P < 0.001; Figure 2c). The incidence of functional restenosis within 1 year was significantly higher in the diabetes group (10.0% vs 4.7%, P = 0.004; Table 2). In addition, multivariable logistic regression analysis confirmed that diabetes (odds ratio [OR] 2.164, 95% confidence interval [CI] 1.210–3.870, P = 0.009) was independently associated with functional restenosis (Table 3).

Clinical outcomes

The diabetes group had a higher incidence of TVF (12.3% vs 4.5%, P < 0.001), which was mainly attributed to the higher incidence of target vessel revascularization (11.8% vs 4.5%, P < 0.001; Table 4). The independent correlates of TVF were diabetes (OR 2.654, 95% CI 1.405–5.012, P = 0.003), LDL-C (OR 2.680, 95% CI 1.163–6.177, P = 0.021) and QFR decline (OR 2.589, 95% CI 1.090–6.150, P = 0.031; Table 5).

DISCUSSION

The main highlights of the current study were as follows: (i) the up-and-coming functional assessment technology (QFR) was first applied in evaluating the effect of diabetes on coronary physiology; (ii) coronary physiology deterioration regarding

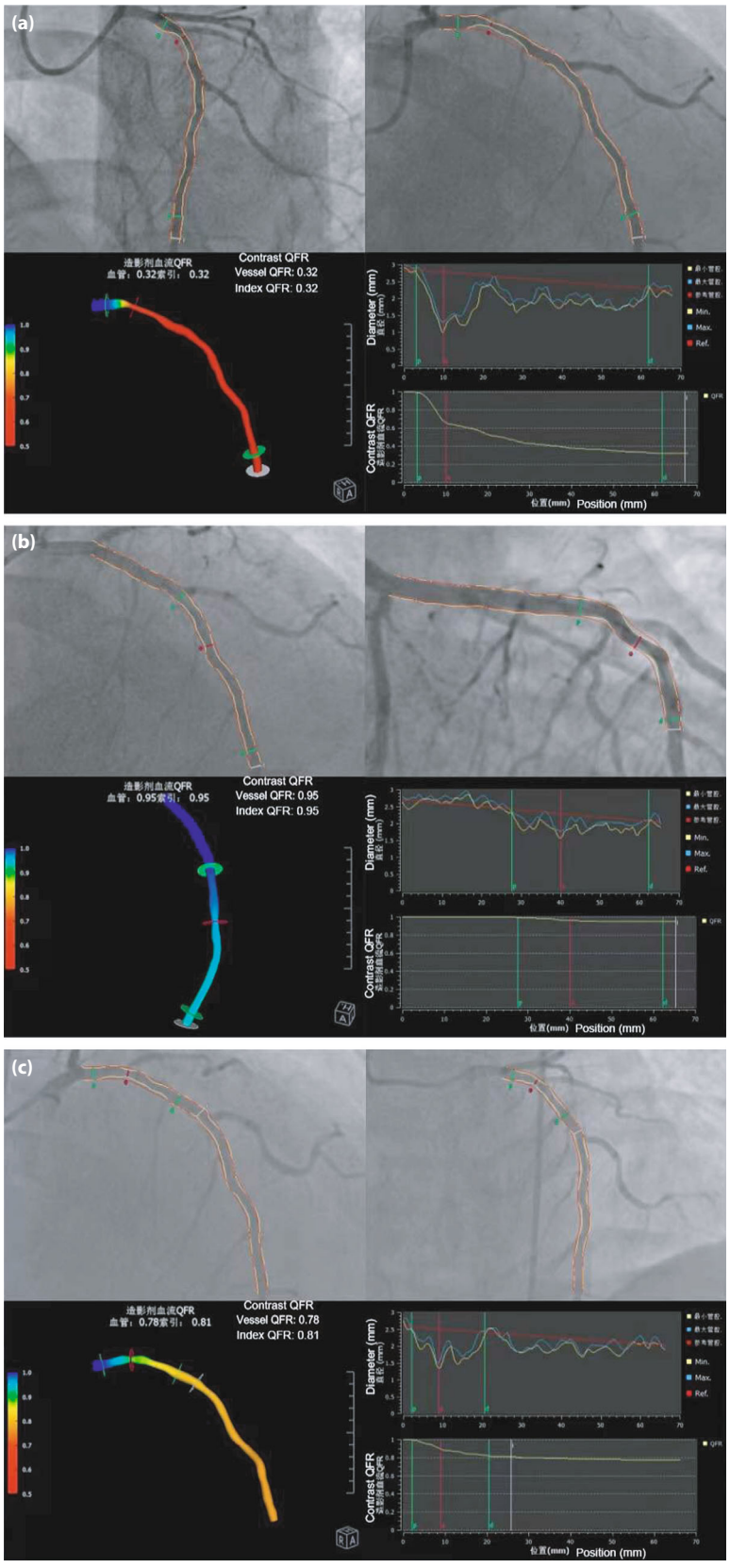

Figure 2 | An example of (a) pre-percutaneous coronary intervention, (b) post-percutaneous coronary intervention and (c) 1-year follow-up quantitative flow ratio (QFR) analysis in a diabetes patient with functional restenosis. Max, maximum lumen diameter; Min, minimum lumen diameter; Ref., reference lumen diameter.

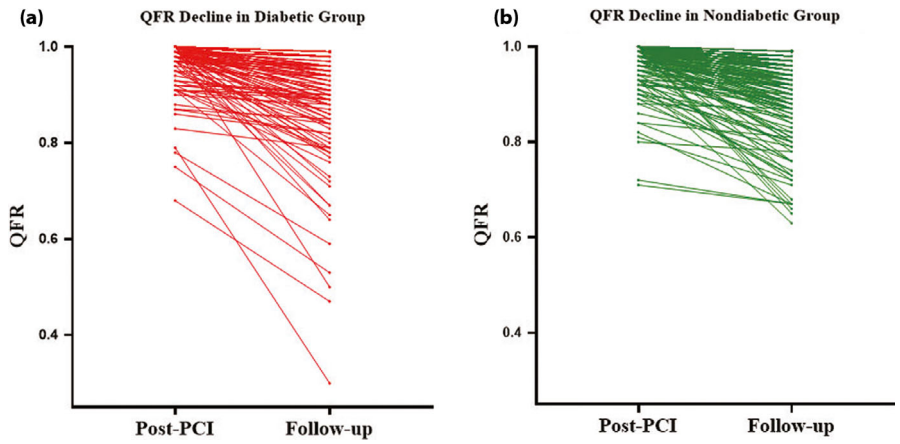

Figure 3 | Quantitative flow ratio (QFR) decline in the (a) diabetes group and (b) non-diabetes group. PCI, percutaneous coronary intervention.

Table 3 | Univariable and multivariable logistic regression analysis of factors for the functional restenosis

	Univariable OR (95% CI)	*P*-value	Multivariable OR (95% CI)	*P*-value
Age >60 years	0.707 (0.399–1.252)	0.235		
Male	1.370 (0.604–3.110)	0.451		
Smoking history	1.488 (0.817–2.712)	0.194		
Diabetes	2.248 (1.271–3.977)	0.005	2.164 (1.210–3.870)	0.009
Hypertension	1.834 (0.944–3.562)	0.074	1.657 (0.841–3.265)	0.144
Renal insufficiency	3.256 (1.188–8.928)	0.022	2.733 (0.978–7.639)	0.055
LDL-C ≥1.8 mmol/L at 1-year follow up	1.778 (0.897–3.526)	0.099	2.000 (0.998–4.008)	0.051
Previous PCI	0.994 (0.456–2.168)	0.988		
STEMI (≥7 days)	0.754 (0.347–1.639)	0.476		
E/e′ at first admission	1.000 (0.976–1.025)	0.977		

Functional restenosis was defined as a 1-year follow-up quantitative flow ratio (QFR) <0.8. LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 4 | Clinical outcomes at 1-year follow up

	Diabetes group (*n* = 211)	Non-diabetes group (*n* = 466)	*P*-value
TVF, *n* (%)	26 (12.3)	21 (4.5)	<0.001
Cardiovascular death, *n* (%)	0	0	/
MI, *n* (%)	2 (0.9)	1 (0.2)	0.183
TVR, *n* (%)	25 (11.8)	21 (4.5)	<0.001
Ischemia-driven revascularization†, *n* (%)	17 (8.1)	18 (3.9)	0.022

MI, myocardial infarction; TVF, target vessel failure. †Target vessel revascularization (TVR) in the patients with angina was thought to be ischemia-driven.

diabetes was confirmed by functional evidence from a 1-year coronary follow-up visit; and (iii) the reduction of physiological benefits from PCI was found to be associated with diabetes from the view of functional assessment.

It has been confirmed that the post-PCI QFR can evaluate the prognosis of PCI[26]. Both patients with and patients without diabetes in the present study were able to reach a satisfactory post-PCI QFR level after successful PCI (0.95 ± 0.09 vs 0.96 ± 0.06, $P = 0.292$); however, the 1-year follow-up QFR was lower (0.93 ± 0.11 vs 0.96 ± 0.07, $P < 0.001$), and the 1-year decrease in QFR was also more significant in diabetes patients (-0.024 ± 0.090 vs -0.008 ± 0.070, $P = 0.023$). These findings derived from functional assessment suggested that the physiological benefits from successful PCI would gradually

Table 5 | Univariable and multivariable logistic regression analysis of factors for the target vessel failure

	Univariable OR (95% CI)	*P*-value	Multivariable OR (95% CI)	*P*-value
Age >60 years	0.867 (0.460–1.635)	0.660		
Male	0.773 (0.361–1.655)	0.508		
Smoking history	1.072 (0.569–2.018)	0.830		
Diabetes	2.614 (1.397–4.893)	0.003	2.654 (1.405–5.012)	0.003
Hypertension	1.228 (0.628–2.402)	0.548		
Renal insufficiency	2.237 (0.647–7.731)	0.203		
LDL-C ≥1.8 mmol/L at 1-year follow-up	2.460 (1.078–5.618)	0.033	2.680 (1.163–6.177)	0.021
Previous PCI	1.728 (0.827-3.613)	0.146		
STEMI (≥7 days)	0.968 (0.439–2.136)	0.937		
E/e′ at first admission	1.006 (0.990–1.023)	0.471		
DS increase†	1.822 (0.918–3.614)	0.086	0.920 (0.367–2.302)	0.858
QFR decline‡	2.595 (1.358–4.959)	0.004	2.589 (1.090–6.150)	0.031

LDL-C, low-density lipoprotein cholesterol; STEMI, ST-segment elevation myocardial infarction; TVF, target vessel failure. †Diameter stenosis (DS) increase was defined as that follow-up DS was higher than post-percutaneous coronary intervention (PCI) DS. ‡Quantitative flow ratio (QFR) decline was defined as that follow-up QFR was lower than post-PCI QFR.

decline as time passed, especially in patients with diabetes. Although the differences in QFR values between the two groups seem small, they might bring some clinical significance. Studies have shown that QFR decline is closely related to myocardial ischemia, and a 0.01 or 0.05 decrease in the QFR value can increase the risk of myocardial ischemia by 1.1-fold and 2.14-fold, respectively[27,28]. The higher levels of follow-up E/e′ (14.72 ± 6.59 vs 12.62 ± 5.03, $P < 0.001$) and follow-up BFR (12.37 [1.69, 44.04] vs 6.15 [1.34, 27.09], $P = 0.009$) in the patients with diabetes reflected cardiac diastolic dysfunction and high microcirculation resistance, which might mean the existence of coronary microvascular dysfunction (CMD)[29]. Lee *et al.* found that CMD can increase FFR values[30]. The QFR is a derivative of the FFR, and QFR values are calculated by integrating all pressure drops along the stenotic segments[15]. CMD can increase BFR and reduce pressure losses, which might increase QFR values. Therefore, CMD might cause us to underestimate the difference in QFR values between diabetes and non-diabetes patients. In addition, the present results were just 1-year follow-up data from functional evaluations, and the gap between the patients with and without diabetes might have further widened as time went by.

Regarding the causes of accelerated QFR decline in the diabetes group, first, the changes in DS% and AS% in the diabetes patients meant that they had rapid progression atherosclerosis. Hyperglycemia, insulin resistance and hyperinsulinemia trigger a series of chain reactions and bidirectional effects, thereby accelerating the progression of atherosclerosis in patients with diabetes[31]. Second, although in the era of drug-eluting stents, patients with diabetes are still at high risk of excessive neointimal hyperplasia and in-stent restenosis[32], which might be another part of the reason for accelerated QFR decline in diabetes patients.

Although the current treatment strategy is optimized, diabetes is still associated with poor PCI effectiveness[33-35]. In line with previous findings, we found that the incidence of functional restenosis (10.0% vs 4.7%, $P = 0.004$) and TVF (12.3% vs 4.5%, $P < 0.001$) increased significantly in the diabetes group. Diabetes in our models also became an important risk factor to predict vessel-oriented outcomes, including functional restenosis (OR 2.164, 95% CI 1.210–3.870, $P = 0.009$) and TVF (OR 2.654, 95% CI 1.405–5.012, $P = 0.003$). Additionally, the present study found that QFR decline was an independent correlate of TVF (OR 2.589, 95% CI 1.090–6.150, $P = 0.031$), which was significantly superior to the DS% derived from QCA. In summary, the present data showed that diabetes can reduce the physiological benefit from PCI and lead to adverse clinical outcomes after PCI.

Therefore, more-stringent disease treatment and management should be advocated for CAD patients with diabetes. Given that coronary angiography cannot fully reflect the physiological significance of intermediate coronary stenosis, a functional assessment can provide a more comprehensive evaluation[10,11]. Thus, we believe that it makes sense to track the coronary physiology by the QFR during follow up to further guide treatment strategies after revascularization. Finally, intensive glucose control, dyslipidemia management and early follow up might contribute to the improvement of coronary physiology in such patients[5,36-38].

The present study still had some limitations. First, it was a retrospective single-center observational study with a small sample size, and further prospective multicenter cohort studies are required to verify the findings. Second, not all images were suitable for QFR analysis, which might have caused selection bias. In addition, we did not include patients with prediabetes, and not all non-diabetes patients were tested for glycated hemoglobin, which made it hard to assess their long-term glucose levels. Finally, we did not have information on adherence to medications.

From the perspective of functional evaluation, the QFR provides new evidence that diabetes correlates with an accelerated deterioration in coronary physiology, which can reduce the coronary physiological benefits from PCI and lead to a worse clinical outcome.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The protocol for this research project was approved by a suitably constituted ethics committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Union Hospital, Fujian Medical University, Approval No. 2020KY098.
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REFERENCES

1. Beckman JA, Creager MA. Vascular complications of diabetes. *Circ Res* 2016; 118: 1771–1785.
2. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. *Cardiovasc Diabetol* 2018; 17: 121.
3. Poznyak A, Grechko AV, Poggio P, *et al*. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. *Int J Mol Sci* 2020; 21: 1835.
4. Chandrasekhar J, Dangas G, Baber U, *et al*. Impact of insulin treated and non-insulin-treated diabetes compared to patients without diabetes on 1-year outcomes following contemporary PCI. *Catheter Cardiovasc Interv* 2020; 96: 298–308.
5. Lee CH, Choi S-W, Jun S-W, *et al*. Clinical impact of diabetes mellitus on 2-year clinical outcomes following PCI with second-generation drug-eluting stents; landmark analysis findings from patient registry: pooled analysis of the Korean multicenter drug-eluting stent registry. *PLoS One* 2020; 15: e0234362.
6. Koskinas KC, Siontis GCM, Piccolo R, *et al*. Impact of diabetic status on outcomes after revascularization with drug-eluting stents in relation to coronary artery disease complexity: patient-level pooled analysis of 6081 patients. *Circ Cardiovasc Interv* 2016; 9: e003255.
7. Farooq V, Serruys PW, Bourantas C, *et al*. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012; 33: 3105–3113.
8. Farooq V, Vergouwe Y, Räber L, *et al*. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. *Eur Heart J* 2012; 33: 3098–3104.
9. Sayadi M, Zibaeenezhad MJ, Safaei K, *et al*. Impact of type II diabetes and gender on major clinical events after percutaneous coronary intervention. *Prim Care Diabetes* 2021; 15: 347–351.
10. Fischer JJ, Samady H, McPherson JA, *et al*. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 2002; 90: 210–215.
11. Toth G, Hamilos M, Pyxaras S, *et al*. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 2014; 35: 2831–2838.
12. Toth GG, Johnson NP, Jeremias A, *et al*. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol* 2016; 68: 742–753.
13. Tonino PAL, De Bruyne B, Pijls NHJ, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360: 213–224.
14. Cesaro A, Gragnano F, Di Girolamo D, *et al*. Functional assessment of coronary stenosis: an overview of available techniques. Is quantitative flow ratio a step to the future? *Expert Rev Cardiovasc Ther* 2018; 16: 951–962.
15. Tu S, Westra J, Yang J, *et al*. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. *JACC Cardiovasc Interv* 2016; 9: 2024–2035.
16. Westra J, Andersen BK, Campo G, *et al*. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc* 2018; 7: e009603.
17. Xu BO, Tu S, Qiao S, *et al*. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol* 2017; 70: 3077–3087.
18. Westra J, Tu S, Winther S, *et al*. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II study (Wire-Free Functional Imaging II). *Circ Cardiovasc Imaging* 2018; 11: e007107.
19. Spitaleri G, Tebaldi M, Biscaglia S, *et al*. Quantitative flow ratio identifies nonculprit coronary lesions requiring revascularization in patients with ST-segment-elevation myocardial infarction and multivessel disease. *Circ Cardiovasc Interv* 2018; 11: e006023.
20. Xu BO, Tu S, Song L, *et al*. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a

multicentre, randomised, sham-controlled trial. *Lancet* 2021; 398: 2149–2159.
21. Tang J, Chu J, Hou H, *et al*. Clinical implication of QFR in patients with ST-segment elevation myocardial infarction after drug-eluting stent implantation. *Int J Cardiovasc Imaging* 2021; 37: 755–766.
22. Alberti KG, Definition ZPZ. diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
23. Windecker S, Kolh P, Alfonso F, *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; 35: 2541–2619.
24. Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018; 138: e618–e651.
25. Garcia-Garcia HM, McFadden EP, Farb A, *et al*. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Eur Heart J* 2018; 39: 2192–2207.
26. Ding D, Huang J, Westra J, *et al*. Immediate post-procedural functional assessment of percutaneous coronary intervention: current evidence and future directions. *Eur Heart J* 2021; 42: 2695–2707.
27. Smit JM, Koning G, van Rosendael AR, *et al*. Relationship between coronary contrast-flow quantitative flow ratio and myocardial ischemia assessed by SPECT MPI. *Eur J Nucl Med Mol Imaging* 2017; 44: 1888–1896.
28. Strähl M, Schindler M, Keller LS, *et al*. Diagnostic performance of angiography-based quantitative flow ratio for the identification of myocardial ischemia as assessed by (13)N-ammonia myocardial perfusion imaging positron emission tomography. *Int J Cardiol* 2020; 314: 13–19.
29. Adameova A, Dhalla NS. Role of microangiopathy in diabetic cardiomyopathy. *Heart Fail Rev* 2014; 19: 25–33.
30. Lee JM, Kim HK, Lim KS, *et al*. Influence of local myocardial damage on index of microcirculatory resistance and fractional flow reserve in target and nontarget vascular territories in a porcine microvascular injury model. *JACC Cardiovasc Interv* 2018; 11: 717–724.
31. Haas AV, McDonnell ME. Pathogenesis of cardiovascular disease in diabetes. *Endocrinol Metab Clin North Am* 2018; 47: 51–63.
32. Yang CD, Shen Y, Lu L, *et al*. Visit-to-visit HbA(1c) variability is associated with in-stent restenosis in patients with type 2 diabetes after percutaneous coronary intervention. *Cardiovasc Diabetol* 2020; 19: 133.
33. Hwang D, Lee JM, Yang S, *et al*. Role of post-stent physiological assessment in a risk prediction model after coronary stent implantation. *JACC Cardiovasc Interv* 2020; 13: 1639–1650.
34. Lee JM, Choi KH, Koo B-K, *et al*. Comparison of major adverse cardiac events between instantaneous wave-free ratio and fractional flow reserve-guided strategy in patients with or without type 2 diabetes: a secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2019; 4: 857–864.
35. Van Belle E, Cosenza A, Baptista SB, *et al*. Usefulness of routine fractional flow reserve for clinical management of coronary artery disease in patients with diabetes. *JAMA Cardiol* 2020; 5: 272–281.
36. Kassaian SE, Goodarzynejad H, Boroumand MA, *et al*. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. *Cardiovasc Diabetol* 2012; 11: 82.
37. Nozue T, Yamamoto S, Tohyama S, *et al*. Statin treatment for coronary artery plaque composition based on intravascular ultrasound radiofrequency data analysis. *Am Heart J* 2012; 163: 191–199.e1.
38. Chen L, Chen Q, Zhong J, *et al*. Effect of low-density lipoprotein cholesterol goal achievement on vascular physiology evaluated by quantitative flow ratio in patients who underwent percutaneous coronary intervention. *Front Cardiovasc Med* 2021; 8: 679599.