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 CAD1–3. 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 PCI4–9. 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 angiography10,11. Fractional flow reserve (FFR) is currently recognized as the gold standard for making revascularization...
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\textsuperscript{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\textsuperscript{15}. The accuracy of QFR compared with the FFR was confirmed by previous landmark studies\textsuperscript{15-19}; furthermore, the recent trial “Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous InterVention in Patients with CORonary Artery Disease : FAVOR III China” confirmed that the QFR-guided strategy of PCI can improve clinical outcomes\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{24}. 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\textsuperscript{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\textsuperscript{24}. Target vessel failure (TVF) was defined as the composite of cardiovascular death, target vessel-related MI and target vessel revascularization\textsuperscript{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\textsuperscript{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 χ²-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/e₀ 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-up.
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 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      |
| HbA1c (%)                | 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      |
| HbA1c (%)                | 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      |
| \( \Delta E/e' \)       | 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; HbA1c, glycated hemoglobin A1c; 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. \( \Delta E/e' = \) follow-up \( E/e' \) – Pre-PCI \( E/e' \).
1-year follow-up

Target vessel

|                     | Diabetes group (n = 261) | Non-diabetes group (n = 533) | P-value |
|---------------------|--------------------------|------------------------------|---------|
| 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 1.405–4.994, 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.
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. 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 decline over time.

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

|                          | Univariable | Multivariable |
|--------------------------|-------------|---------------|
|                          | OR (95% CI) | P-value       | OR (95% CI)   | P-value       |
| Age >60 years            | 0.707 (0.399–1.252) | 0.235 | 2.164 (1.210–3.870) | 0.009 |
| 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 | 2.248 (1.271–3.977) | 0.005 |
| 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.

Figure 3 | Quantitative flow ratio (QFR) decline in the (a) diabetes group and (b) non-diabetes group. PCI, percutaneous coronary intervention.
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. 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). Lee et al. found that CMD can increase FFR values. The QFR is a derivative of the FFR, and QFR values are calculated by integrating all pressure drops along the stenotic segments. 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. 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, 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. 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. 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.

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.

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