

Quantitative flow ratio-guided surgical intervention in symptomatic myocardial bridging

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Abstract

Background: *Patients with myocardial bridging (MB) are associated with adverse cardiovascular events, but a decision to perform surgical intervention, especially for patients with systolic intermediate stenosis, is a difficult clinical issue. Fractional flow reserve (FFR) represents a novel method for the functional evaluation of coronary stenosis, but the relationship between FFR and MB remains controversial because of the cyclic dynamic stenosis of MB. Quantitative flow ratio (QFR) is a novel index allowing fast assessment of FFR from a diagnostic coronary angiography. This study aimed to investigate the relationship between QFR and MB patients and to further develop a prediction model of QFR-guided surgical intervention for these patients.*

Methods: *Forty-five symptomatic lone MB patients who had undergone coronary angiography were consecutively enrolled in this study. MB was located in the middle of left anterior descending artery with intermediate stenosis during systole. The patients were retrospectively divided into a medical therapy group or a surgical therapy group. Systolic geometry based QFR (SG-QFR) and diastolic geometry based QFR (DG-QFR) were calculated based on three-dimensional quantitative coronary angiography and patient-specific flow velocity. Subsequently, time-averaged QFR (TA-QFR) is defined as the average of SG-QFR and DG-QFR.*

Results: *Receiver operating characteristic curve analysis revealed that TA-QFR (AUC = 0.91; 95% CI: 0.79–0.98) was found to be the best pre-operative index for surgical intervention to MB, when compared with DG-QFR (AUC = 0.69; 95% CI: 0.53–0.82; difference: 0.22; 95% CI: 0.04–0.41; $p = 0.02$) and SG-QFR (AUC = 0.87; 95% CI: 0.74–0.95; difference: 0.04; 95% CI: 0.00–0.08; $p = 0.03$).*

Conclusions: *TA-QFR improved the performance of functional evaluation in MB patients with intermediate stenosis during systole and is useful for guiding surgical intervention. (Cardiol J XXXX; XX, X: xx–xx)*

Key words: quantitative flow ratio, surgical intervention, myocardial bridging

Introduction

Myocardial bridging (MB) is a band of myocardial tissue, under which a segment of the coronary

artery running in the epicardial tissue. The characteristic angiographic appearance of MB shows systolic narrowing of the artery with relatively normal vessel diameter during diastole. MB has once been

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considered as a benign condition. However, recent studies have suggested that MB was associated with myocardial ischemia, atrioventricular block, arrhythmias, and even sudden cardiac death [1–3]. Therefore, an effective assessment model is desirable for clinical decision making in patients with MB, especially when coupled with intermediate stenosis during systole.

The concept of the fractional flow reserve (FFR) was developed by Pijls in 1995 [4]. The measurement of FFR is increasingly used to evaluate the functional significance of coronary stenosis and it was demonstrated to be a good performance [5]. However, because of potential limitations of conventional FFR, like time-consuming, high expense, and other factors, utilization of FFR worldwide make it a poor choice, in general, with a few exceptions [6]. Quantitative flow ratio (QFR) is a novel index allowing a quick assessment of FFR from a diagnostic coronary angiography, which has the potential to resolve the limitations of FFR, as mentioned above [7–9]. Due to the cyclical, dynamic nature of stenosis in MB patients (dynamic compression of the coronary artery extending from the systole into the diastole), using the conventional QFR computation is not adequate in evaluating MB [10]. On the other hand, QFR can be computed from specific stenotic geometry during cardiac cycle. The objective of this study was to demonstrate that a combination of QFR computations at different cardiac phases could be used to predict patients with MB who require surgical intervention.

Methods

Study design

This was a retrospective and observational study. Symptomatic lone MB patients who had undergone coronary angiography were included. All patients were given optimal doses of beta-blockers (BB) and calcium channel blockers (CCB). During follow-up, if medical therapy was not adequate to relieve symptoms of patients with MB, then coronary artery bypass grafting or surgical myotomy was performed. The other patients were continued on medical therapy. So, the patients were divided into two groups: the medical therapy group or the surgical therapy group. An overview of the study design is demonstrated in Figure 1. It was hypothesized that a combination of QFR computations at different cardiac phases can be used to predict

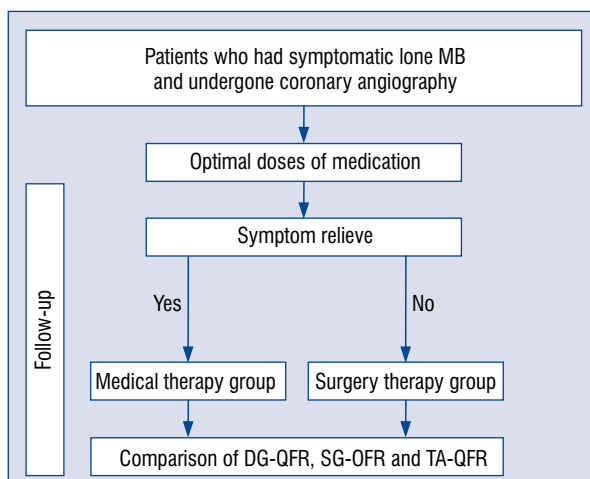


Figure 1. Overview of the study design; MB — myocardial bridging; SG-QFR — systolic geometry based quantitative flow ratio; DG-QFR — diastolic geometry based quantitative flow ratio; TA-QFR — time-averaged quantitative flow ratio.

patients with MB who require surgical intervention. The study protocol was approved by the ethics committee of the documented hospital.

Study population

A total of 45 symptomatic lone MB patients who underwent invasive coronary angiography at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, from September 2016 to January 2019, were consecutively enrolled in this study. Inclusion criteria were: 1) age > 18 years; 2) all patients were diagnosed with MB in a catheterization laboratory. The characteristic angiographic appearance of MB includes systolic narrowing or the so called “milking effect” of the artery with a relatively normal vessel diameter during the diastolic period; 3) MB patients who were identified as having systolic stenosis in mid-left anterior descending coronary artery segment; 4) the MB in all patients had intermediate stenosis during systole (defined by a percent diameter stenosis 50% to 90% during systole by visual estimation); 5) all patients were given optimal doses of BB and CCB with the objective of relieving symptoms and signs of myocardial ischemia; 6) two angiographic projections > 25° apart were recorded by flat-panel X-ray systems; 7) nitroglycerine was given prior to the angiographic acquisitions. Exclusion criteria were: 1) overlap or foreshortening (> 90%) between nearby vessels in invasive coronary angiography (ICA) images; 2) poor ICA image quality.

Invasive coronary angiography image acquisition, geometrical reconstruction and QFR computation

Angiographic images were recorded at 15 frames/s by monoplane X-ray systems (Innova 2100, GE). ICA images were analyzed by an experienced analyst who had been trained in three-dimensional quantitative coronary angiography (3D QCA) and QFR. Angiographic projections with minimal overlap and foreshortening were selected, then 3D geometrical reconstruction was performed and QFR was computed, using a prototype software package (QAngio XA 3D prototype, Medis special bv, Leiden, the Netherlands) [8]. Angiographic views at end-systolic and end-diastolic phases were selected and the interrogated vessel was reconstructed at both end-systolic and end-diastolic phases. Subsequently, the systolic geometry based QFR (SG-QFR) and diastolic geometry based QFR (DG-QFR) were derived using patient-specific flow velocity and a recently developed QFR computational algorithm [8, 11]. Vessel QFR at the most distal position of the reconstructed vessel was used. The time-averaged QFR (TA-QFR) is defined as the average of SG-QFR and DG-QFR.

Statistical analysis

Normally distributed continuous variables are expressed as mean \pm standard deviation or as median if abnormally distributed, whereas categorical variables are expressed as percentages. Clinical characteristics data were collected per-patient and remaining calculations were on a per-vessel basis. The performance of TA-QFR, SG-QFR and DG-QFR in predicting lesions was assessed by using accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) together with their 95% confidence intervals (CIs), then by making a comparison between prognostic performance of TA-QFR, SG-QFR and DG-QFR. Receiver-operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated. The Youden index was used as a criterion to identify the optimal cutoff value for TA-QFR, SG-QFR and DG-QFR in predicting surgical intervention. Paired comparisons in ROC curves were performed by the DeLong method using MedCalc (version 13.0, MedCalc Software BVBA, Ostend, Belgium). Comparisons between the two groups were performed using the Student t-test with IBM SPSS (version 19.0, Armonk, New York). $p < 0.05$ was considered to be statistically significant.

Results

Patient baseline clinical and stenosis characteristics

A total of 45 symptomatic MB patients with intermediate stenosis during systole were consecutively included. Twenty (44.4%) patients remained symptomatic despite optimal doses of BB or CCB. No major cardiac events were observed and all patients were asymptomatic during follow-up in both groups. Patient baseline clinical characteristics are listed in Table 1. There were no statistically significant differences between the two groups regarding patient clinical characteristics. Stenosis characteristics are listed in Table 2. At the end-diastolic phase, interrogated vessels had an average percent diameter stenosis (DS%), minimum lumen diameter (MLD), reference vessel diameter and minimum lumen area (MLA) of $26.1 \pm 6.7\%$ vs. $33.2 \pm 11.5\%$ ($p = 0.02$), 1.57 ± 0.29 mm vs. 1.55 ± 0.29 mm ($p = 0.80$), 2.20 ± 0.40 mm vs. 2.36 ± 0.27 mm ($p = 0.12$), 2.07 ± 0.81 mm² vs. 2.22 ± 0.79 mm² ($p = 0.52$) for the medical therapy group compared with the surgical therapy group whereas at the end-systolic phase, the same vessels interrogated had an average DS%, MLD, reference vessel diameter and MLA of $41.4 \pm 9.1\%$ vs. $57.3 \pm 9.5\%$ ($p = 0.00$), 1.29 ± 0.30 mm vs. 1.02 ± 0.19 mm ($p = 0.00$), 2.20 ± 0.40 mm vs. 2.41 ± 0.29 mm ($p = 0.05$), 1.52 ± 0.61 mm² vs. 1.13 ± 0.40 mm² ($p = 0.02$) during systole between two groups, respectively. Representative examples of X-ray angiography, 3D angiographic reconstruction and computation of QFR are shown in Figures 2 and 3.

Computation of QFR

The computed QFR values are listed in Table 3. DG-QFR between the two groups was 0.96 ± 0.02 vs. 0.93 ± 0.06 ($p = 0.03$) and SG-QFR between the two groups was 0.89 ± 0.07 vs. 0.74 ± 0.10 ($p = 0.00$). TA-QFR between the two groups was 0.92 ± 0.03 vs. 0.83 ± 0.06 ($p = 0.00$).

Accuracy of TA-QFR for diagnostic performance

TA-QFR had a greater area under the curve (AUC = 0.91; 95% CI 0.79–0.98), when compared with DG-QFR (AUC = 0.69; 95% CI 0.53–0.82]; difference: 0.22; 95% CI 0.04–0.41; $p = 0.02$) and SG-QFR (AUC = 0.87; 95% CI 0.74–0.95; difference: 0.04; 95% CI 0.00–0.08; $p = 0.03$) (Fig. 4). From the ROC curve, the best cutoff value for

Table 1. Patient baseline clinical characteristics (n = 45).

Risk factors	Medical therapy group (n = 25)	Surgical therapy group (n = 20)	P
Age [years]	59.16 ± 9.67	55.80 ± 7.61	0.21
Female, sex	14 (25%)	6 (20%)	0.08
Body mass index [kg/m ²]	23.35 ± 3.70	24.59 ± 2.87	0.22
History of blood pressure	5 (24%)	3 (21%)	0.86
Diabetes	3 (24%)	5 (21%)	0.55
Hypercholesteremia	3 (24%)	3 (21%)	1.00
Smoking	7 (24%)	5 (21%)	0.69
EuroSCORE	0.64 ± 0.12	0.62 ± 0.16	0.58
Percent of medical therapy:			
Beta-blocker	18 (25%)	14 (20%)	0.88
Dose/day [mg]	36.94 ± 12.14	33.93 ± 12.20	0.49
CCB	7 (25%)	6 (20%)	0.88
Dose/day [mg]	62.50 ± 22.57	67.50 ± 23.35	0.55
Time (follow-up) [months]	22.76 ± 10.30	23.15 ± 8.53	0.89

Variables are in number (%), mean ± standard deviation; CCB — calcium channel blocker

Table 2. Baseline lesion characteristics (n = 45).

Baseline lesion characteristics	Diastole			Systole		
	Medical therapy group	Surgical therapy group	P	Medical therapy group	Surgical therapy group	P
Percent diameter stenosis	26.1 ± 6.7	33.2 ± 11.5	0.02	41.4 ± 9.1	57.3 ± 9.5	0.00
Minimum lumen diameter [mm]	1.57 ± 0.29	1.55 ± 0.29	0.80	1.29 ± 0.30	1.02 ± 0.19	0.00
Reference vessel diameter [mm]	2.20 ± 0.40	2.36 ± 0.27	0.12	2.20 ± 0.40	2.41 ± 0.29	0.06
Minimum lumen area [mm ²]	2.07 ± 0.81	2.22 ± 0.79	0.52	1.52 ± 0.61	1.13 ± 0.40	0.02

Variables are mean ± standard deviation. Anatomical parameters were quantified by three-dimensional quantitative coronary.

TA-QFR in predicting patients requiring surgical therapy was found at 0.88. This resulted in a better diagnostic performance, with an accuracy of 89%, sensitivity of 85%, specificity of 92%, PPV of 90%, and NPV of 89%. Applying a cutoff value of 0.88 to TA-QFR resulted in 23 true positives, 17 true negatives, 2 false positives, and 3 false negatives. The diagnostic performance of TA-QFR vs. DG-QFR, and SG-QFR was listed in Table 4.

Discussion

The main findings of the present study are: 1) TA-QFR is a novel index to assess patients with MB; 2) TA-QFR has a higher value in predicting MB patients who require surgical intervention,

when compared with DG-QFR and SG-QFR; 3) The optimal cut-off value of TA-QFR in predicting MB patients who require surgical intervention was 0.88, with an overall accuracy of 89%, sensitivity of 85%, specificity of 92%, PPV of 90%, and NPV of 89%, respectively.

Myocardial bridging is a congenital coronary anomaly, and the incidence of MB is highest in the left anterior descending coronary artery [12]. MB appears as systolic compression by invasive coronary with relatively normal vessel diameter during diastole. It has been acknowledged that MB can influence dynamic nature of coronary arteries. Furthermore, some studies showed that myocardial vessel compression existed not only in systole but was also persistent during diastole [13]. In some

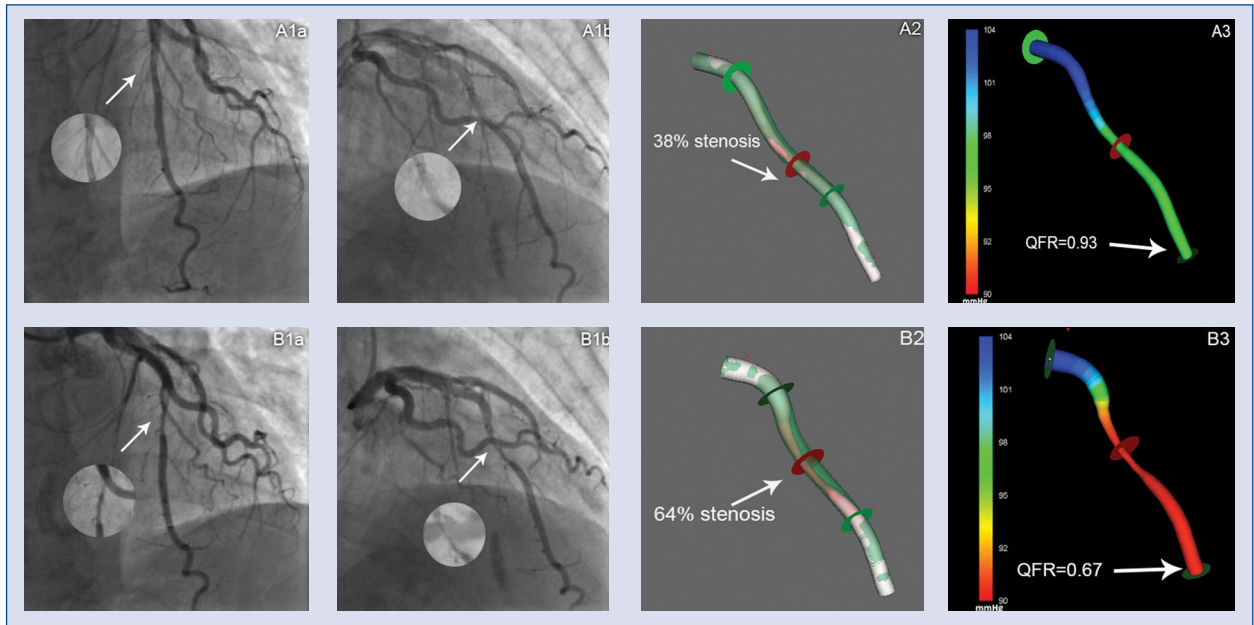


Figure 2. Three-dimensional angiographic reconstruction and computation of quantitative flow ratio (QFR) in the surgical therapy group; **A1a, A1b.** X-ray angiographic projections at end-diastolic phase; **B1a, B1b.** X-ray angiographic projections at end-systolic phase; **A2.** Diastolic geometry reconstructed from panel 1a and panel 1b; **B2.** Systolic geometry reconstructed from panel B1a and panel B1b; **A3.** DG-QFR computed from the diastolic geometry; **B3.** SG-QFR computed from the systolic geometry.

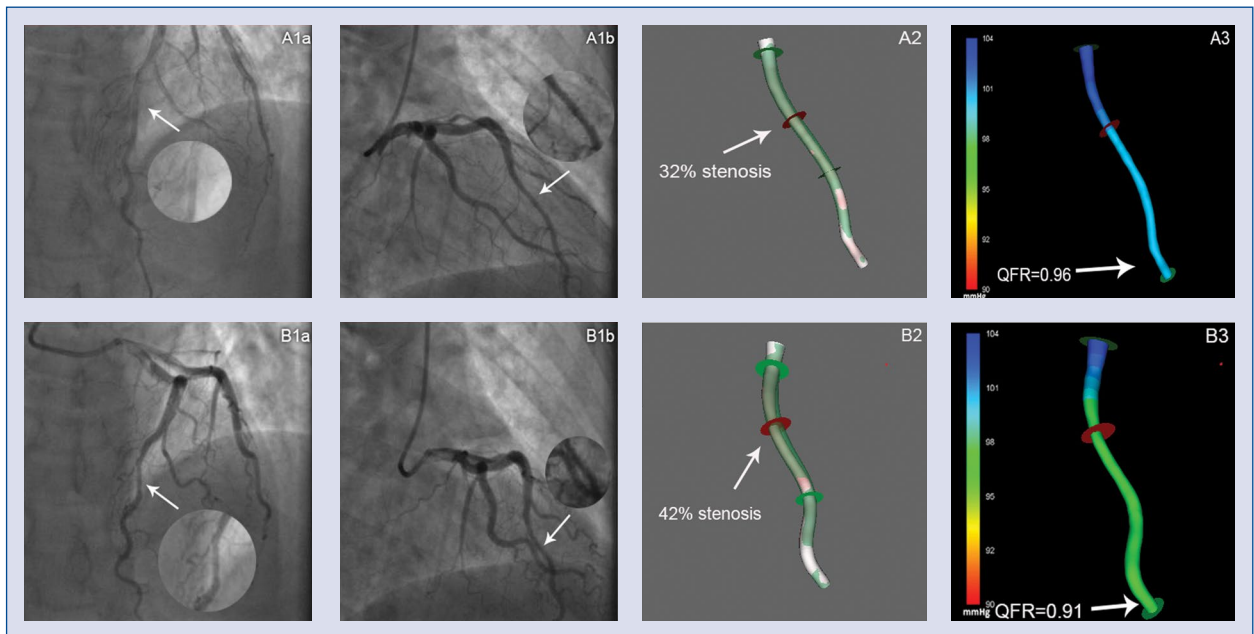


Figure 3. Three-dimensional angiographic reconstruction and computation of quantitative flow ratio (QFR) in the medical therapy group; **A1a, A1b.** X-ray angiographic projections at end-diastolic phase; **B1a, B1b.** X-ray angiographic projections at end-systolic phase; **A2.** Diastolic geometry reconstructed from panel 1a and panel 1b; **B2.** Systolic geometry reconstructed from panel B1a and panel B1b; **A3.** DG-QFR computed from the diastolic geometry; **B3.** SG-QFR computed from the systolic geometry.

studies, and case reports, it was associated with cardiac ischemia, angina, arrhythmias, or even sudden death [14, 15]. However, the optimal ap-

proach to assess MB by coronary angiography as well as by FFR remains unclear, due to the cyclic dynamic stenosis of MB [16]. Therefore, MB of-

Table 3. Quantitative flow ratio (QFR) between the two groups (n = 45).

QFR	Medical therapy group	Surgical therapy group	P
DG-QFR	0.96 ± 0.02	0.93 ± 0.06	0.03
SG-QFR	0.89 ± 0.07	0.74 ± 0.10	0.00
TA-QFR	0.92 ± 0.03	0.83 ± 0.06	0.00

Variables are mean ± standard deviation. SG-QFR — systolic geometry based QFR; DG-QFR — diastolic geometry based QFR; TA-QFR — time-averaged QFR

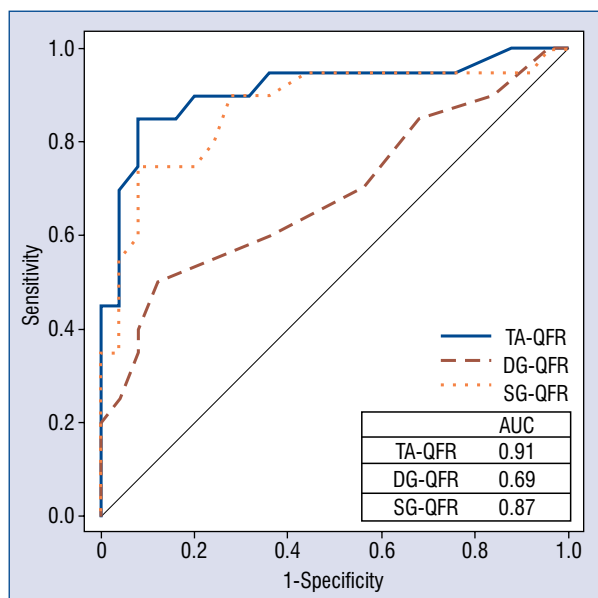


Figure 4. Receiver operating characteristic (ROC) curves for the discrimination of functionally significant stenosis. ROC curves compare sensitivity and specificity of TA-QFR versus DG-QFR (p = 0.02) and SG-QFR (p = 0.03) for the prediction of surgical intervention for myocardial bridging patients; SG-QFR — systolic geometry based quantitative flow ratio; DG-QFR — diastolic geometry based quantitative flow ratio; TA-QFR — time-averaged quantitative flow ratio.

ten causes clinical dilemmas, which widely raise concerns [17].

Fractional flow reserve has been recommended as class IA evidence for identifying hemodynamically significant coronary lesions when evidence of myocardial ischemia is unavailable according to the European Society of Cardiology guidelines and is increasingly applied in clinical settings for the time being [18, 19]. However, the adoption of conventional FFR is limited due to aforementioned practical drawbacks. QFR emerges as a novel, fast,

Table 4. Diagnostic performance of quantitative flow ratio (QFR) and three-dimensional quantitative coronary angiography anatomical indices.

	TA-QFR ≤ 0.88	DG-QFR ≤ 0.93	SG-QFR ≤ 0.78
Accuracy	89 (80–98)	71 (58–84)	84 (73–96)
Sensitivity	85 (62–97)	50 (27–73)	75 (51–91)
Specificity	92 (74–99)	88 (69–98)	92 (74–99)
PPV	90 (69–97)	77 (51–91)	88 (66–97)
NPV	89 (73–96)	69 (58–78)	82 (68–91)

Values are number (95% confidence interval). SG-QFR — systolic geometry based QFR; DG-QFR — diastolic geometry based QFR; TA-QFR — time-averaged QFR; PPV — positive predictive value; NPV — negative predictive value

non-invasive method for the assessment of FFR, which based on patient-specific flow velocity and a coronary geometric model, shows good correlation and agreement with pressure-derived FFR, with a diagnostic accuracy of 86% (95% CI 78% to 93%) [8, 20].

Fractional flow reserve assessment of MB has caused longstanding concerns. It has been reported that diagnostic functional severity of MB was facilitated after inotropic stimulation, which can increase vessel compression in MB [21]. Escaned demonstrated that a combination of diastolic FFR with dobutamine being chosen as an inotropic challenge among patients with MB, improved the assessment of myocardial ischemia. However, the significance of dobutamine testing for clinical decision-making remained unclear and the acquisition of diastolic FFR was a sophisticated procedure with measuring errors [10, 22]. Moreover, limited application of conventional FFR was found among patients with MB, as time-consuming, side effects associated with vasodilator administration, higher expense, etc. Conventional FFR is inadequate for MB assessment since cyclic dynamic stenosis during cardiac cycle, results in an underestimation of functional stenosis severity of MB [10, 23]. Therefore, a reasonable FFR-guided assessment model is demanded for guiding therapeutic strategies of patients with symptomatic lone MB.

In the present study, SG-QFR, DG-QFR was calculated for each patient and geometric models were reconstructed at the end-systolic phase and at the end-diastolic phase, respectively. As the existence of cyclic dynamic stenosis, that is, systolic compression and diastolic are relatively normal, hemodynamic significance might be overestimated or underestimated in the systolic phase or dias-

tolic phase. FFR measurement during the diastolic phase seems inadequate for MB assessment [10]. However, QFR computation was not done during the whole systolic phase nor the diastolic phase. Thus, computational deviation cannot be neglected. TA-QFR, unlike conventional FFR which is measured during the whole cardiac cycle, and is defined as the average of SG-QFR and DG-QFR, can both consider the systolic phase and the diastolic phase and then compensate for the downsides of SG-QFR, DG-QFR. As shown in Figure 4, AUC was significantly higher for TA-QFR (AUC = 0.91; 95% CI 0.79–0.98) compared with DG-QFR (AUC = 0.69; 95% CI 0.53–0.82) and SG-QFR (AUC = 0.87; 95% CI 0.74–0.95]. So TA-QFR can improve the performance of a functional evaluation in MB patients with intermediate stenosis during systole, with an accuracy of 89% (SG-QFR \leq 0.88) and shows the superiority of TA-QFR over other conventional methods for the assessment of patients with MB who require surgical intervention with an optimal cut-off value of 0.88.

Conclusions

The time-averaged QFR improved the performance of functional evaluation in MB patients with intermediate stenosis during systole and is useful for guiding surgical intervention.

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