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Clinical applications of fractional flow reserve in bifurcation lesions

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Abstract

Percutaneous coronary intervention (PCI) for coronary bifurcation lesions has been associated with lower procedural success rates and worse clinical outcomes compared with PCI for simple coronary lesions. Angiographic evaluation alone is sometimes inaccurate and does not reflect the functional significance of bifurcation lesions. The fractional flow reserve (FFR) is an easily obtainable, reliable, and reproducible physiologic parameter. This parameter is epicardial lesion specific and reflects both degree of stenosis and the myocardial territory supplied by the specific artery. Recent studies have shown that FFR-guided provisional side branch intervention strategy for bifurcation lesions is feasible and effective and can reduce unnecessary complex interventions and related complications. However, an adequate understanding of coronary physiology and the pitfalls of FFR is essential to properly use FFR for PCI of complex bifurcation lesions.

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1 Introduction

Coronary bifurcation lesions have been one of the most challenging lesion subsets in the field of percutaneous coronary intervention (PCI). Bifurcation intervention is associated with higher procedural cost, higher complication rate, higher restenosis rate and worse outcomes when compared with PCI of simple coronary artery lesions.[1–4] The provisional side branch (SB) interventional strategy is preferred for most bifurcation lesions as most previous studies have failed to show the benefit of systematic two stenting over this strategy.[3–7]

Though there have been many studies about how to treat bifurcation lesions, it is still not clear which SB should be treated and how the functional significance of these lesions ought to be assessed. Although various angiographic or flow criteria are currently used for the decision of SB intervention, there is no validated criteria yet. Furthermore, angiographic assessment of bifurcation lesions is sometimes inaccurate because of the innate limitations of angiography. Therefore, a more physiologic and standardized measurement modality is required for better evaluation in the treatment of bifurcation lesions.

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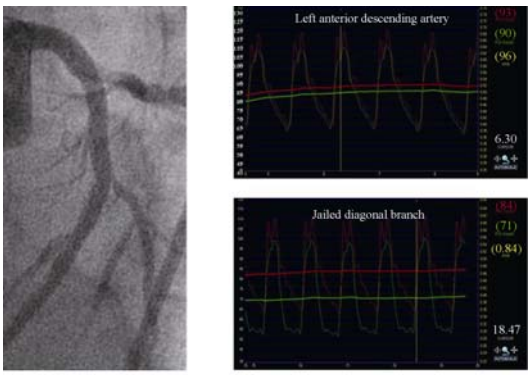
2 What is fractional flow reserve (FFR)?

FFR is a parameter that defines the physiologic significance of a coronary artery stenosis and is the ratio of maximal blood flow in a stenotic artery to normal maximal flow.[8] Since the resistance is minimal under maximal hyperemia and the venous pressure is negligible compared to coronary arterial pressure, FFR can be simply calculated as the ratio of distal coronary pressure (Pd) to proximal aortic pressure (Pa) (Figure 1). It can be easily determined during coronary angiography by calculating the fraction of distal coronary pressure measured with a coronary pressure wire to aortic pressure measured simultaneously with the guide catheter as shown in Figure 1.

FFR is an epicardial lesion-specific physiologic parameter reflecting both the degree of stenosis and the myocardial territory supplied by the specific artery.[8–12] This parameter is nearly independent of hemodynamic conditions such as heart rate, blood pressure, and myocardial contractility.[11] In a study by Pijls *et al*.,[8] an FFR value of 0.75 or less almost invariably identified ischemia-causing coronary artery stenoses with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). Considering the presence of a grey zone (0.75–0.80) and the results of the FAME study,[13] an FFR cutoff value of 0.8 has become more popular in recent days. An FFR-guided revascularization strategy has been validated in various lesion subsets. In the DEFER study, the rate of cardiac death or myocardial infarction in the DEFER group according to



$$FFR=\frac{Q^{S}max}{Q^{N}max}=\frac{(Pd-Pv)/R}{(Pa-Pv)/R}=\frac{Pd}{Pa}$$

Figure 1. Concept and measurement of fractional flow reserve (FFR). $Q^{S}max$: hyperaemic myocardial blood flow in the presence of a stenosis; $Q^{N}max$: normal hyperaemic myocardial blood flow; Pd: distal coronary pressure; Pa: aortic pressure; Pv: venous pressure; R: hyperaemic myocardial resistance.

FFR was < 1% per year.[14] In patients with multivessel disease, an FFR-guided revascularization strategy improved the outcomes of patients and saved cost compared to an angiography-guided strategy.[13,15,16] Therefore, FFR-guided PCI was graded as a class I (level of evidence A) indication in 2010 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines when objective evidence of vessel-related ischemia was not available.[17]

3 FFR before bifurcation intervention

Best clinical practice suggests that revascularization procedures should be based not only on the coronary anatomy but also on the presence of myocardial ischemia.[18,19] Angiographic assessment of the severity of a bifurcation lesion is sometimes difficult due to the inherent limitations of angiography such as vessel overlap, angulation and foreshortening.[20] Therefore, visual estimation of the bifurcation lesion by angiography can be inaccurate to predict the true anatomical or functional significance of the bifurcation lesion. Other invasive anatomical assessment tools such as intravascular ultrasound (IVUS) and optical coherence tomography can provide detailed anatomical information, but they still have limitations in assessment of the functional significance of a stenosis.[21–24] Previous studies showed that there can be discrepancies between anatomical parameters and functional significance in ostial lesions.[20,25] When FFR and IVUS parameters were compared in pure SB ostial lesions in a study by Koh, *et al*.,[25] an IVUS minimal luminal area (1.8 mm^2) and percent plaque burden (56%) had negative predictive values of 82% and 89% to determine the functional significance, but their positive predictive values were only 50% and 44%, respectively. This limitation of anatomical evaluation seems to be natural considering the variability in vessel size or myocardial territory of SB and the influence of vessel remodeling.

In contrast, the functional significance of a bifurcation lesion and the need for revascularization can be reliably assessed by FFR as this physiologic parameter reflects the interaction between the anatomic stenosis and the area of perfusion. Current pressure wires have a similar handling profile to conventional angioplasty guidewires; therefore, FFR can be easily measured in bifurcation lesions both before and after the intervention. However, when FFR of a SB lesion is measured, the influence of proximal and distal stenotic lesions should be taken into account. If a significant stenosis exists at the proximal main branch (MB), SB FFR overestimates the functional severity of the SB lesion due to pressure decrease by the proximal stenosis. On the contrary, if a significant stenosis exists distal to a SB ostial lesion and FFR was measured before that stenosis, FFR underestimates the lesion severity by submaximal flow through the SB ostial lesion by the distal lesion.[26] Therefore, when pre-intervention SB FFR is measured and is significant, the pullback pressure recording during sustained hyperemia should be performed along the length of a coronary artery to assess the functional significance of the SB lesion and to determine the necessity for intervention (Figure 2). In a pure SB ostial lesion, significant pressure step-up occurs only at the SB ostium. However, when SB plaque is connected to the plaque of a proximal MB, it is impossible to discriminate the influence of the MB lesion on SB FFR. Therefore, when SB FFR was measured, the following aspects need to be considered: clinical relevance of a SB compared to a MB, influence of MB plaque and distal SB plaque and the inability of pre-intervention SB FFR to predict jailed SB FFR.

4 FFR after MB stenting

A SB ostial lesion is generally aggravated after MB stenting (SB jailing). This phenomenon occurs due to the combination of spasm, thrombus, stent struts, plaque shift and carina shift.[27–30] However, there is no validated criterion for SB intervention after MB stenting. Previous bifurcation studies used different angiographic and flow criteria for jailed SB intervention, and resulted in different portions of SB angioplasty (Figure 3). However, angiographic assessment for jailed SB ostial lesion is difficult due to stent radiopacity, image filtering and edge enhancement by digital angiography, along with incomplete mixing of blood and contrast medium because of turbulence, contributing to impaired visualization.[31]

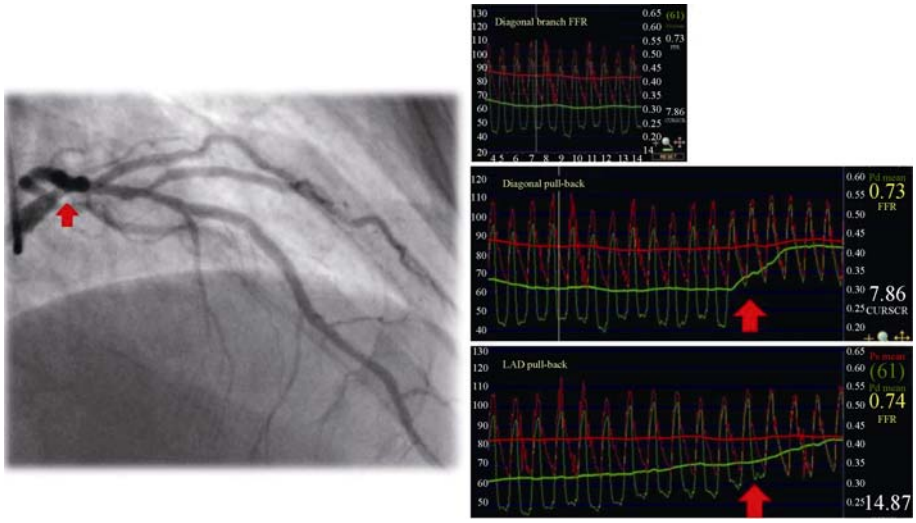


Figure 2. The influence of proximal stenotic lesion on SB FFR. Coronary angiography shows a significant stenosis at the ostium of a diagonal branch (left panel) and FFR measured at a diagonal branch was 0.73. However, pullback pressure recording from distal diagonal branch to left main ostium shows a pressure step-up at the distal left main (right mid panel, arrow). This was confirmed by another pullback pressure recording from distal LAD to left main ostium (right lower panel). Pressure step-up was located mainly at the distal left main lesion. FFR: fractional flow reserve; LAD: left anterior descending artery; SB: side branch.

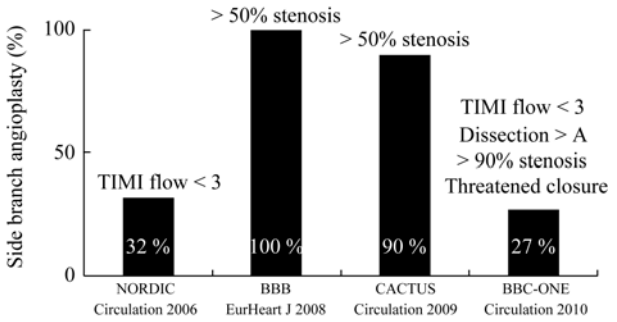


Figure 3. Different criteria and different portions of side branch angioplasty in a provisional arm of recent major randomized clinical trials.[5,7,47,48] TIMI: thrombolysis in myocardial infarction.

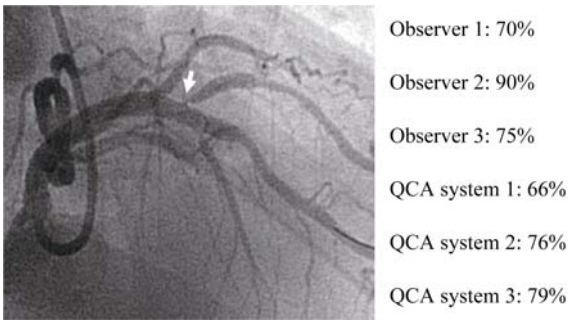


Figure 4. Case example of variability of visual estimation and quantitative coronary angiography (QCA) for jailed side branch lesions. Angiographic percent diameter stenosis was assessed by 3 observers and 3 different QCA systems (Data from the study by Shin DH *et al*.[32]).

Moreover, it is well known that there is a variability in a visual and quantitative coronary angiography (QCA) assessment for jailed SB lesion, as shown in Figure 4.[32]

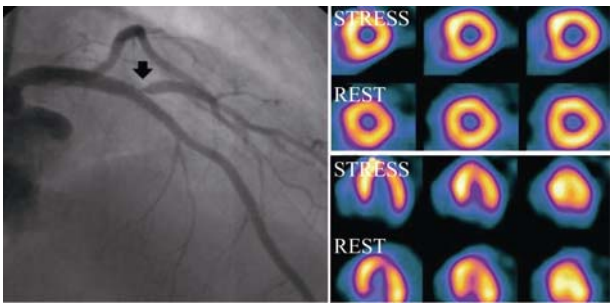


Figure 5. Mismatch between angiographic severity and functional significance. Despite the tight angiographic stenosis, no perfusion defect was found on myocardial SPECT scan (right panel). FFR at this jailed diagonal branch was 0.81.

Previous studies have demonstrated that angiographic evaluation of SB compromised by the MB stent does not reflect functional significance (Figure 5).[33–38] Figure 6 shows the comparison between FFR and angiographic percent diameter stenosis in jailed SB after MB stent implantation from our registry data. Angiographic percent diameter stenosis overestimates the functional severity in general and lesions with similar anatomical severity can have a wide range of FFR. Therefore, when jailed SB is clinically important, only FFR can provide accurate information on whether revascularization is indicated. Moreover, functional and clinical outcomes of FFR-guided revascularization strategy in jailed SB are reported to be excellent. In a study by Koo *et al*.,[34] SB FFR was measured in 91 patients after MB stent implantation and this SB FFR measurement was repeated at 6-month follow-up angiography. During 6-month

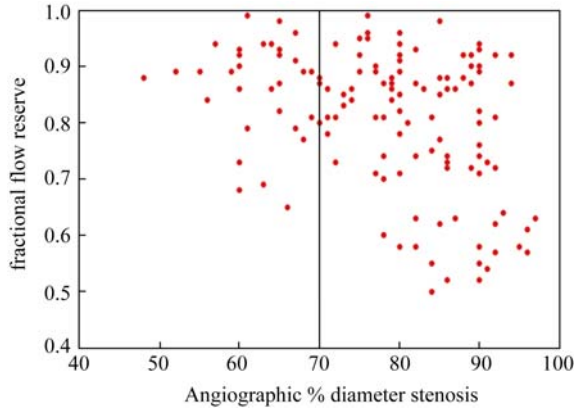


Figure 6. Comparison between FFR and angiographic percent diameter stenosis in jailed side branches.

follow-up, there was no change in SB FFR in lesions without SB angioplasty (0.87 ± 0.06 to 0.89 ± 0.07, P = 0.1). When compared to the conventional angiography-guided group, FFR-guided intervention strategy required less SB intervention (30% *vs*. 45%, P = 0.03) and showed similar nine month cardiac event rates (4.6% *vs*. 3.7%, P = 0.7). In the SB FFR sub-study of the Nordic-Baltic Bifurcation III trial, complete angiographic and FFR eight month follow up was obtained in 21 of the no-kissing balloon dilatation group,[38] and there was no significant change in mean SB FFR during the follow-up period in these patients (0.87 *vs*. 0.87; P = 0.91). These results suggest that FFR- guided revascularization strategy can guide revascularization for jailed SB and can reduce unnecessary complex interventions. Moreover, a computational fluid dynamic study demonstrated that the additional balloon angioplasty of a functionally insignificant SB lesion cannot improve local flow conditions.[39]

However, it should be remembered that published data which compared the FFR and angiographic percent diameter stenosis were obtained in short SB ostial lesions and that any visual or QCA assessment cannot be free from subjectivity. Therefore, the results, especially percent diameter stenosis, cannot be applied to diffuse, multiple or non-ostial SB lesions. Moreover, considering the technical difficulty of SB re-crossing of the pressure wire through the MB strut and the mechanism of discrepancy between FFR and angiographic severity, FFR measurement for jailed SB is not recommended in SB with severe angulation, heavy calcification and in lesions with diffuse and/or multiple stenoses. Finally, regardless of stenosis severity, FFR should be measured in a clinically significant SB which warrants complex interventions.

5 FFR after SB balloon angioplasty

Although various criteria for SB stenting after balloon angioplasty are currently in use, none of them have yet been validated (Figure 7). An aggressive SB angioplasty with a large balloon and with high pressure can cause vessel dissection requiring SB stent implantation, which may increase the risk of stent thrombosis,[40,41] and may have a worse influence on flow dynamics of the MB.[39, 42] Therefore, adequate assessment of SB lesion after balloon angioplasty is very important.

As shown in previous studies, the application of the angiographic criterion may overestimate lesion severity after SB angioplasty and IVUS also have limited ability to assess the functional significance of SB lesions. Therefore, SB FFR measurement after SB balloon angioplasty in bifurcation lesions maybe a better tool to guide interventional treatment compared to angiographic assessment. However, there is a possibility that SB FFR measured immediately

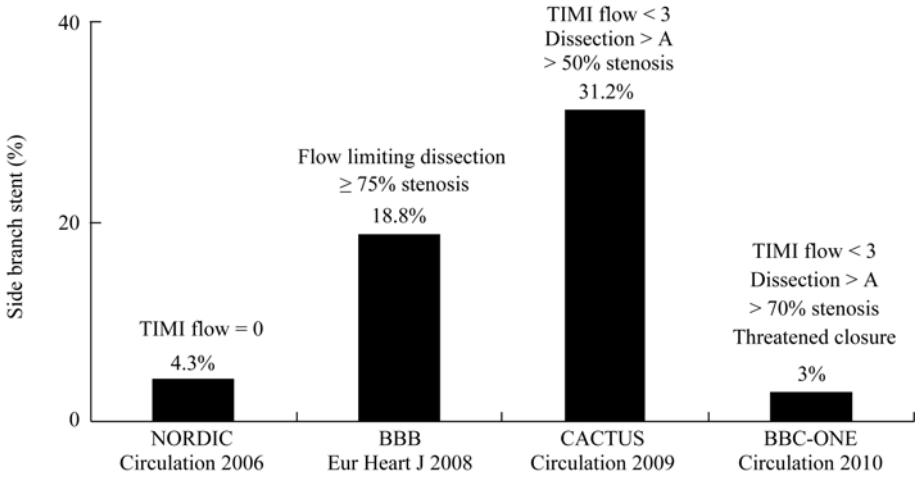


Figure 7. Different criteria and different portions of side branch stenting in a provisional arm of recent major randomized clinical trials.[5,7,47,48] TIMI: thrombolysis in myocardial infarction.

after angioplasty may not reflect the functional and clinical outcomes during follow-up due to influence of thrombus or edema related to the intervention.[43] Two studies evaluated the changes of SB FFR between immediate post-procedure and follow-up.[34,38] There was no significant interval change of SB FFR between post-angioplasty and follow-up in both studies (0.86 ± 0.05 to 0.84 ± 0.01, P = 0.4 by Koo *et al*.[34] and 0.92 to 0.91, P = 0.8 by Kumsars *et al*.[38]). Therefore, immediate post-procedural SB FFR appears to be a useful index that can predict the functional patency of these lesions during follow-up. However, it should be noted that the functional and angiographic late loss depends on the degree of injury sustained during the procedure. In cases of severe SB dissection or slow flow after SB balloon angioplasty, SB stenting or additional SB balloon angioplasty should be considered without measuring SB FFR.

6 FFR after SB stenting

Previous multicenter registry data suggested that FFR values after bare metal stent implantation was a strong independent predictor of outcomes, and patients with an FFR > 0.90 after stenting had very low event rates.[44] Physiologic evaluation using FFR can give additional information on the appropriateness of complex intervention for bifurcation lesions. In a study by Lee *et al*.,[45] SB FFR was measured before and after kissing balloon dilatation in patients treated with the crush technique, and kissing balloon dilatation increased FFR from 0.94 ± 0.04 to 0.97 ± 0.03 (P = 0.011). Another study reported that double kissing crush stenting was associated with higher SB FFR as compared with the provisional strategy in true bifurcation lesions (0.94 ± 0.3 in crush *vs*. 0.90 ± 0.08 in provisional group, P = 0.028).[46] These results suggest that SB FFR can be helpful to assess the procedural success after SB stenting. However, it should be noted that high FFR does not always guarantee excellent outcomes of complex intervention for bifurcation lesions. In a study by Lee *et al*.,[45] SB FFR was already 0.94 ± 0.4 even before the kissing balloon dilatation. Therefore, SB FFR has a limitation in the prediction of long-term procedural outcomes after SB stent implantation.

7 FFR in left main bifurcation lesion

In general, same tips and tricks for non-left main bifurcation lesions can be applied to the left main bifurcation lesions. However, the application of FFR to the left main bifurcation lesions is more complicated as most left main bifurcation lesions are associated with other lesions.

8 Conclusions

Current angiographic evaluation frequently overestimates the functional severity of bifurcation lesions and can lead to unnecessary complex intervention. Therefore, a functional assessment by FFR in conjunction with an anatomical evaluation can be a useful approach to guide appropriate interventional treatment for bifurcation lesions. However, adequate knowledge of coronary physiology and the pitfalls of FFR is required to optimize the clinical utility of FFR in complex bifurcation lesion procedures.

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