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FFR in bifurcation stenting: what have we learned?

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Abstract

Although various angiographic or flow criteria are currently used to evaluate the severity of side branch lesions, none of these has been validated yet. Moreover, angiographic evaluation alone is sometimes inaccurate and does not reflect the functional severity of stenosis, especially in ostial lesions. Fractional flow reserve (FFR) is an easily obtainable lesion-specific parameter for the physiologic evaluation of epicardial coronary artery stenosis, which takes into account the interaction between the anatomic stenosis and the area of perfusion supplied by a specific coronary artery. Recently, a series of investigations was performed to compare the functional severity and angiographic severity in side branch lesions and to evaluate the functional outcomes of jailed side branch lesions during follow-up. From these studies, it was found that 1) FFR-guided provisional side branch intervention strategy is feasible and effective, 2) angiographic evaluation overestimates the functional severity of jailed side branch lesions in every step of the provisional strategy for bifurcation lesions and 3) functional status of jailed side branch lesions after drug-eluting stent implantation does not change significantly during follow-up.

Introduction

The bifurcation lesion is one of the most challenging lesion subsets in the field of percutaneous coronary intervention (PCI). During the intervention for bifurcation lesions, the operator needs to decide whether to intervene on the side branch (SB) lesions and whether to implant SB stent after balloon angioplasty in each patient. Although various angiographic or flow criteria are currently being used in the decision making for SB interventions,[1-4] none of these has been validated yet. Moreover, the bifurcation lesion is very unique as it is the only lesion in which stenting is not better than angioplasty[1-4] and even angioplasty is not better than a "leave it alone" strategy.[5] To overcome this complexity and uniqueness, better understanding of this lesion subset is required.

What is fractional flow reserve?

Fractional flow reserve (FFR) is a physiologic parameter which represents the fraction of maximal myocardial flow that can be maintained in the presence of epicardial coronary stenosis.[6,7] The flow is determined by pressure difference and resistance. Since resistance is minimal under maximal hyperaemia and venous pressure is negligible when compared to coronary arterial pressure, FFR can be obtained by the ratio of distal coronary pressure and proximal aortic pressure. Distal and proximal pressures can be easily measured by the pressure wire and the guiding catheter, respectively.

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

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 is an epicardial lesion-specific index and is nearly independent of haemodynamic conditions such as heart rate, blood pressure, and myocardial contractility. Epicardial stenoses with an FFR <0.75 are almost invariably associated with inducible myocardial

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ischaemia. This cutoff value has been validated in more than 1,000 patients and FFR-guided intervention strategy has shown the clinical benefit over angiography-guided intervention in both single and multivessel diseases.[8-10]

Why FFR for bifurcation lesions?

Invasive anatomical evaluation tools such as angiography, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can provide accurate anatomical information. However, it is not easy to assess the functional significance of bifurcation lesions, especially in SB lesions, due to the following unique characteristics of bifurcation lesions and the limitations of these tools.

Unique nature of bifurcation lesions:

1) The amount of myocardium supplied by SB is relatively small and highly variable.
2) SB ostium is usually negatively remodelled and the plaque is eccentric.
3) The mechanism of luminal narrowing in jailed SB is very complex: underlying plaque, stent struts, shifted plaque, shifted carina, thrombus, spasm, and dissected flap, etc.

Limitations of anatomical evaluations:

1) Angiographic evaluation is more difficult for bifurcation lesions due to vessel overlap, angulations, stent struts across the branch and image foreshortening. Furthermore, measurements by quantitative coronary angiography (QCA) are reported to have variability as well as those by visual estimation.
2) Optimal IVUS or OCT criteria to define the functional significance of SB lesion are not known yet. Moreover, it is technically difficult to perform IVUS or OCT in jailed SB lesions.

FFR for bifurcation lesions

FFR can be used for the evaluation of the functional significance or the necessity of revascularisation in bifurcation lesions. As this is a physiologic parameter which reflects both the severity of epicardial stenosis and the amount of myocardium supplied, same cutoff point can be applied for both main and side branches. It is reported that the discrepancy exists between the angiographic % diameter stenosis and FFR in ostial lesions.[11] As the bifurcation lesion is basically the combination of three ostial lesions, a greater discrepancy can exist between the anatomical evaluations and FFR as shown in Figure 1. FFR can be easily measured in bifurcation lesions both before and during intervention as the current pressure guidewires have similar handling characteristics to conventional angioplasty guidewires. However, jailing of a pressure wire between the stent and vessel wall is not recommended.

When FFR is measured for SB ostial lesions, the influence of proximal and distal lesions should be considered. If there is a significant proximal stenosis, FFR overestimates the severity of SB ostial lesion. In contrast, FFR underestimates the lesion severity when there is a significant distal SB lesion and FFR is measured at a proximal segment to that lesion.

FFR for jailed SB lesions

FFR can be safely used during the intervention of bifurcation lesions (Figure 2). Our group performed a series of investigations[12,13] to compare the functional severity and angiographic severity in jailed SB lesions and to evaluate the functional outcomes of jailed SB lesions during follow-up.

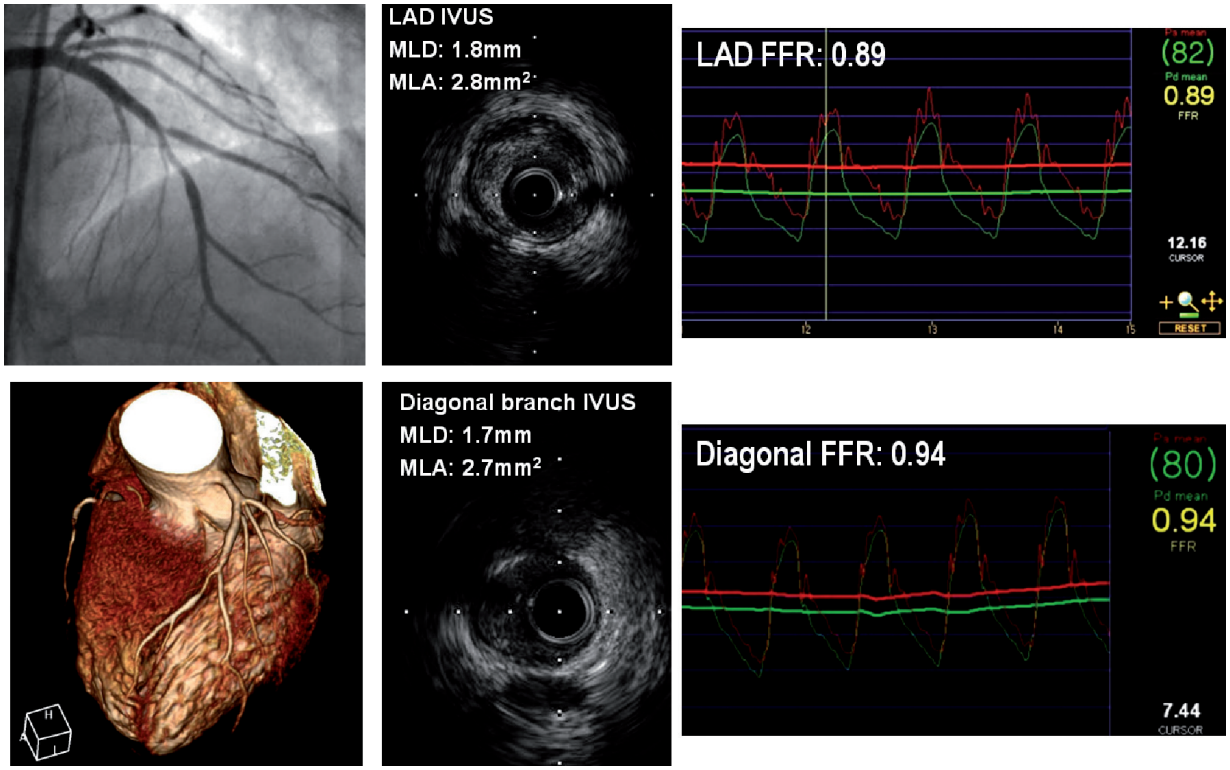

Figure 1. A case example which shows the discrepancy between the results of anatomical evaluations and fractional flow reserve. LAD: left anterior descending coronary artery; IVUS: intravascular ultrasound: MLD, minimum lumen diameter; MLA: minimum lumen area; FFR: fractional flow reserve

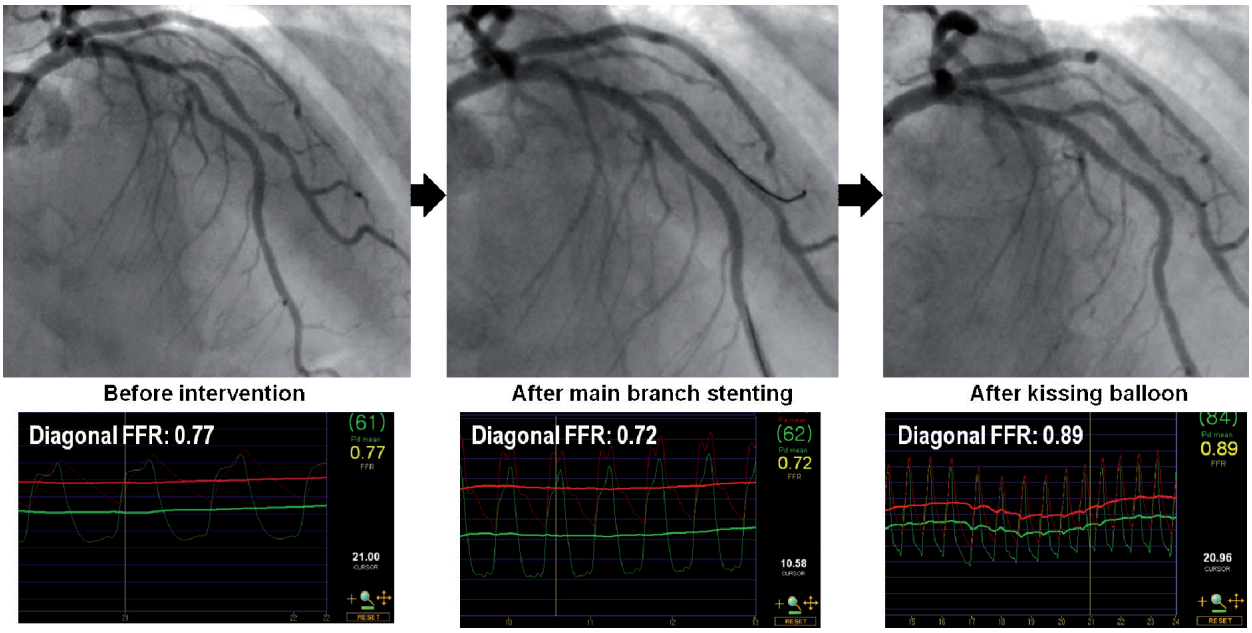

Figure 2. Use of a pressure wire during provisional side branch interventional strategy. After main branch stent implantation, side branch ostial lesions has become functionally significant. After kissing balloon inflation, fractional flow reserve has increased to 0.89 despite the angiographically significant residual stenosis.

In the first part of our study, FFR was measured in 94 jailed SB and it was compared with the stenosis severity assessed by QCA.[12] There was a negative correlation between the angiographic % diameter stenosis and FFR (r=-0.464, p<0.001). However, a wide variation of functional significance was found even among lesions with angiographically tight stenosis. Among 73 lesions with ≥75% stenosis, only 20 lesions were functionally significant. Therefore, it was found that angiographic evaluation is unreliable in the assessment of jailed SB lesions and generally overestimates the functional severity of stenosis. These findings were reproduced by later studies[13-15] and Figure 3 shows the comparison between FFR and angiographic % diameter stenosis in jailed SB in a recently published PRESSURE trial. However, it should be remembered that the lesions included in these studies were relatively short ostial SB lesions and a dedicated bifurcation QCA system was not used. Therefore, these results can not be applied as they are to diffuse or non-ostial SB lesions and stenosis severity assessed by other QCA systems.

In the second part of our study, SB FFR was measured in 91 patients after main branch stent implantation and this measurement was repeated after SB intervention and at six months follow-up.[13] SB intervention was allowed when FFR was <0.75. Kissing balloon angioplasty was performed in 26 of 28 SB lesions with FFR <0.75, and FFR ≥0.75 was achieved in 92% of the lesions although the mean residual stenosis was 69±10%. During follow-up there were no changes in mean FFR at both main and side branches. SB FFR changes during follow-up were 0.01±0.05 and –0.02±0.09 in lesions with and without kissing balloon inflation, respectively (Figure 4). Functional restenosis (FFR <0.75) rate at 6-month follow-up was only 8%. When compared to non-FFR guided intervention, FFR-guided strategy resulted in similar clinical outcomes with less frequent SB intervention (45% in angiography-guided vs. 30% in FFR-guided, p=0.03). These results were reproduced in a recently presented SB FFR substudy of Nordic Baltic Bifurcation III trial[16] and suggest that the angiographic evaluation overestimates the severity of jailed SB lesions in every step of the provisional strategy and the outcomes of FFR-guided provisional strategy seem to be favourable. Moreover, computational fluid dynamic study showed that the additional intervention of functionally insignificant SB lesion does not improve the local flow conditions in bifurcation lesions.[17]

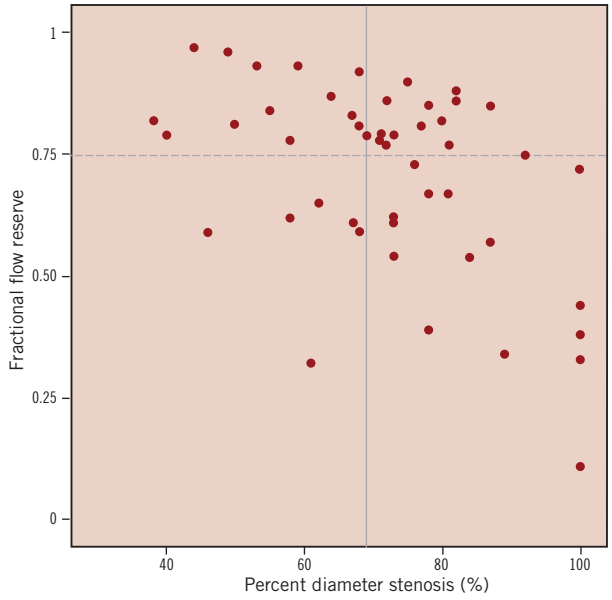

Figure 3. Comparison between fractional flow reserve and angiographic percent diameter stenosis in jailed side branches.

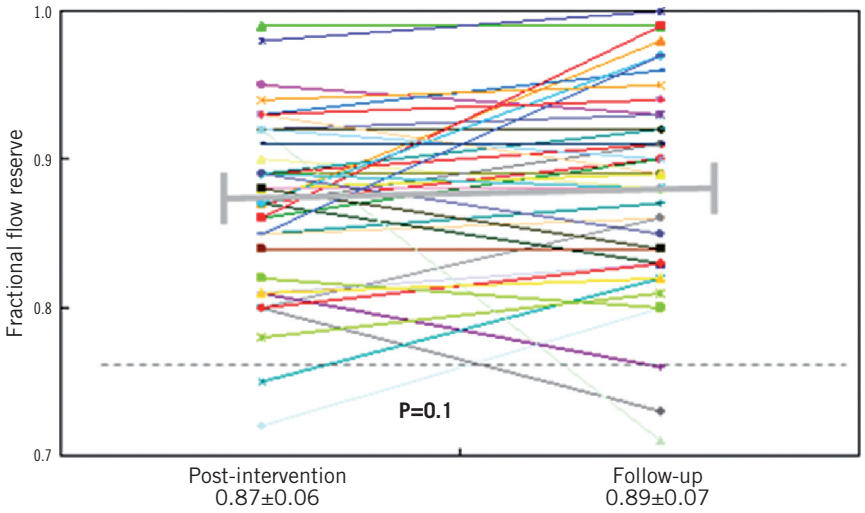

Figure 4. Changes of fractional flow reserve in non-intervened jailed side branches during six month follow-up after percutaneous coronary intervention.

Mechanism and predictors of side branch jailing

In a recently published PRESSURE study,[15] the mechanism of geometric changes after main branch stent implantation and the predictors of significant SB jailing were investigated using both IVUS and FFR. In this multicentre prospective study, success rate of recrossing the SB using pressure wire was 91%. FFR was <0.75 in 18 out of 33 jailed SB lesions (54.5%) with ≥75% diameter stenosis and in 10 lesions (29.4%) with <75% stenosis.

IVUS analyses revealed that SB jailing can occur by both carina shift and plaque shift (Figure 5).

Angiographic determinants of a functionally significant SB lesion (FFR<0.75) were the pre-intervention SB % diameter stenosis and the main branch minimum lumen diameter located distal to the SB ostium, reflecting the degree of underlying disease and carina shift, respectively. SB FFR correlated with the parameters representing underlying SB disease (SB minimal lumen diameter and SB percent stenosis), carina shift (lumen volume index of distal main branch) and plaque shift (plaque volume index of proximal main branch, plaque burden in main branch). However, it was difficult to predict the functional significance of each jailed SB lesion based on anatomic characteristics due to the complex mechanism of luminal narrowing and its individual variability. The degree of underestimation of the SB lumen area can be different in each case according to the relative contribution of each component (amount and location of underlying plaque, degree of remodelling, bifurcation angle and the extent of plaque and carina shift) on luminal narrowing of the SB.

FFR for complex stenting strategies

There are not much data on FFR during two stenting strategy for bifurcation lesions. Angiographic evaluation is sometimes difficult and inaccurate and IVUS criteria may not be applicable to all bifurcation lesions during complex intervention. Physiologic evaluation can give additional information on the appropriateness of complex intervention for bifurcation lesions and it can be applied to all bifurcation lesions regardless of the vessel size and the amount of viable myocardium. Even though the pressure wire is not the best one for the access of jailed SB and complex SB interventions, most procedures can be easily performed through the pressure wire. However, considering the complexity of two stenting procedures, previous results of post-stenting FFR in non-bifurcation lesions may not be applied as they are to this more complex situation.[18]

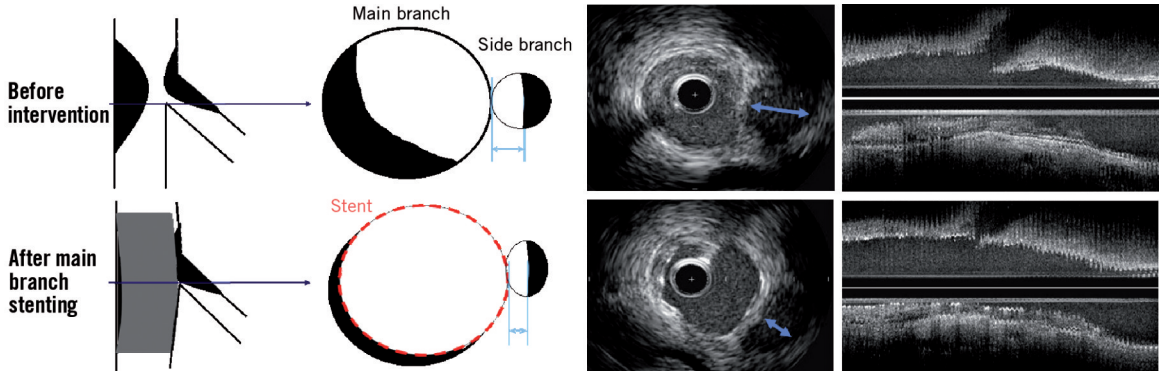

Figure 5. The concept and an exemplary case of carina shift after main branch stent implantation. After stent implantation, the carina is shifted to the side branch side and this shift results in the eccentric luminal narrowing of the side branch ostium. Therefore, the loss of angiographic lumen diameter (arrows) overestimates that of true lumen area in jailed side branch lesions.

Summary

As there are no data which proved the clinical benefit of an FFR-guided strategy for bifurcation lesions, it can not be advocated in all bifurcation lesions. However, the results of FFR studies can be summarised as follows: 1) FFR-guided provisional SB intervention strategy is feasible and effective, 2) angiographic evaluation overestimates the functional severity of jailed SB lesions in every step of the provisional strategy for bifurcation lesions and 3) functional status of jailed SB lesions after drug-eluting stent implantation does not change significantly during follow-up. These results indicate that FFR measurements in bifurcation lesions can be helpful in decision making for SB treatment and can prevent unnecessary complex coronary interventions and related complications in patients with bifurcation lesions.

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