The International Journal of Cardiovascular Imaging (2019) 35:1945–1954
https://doi.org/10.1007/s10554-019-01649-y

ORIGINAL PAPER

Comparison of fractional flow reserve and angiographic characteristics after balloon angioplasty in de novo coronary lesions

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Received: 25 January 2019 / Accepted: 12 June 2019 / Published online: 18 June 2019

Abstract

Lesion characteristics determined by angiography after balloon angioplasty such as residual dimeter stenosis (DS) or dissection type has been used to determine the treatment method of drug-coated balloon (DCB) or metal stent for de novo coronary lesions. The aim of this study is to identify angiographic and functional mismatch using residual DS, dissection type and fractional flow reserve (FFR). Baseline and post-balloon parameters were obtained from 151 patients with 167 lesions. Angiographically significant parameters after balloon angioplasty are residual DS > 30% or dissection type C or more. Post-balloon FFR cutoff value of 0.75 was used to define functionally significant lesions. The weak correlation was found between residual DS and post-balloon FFR ($r = -0.317$, $p < 0.001$). There were 68.7% of mismatch population (residual DS > 30% and post-balloon FFR ≥ 0.75) and 7.1% of reverse mismatch population (residual DS ≤ 30% and post-balloon FFR < 0.75). All reverse mismatch lesions were found in left anterior descending artery. There was no correlation between dissection severity and post-balloon FFR ($p = 0.654$). In high post-balloon FFR group, long-term clinical outcomes showed no difference between DCB and stent groups with ($p = 0.788$) or without ($p = 0.426$) the adjustment of lesion characteristics. There were high frequencies of mismatch between angiographic lesion characteristics and FFR values after balloon angioplasty. Post-balloon FFR measurements may be safe and effective compared to angiography-guided treatment if DCB only treatment is considered.

Keywords Drug-coated balloon · Paclitaxel-coated balloon · Fractional flow reserve · De novo lesion · Balloon angioplasty · Dissection

Abbreviations

BA	Balloon angioplasty
DCB	Drug-coated balloon
DS	Diameter stenosis
FFR	Fractional flow reserve

Introduction

Although drug-coated balloon (DCB) is an established treatment option for in-stent restenosis [1–4], there is scarce evidence about the efficacy and safety of DCB in native coronary artery disease. Recently BASKET-SMALL 2 trial showed that DCB was non-inferior to drug

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eluting stent (DES) regarding major adverse cardiac events (MACE) up to 12 months [5]. They showed that the use of DCB in small vessel coronary artery disease is safe if an acceptable angiographic result can be obtained after successful pre-dilatation. The next question is whether DCB are effective in de-novo large coronary vessels. However, for large de novo epicardial coronary lesions, there are limited numbers of studies for DCB treatment. Recently we showed that after balloon angioplasty (BA), fractional flow reserve (FFR)-guided DCB treatment is safe and effective for de novo coronary lesions with good anatomical and physiological patency at mid-term follow-up [6–9]. A German consensus group recommended a DCB treatment if there are acceptable angiographic results such as no flow-limiting dissection (type A or B) and non-significant residual diameter stenosis (DS ≤ 30%) after BA [10]. Although this angiography-based decision can be useful, it is necessary to compare it with the reliable predictor of coronary flow such as FFR. In this study, we attempted to identify the correlation between FFR and angiographic characteristics after BA for the DCB treatment.

Methods

Study population

This prospective observational registry enrolled patients from June 2012 to January 2015 from a single center (Ulsan University Hospital) registry of post-balloon FFR. Patients with significant de novo major epicardial coronary artery disease (DS ≥ 50% on angiography) with documented ischemia by FFR who were scheduled to undergo percutaneous coronary intervention (PCI) were considered eligible for this study. The angiographic inclusion criteria were the presence of a single de novo coronary lesion with reference vessel diameter between 2.5 and 3.5 mm, lesion length ≤ 24 mm and thrombolysis in myocardial infarction (TIMI) 3 flow after BA. Exclusion criteria were those with severe left ventricular dysfunction (ejection fraction < 35%), chronic kidney disease, ST-segment elevation myocardial infarction requiring primary PCI, significant left main coronary artery disease, multivessel stenosis, ostial lesion, heavily calcified or thrombotic lesion, contraindication to adenosine and a life expectancy of < 1 year. Patients with small-sized target arteries (reference diameter < 2.5 mm) were excluded. A total of 167 lesions were included for the study. Among high post-balloon FFR group, 77 lesions were treated with DCB and 58 lesions were treated with a stent. All low post-balloon FFR group (32 lesions) were treated with stent. This study was performed with the patients' written informed consent and approval of the institutional review board.

Angiographic characteristics

Angiography was performed after the administration of 200 μg of intracoronary nitroglycerine in at least two orthogonal projections before and after the procedure. All coronary angiographies were analyzed with the Cardiovascular Angiography Analysis System (CAAS 5.10, Pie Medical Imaging B.V., Maastricht, The Netherlands). Using the guiding catheter as a scaling device, reference diameter, minimum lumen diameter and percent diameter stenosis were measured before and after the procedure. Measurements included the whole segment treated plus 5 mm proximally and distally and the severity of edge dissections was classified as type A to F using the 1985–1986 NHLBI PTCA Registry criteria [11, 12].

FFR measurements

FFR was measured before and immediately after BA following an intracoronary injection of 200 μg of nitroglycerine using a 0.014-in. coronary pressure wire (Radi, St. Jude Medical, Minneapolis, MN). Hyperemia was induced by intravenous infusion of adenosine (140–180 mg/kg/min) through a peripheral or central vein, or intracoronary bolus injection of nicorandil (2 mg) [13]. After the treatment of either DCB or stent implantation, a final FFR was measured in the same position.

Target lesion treatment

The target lesion was treated with a DCB or stent after adequate lesion preparation using an optimal sized semi-compliant balloon based on angiography and a balloon-to-artery ratio of 1.0. In case of DCB treatment, a SeQuent Please was used (B. Braun, Melsungen, Germany) which was delivered to the target lesion and inflated with nominal pressure for 60 s. For stent implantation, either a second generation zotarolimus- or everolimus-eluting DES (Resolute Integrity® or Xience prime®) or a bare metal stent (Vision®) were used. A DES was recommended preferentially over bare metal stent except for cases where there was a high risk of bleeding or planned surgery. Procedural success was defined as TIMI 3 flow without bailout stenting after the procedure. The cutoff value of post-balloon FFR used in the current study was 0.75 based on our previous studies [8, 9].

Patient follow-up

Patient demographic data, cardiovascular risk factors and clinical diagnoses were recorded at the time of index PCI. Clinical follow-up was performed at 1, 6, 12 months and

annually by outpatient clinical visits or telephone contact. The median follow-up duration of the study population was 40.3 months. Occurrence of MACE including cardiac death, target vessel related myocardial infarction (MI), and clinically driven target vessel revascularization (TVR) were recorded. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputed noncardiac cause was present. Periprocedural MI was not accounted as a clinical event. Revascularization was considered clinically indicated in the presence of DS ≥ 50% on angiography and if one of the following occurred: (1) recurrence of anginal symptoms; (2) positive noninvasive test; (3) positive invasive physiologic test; or (4) presence of diameter stenosis ≥ 70%, even in the absence of other criteria. Repeat revascularization events were separately assessed with target lesion revascularization (TLR), non-TLR, TVR, and non-TVR.

Statistical analysis

Analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies with percentages and compared with two-sided Fisher's exact test or Chi square test. Continuous variables are presented as mean ± SD and compared with Student's *t* test or Mann–Whitney's test. The relationship between the variables were analyzed by Pearson correlation analysis. The comparison between groups was performed using ANOVA or Kruskal–Wallis test after exploring normal distribution with Shapiro–Wilk test. Patient's clinical outcomes were compared with the log rank test. A two-sided p value of < 0.05 was used to indicate statistical significance.

Results

Baseline characteristics of patients and lesions

Figure 1 shows the distribution of baseline FFR and post-balloon FFR. The optimal cutoff value of post-balloon FFR for the occurrence of MACE was 0.75. The median post-balloon FFR was 0.82 [interquartile range (IQR) 0.76 to 0.88] and median residual DS was 30.0% (IQR 20.0% to 40.0%). A total of 30 (19.9%) patients demonstrated post-balloon FFR < 0.75. The baseline characteristics of 151 patients are provided in Table 1. Grouping variables were residual DS of 30% and post-balloon FFR of 0.75. All characteristics were similar between groups except significantly smaller left ventricular ejection for the patients with residual DS > 30% and post-balloon FFR < 0.75. The comparison of lesion and procedure characteristics of 167 lesions is summarized in Table 2. Left anterior descending artery (LAD) was the most common site on all groups and severe dissections such as type C or more were found the most in mismatch population (22.8%). The functionally significant match population (residual DS > 30% and post-balloon FFR < 0.75) showed the highest residual DS (43.3 ± 10.2%), the lowest post-balloon FFR (0.68 [0.65–0.71]) and the lowest final FFR (0.82 [0.75–0.87]). While no DCB was used in the low post-balloon FFR group, the high post-balloon FFR group was treated with either DCB or stent according to the operator's discretion.

Post-balloon FFR and angiographic characteristics

Distributions of post-balloon FFR according to angiographic parameters such as residual DS and dissection type after BA are provided in Fig. 2 to identify if increase in residual DS

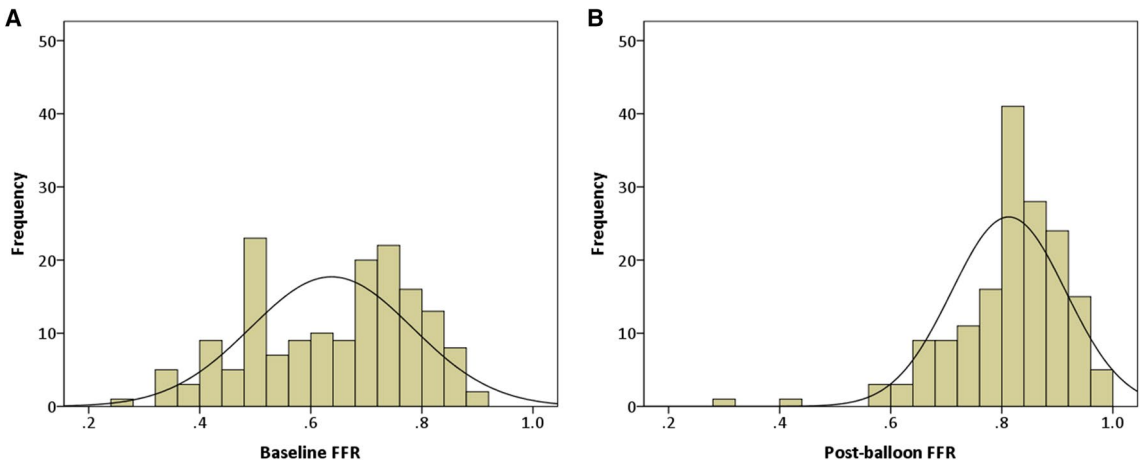

Fig. 1 Distribution of baseline and post-balloon FFR. **a** Baseline FFR. **b** Post-balloon FFR. *FFR* fractional flow reserve

Table 1 Baseline characteristics

	Residual DS > 30%		Residual DS ≤ 30%		p value*
	Post-balloon FFR < 0.75 n = 24	Post-balloon FFR ≥ 0.75 ("mismatch") n = 53	Post-balloon FFR ≥ 0.75 n = 68	Post-balloon FFR < 0.75 ("reverse mismatch") n = 6	
Men	20 (83.3)	41 (77.4)	51 (75.0)	2 (33.3)	0.083
Age (years)	60.1 ± 11.5	59.6 ± 9.4	58.8 ± 7.8	59.3 ± 10.5	0.933
Body mass index (kg/m^2)	25.4 ± 2.9	24.5 ± 2.5	24.0 ± 2.9	24.5 ± 2.4	0.161
Cardiovascular risk factors					
Diabetes	7 (29.2)	13 (24.5)	15 (22.1)	1 (16.7)	0.878
Hyperlipidemia	12 (50.0)	22 (41.5)	38 (55.9)	3 (50.0)	0.482
Hypertension	10 (41.7)	22 (41.5)	37 (54.4)	2 (33.3)	0.413
Current smoking	6 (25.0)	16 (30.2)	16 (23.5)	1 (16.7)	0.800
Previous MI	0	2 (3.8)	7 (10.3)	0	0.201
Family history of CAD	1 (4.2)	7 (13.2)	10 (14.7)	1 (16.7)	0.586
Clinical manifestations					0.314
Stable angina	7 (29.2)	25 (47.2)	33 (48.5)	1 (16.7)	
Unstable angina	15 (62.5)	22 (41.5)	30 (44.1)	5 (83.3)	
NSTEMI	2 (8.3)	6 (11.3)	5 (7.4)	0	
LV ejection fraction (%)	58.4 ± 10.4	62.7 ± 7.8	63.2 ± 7.3	67.0 ± 5.1	0.045
Hospital stay (days)	5.0 ± 2.8	4.5 ± 2.4	5.4 ± 7.4	3.7 ± 0.8	0.750
hs-CRP (mg/Dl)	0.65 ± 1.97	0.33 ± 0.42	0.12 ± 0.17	0.15 ± 0.17	0.078

Values are n (%) or mean ± SD

CAD coronary artery disease, *hs-CRP* high-sensitivity C-reactive protein, *LV* left ventricular, *MI* myocardial infarction, *NSTEMI* non-ST segment elevation MI

*p values are from the comparison of four groups

and increased severity of dissection type result in decrease in post-balloon FFR value. The weak correlation was found between residual DS and post-balloon FFR ($r = -0.317$, $p < 0.001$). When subdivided into 5 groups by the severity of residual DS, the difference between groups was significant ($p = 0.001$). This is because of the extremely high post-balloon FFR value of one group ($DS \leq 20\%$, 0.85 ± 0.08) compared with other groups ($20\% < DS \leq 30\%$, 0.82 ± 0.08, $p = 0.011$; $30\% < DS \leq 40\%$, 0.80 ± 0.11, $p = 0.001$; $40\% < DS \leq 50\%$, 0.77 ± 0.10, $p = 0.001$; $DS > 50\%$, 0.76 ± 0.10, $p = 0.009$). As another representation of angiographic parameter, dissection type was analyzed to identify its correlation with post-balloon FFR. There was no correlation between dissection severity and post-balloon FFR ($p = 0.654$ between groups). Further analysis showed no statistical differences between any two groups. In Fig. 2b, the group of dissection type D had lower post-balloon FFR (0.77 ± 0.13) compared with other groups (0.83 ± 0.09, 0.81 ± 0.11, 0.81 ± 0.09 and 0.82 ± 0.08 for no dissection, dissection types A, B and C, respectively). But the group had only 4 lesions and it was not statistically different compared with other groups.

Another representation for the distribution of high and low post-balloon FFR groups in each category are shown in Fig. 3. The proportion of low post-balloon FFR group was steadily increased from 6.3% to 39.1% with increased residual DS up to 50%. But with residual DS > 50%, the proportion was not increased. For the dissection type after BA, the proportion of low post-balloon FFR group increased as the dissection severity increased except for type C.

Correlation of post-balloon FFR and residual DS

Scatterplots to identify correlations between post-balloon FFR and residual DS after BA are shown in Fig. 4. Overall, there were 68.7% of mismatch population (residual DS > 30% and post-balloon FFR ≥ 0.75) among lesions with residual DS > 30%, and 7.1% of reverse mismatch population (residual DS ≤ 30% and post-balloon FFR < 0.75) among lesions with residual DS ≤ 30%. Severe dissections (type C or more) showed high post-balloon FFR (83.3%) and there was no relation with the severity of residual DS.

Among the lesions with residual DS > 30%, the proportions of mismatch for each target vessel were 65.3% in LAD, 68.8% in left circumflex artery (LCX), and 77.8% in right coronary artery (RCA). For reverse mismatch population, all 6 lesions were found in LAD lesions (7.1% of residual DS ≤ 30%), and there were 2 type A, 3 type B and 1 type D

Table 2 Lesion and procedure characteristics

	Residual DS > 30%		Residual DS ≤ 30%		p value*
	Post-balloon FFR < 0.75 n = 26	Post-balloon FFR ≥ 0.75 ("mismatch") n = 57	Post-balloon FFR ≥ 0.75 n = 78	Post-balloon FFR < 0.75 ("reverse mismatch") n = 6	
Coronary artery					0.185
Left anterior descending	17 (65.4)	32 (56.1)	36 (46.2)	6 (100)	
Left circumflex	5 (19.2)	11 (19.3)	20 (25.6)	0	
Right coronary	4 (15.4)	14 (24.6)	22 (28.2)	0	
Lesion type					0.310
A, B1	7 (26.9)	16 (28.1)	27 (34.6)	0	
B2, C	19 (73.1)	41 (71.9)	51 (65.4)	6 (100)	
Dissection type					0.709
None, A, B	22 (84.6)	44 (77.2)	66 (84.6)	5 (83.3)	
C, D	4 (15.4)	13 (22.8)	12 (15.4)	1 (16.7)	
Diameter stenosis (%)					
Baseline	80.0 ± 14.8	73.1 ± 16.8	74.9 ± 17.1	79.2 ± 15.7	0.328
Post-balloon	43.3 ± 10.2	41.1 ± 8.7	18.5 ± 7.6	21.0 ± 6.3	< 0.001
FFR					
Baseline	0.62 ± 0.15	0.65 ± 0.13	0.63 ± 0.15	0.63 ± 0.16	0.686
Post-balloon	0.68 [0.65–0.71]	0.82 [0.80–0.89]	0.85 [0.81–0.90]	0.62 [0.59–0.68]	< 0.001
Post-procedure	0.82 [0.75–0.87]	0.88 [0.84–0.93]	0.88 [0.84–0.92]	0.87 [0.74–0.87]	0.002
Reference diameter (mm)	2.63 ± 0.53	2.62 ± 0.48	2.43 ± 0.55	2.52 ± 0.36	0.155
Balloon angioplasty					
Balloon diameter (mm)	3.00 ± 0.45	2.95 ± 0.42	2.86 ± 0.54	3.25 ± 0.27	0.163
Balloon pressure (atm)	11.2 ± 3.1	10.8 ± 3.2	10.5 ± 2.1	8.8 ± 2.0	0.095
Balloon to artery ratio	1.17 ± 0.21	1.15 ± 0.16	1.20 ± 0.22	1.31 ± 0.25	0.154
Device type					< 0.001
Drug-coated balloon	0	19 (33.3)	58 (74.4)	0	
Drug-eluting stent	19 (73.1)	30 (52.6)	12 (15.4)	4 (66.7)	
Bare-metal stent	7 (26.9)	8 (14.0)	8 (10.3)	2 (33.3)	
Device size					
Device diameter (mm)	3.28 ± 0.46	3.18 ± 0.43	3.00 ± 0.51	3.38 ± 0.21	0.018
Device length (mm)	25.8 ± 7.2	25.2 ± 5.9	22.8 ± 5.0	28.7 ± 5.0	0.007
Max. device pressure (atm)	14.8 ± 4.5	12.4 ± 3.8	10.6 ± 3.4	12.2 ± 3.4	< 0.001
Max. device size (mm)	3.48 ± 0.51	3.35 ± 0.46	3.15 ± 0.54	3.48 ± 0.20	0.011

Values are n (%), mean ± SD or median [IQR]

FFR fractional flow reserve

*p values are from the comparison of four groups

dissections. In LCX and RCA, there were 4 type C and 7 type C dissections, but their post-balloon FFR values were all higher than the cutoff value of 0.75. No type D dissections were found in LCX and RCA. In LAD, 26.3% of severe dissections showed post-balloon FFR < 0.75. But in LCX and RCA, none of severe dissections showed post-balloon FFR < 0.75.

Additional quantitative evaluation of each quadrant for each target vessel is shown in Fig. 5. Functionally non-significant matched population (residual DS ≤ 30% and post-balloon FFR ≥ 0.75) was dominant for all three vessels, while LAD showed numerically lower percentage compared with other vessels (39.6%, 55.6%, and 55.0%, p = 0.128 for LAD, LCX and RCA, respectively). However, LAD showed numerically higher rate of functionally significant matched population (residual DS > 30% and post-balloon FFR < 0.75) compared with LCX and RCA (18.7%, 13.9% and 10.0%, p = 0.429). There were 6.6% (6 lesions out of all LAD lesions) of revere mismatch population in LAD but none was found in LCX or RCA.

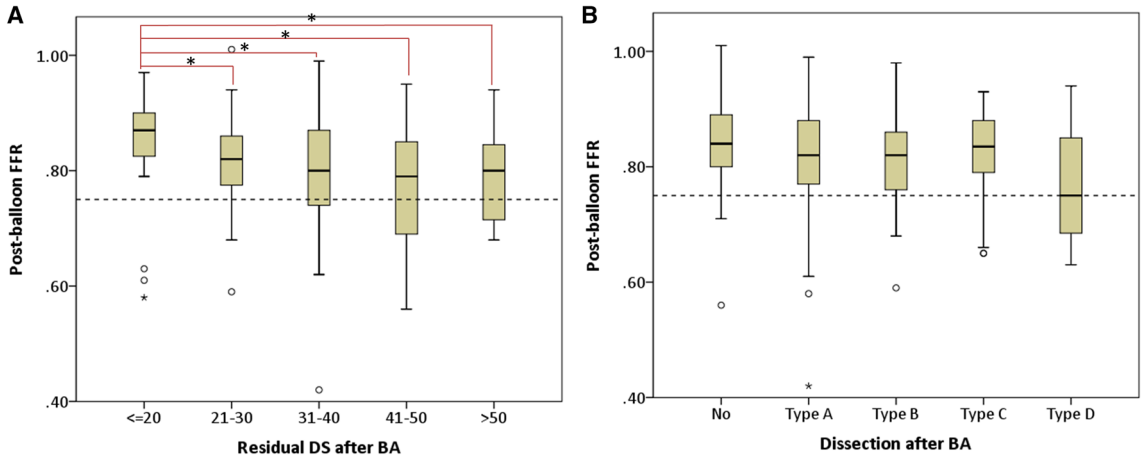

Fig. 2 Post-balloon FFR according to residual DS and dissection type. **a** Residual DS after BA. **b** Dissection type after BA. *p < 0.05. *BA* balloon angioplasty, *DS* diameter stenosis, *FFR* fractional flow reserve

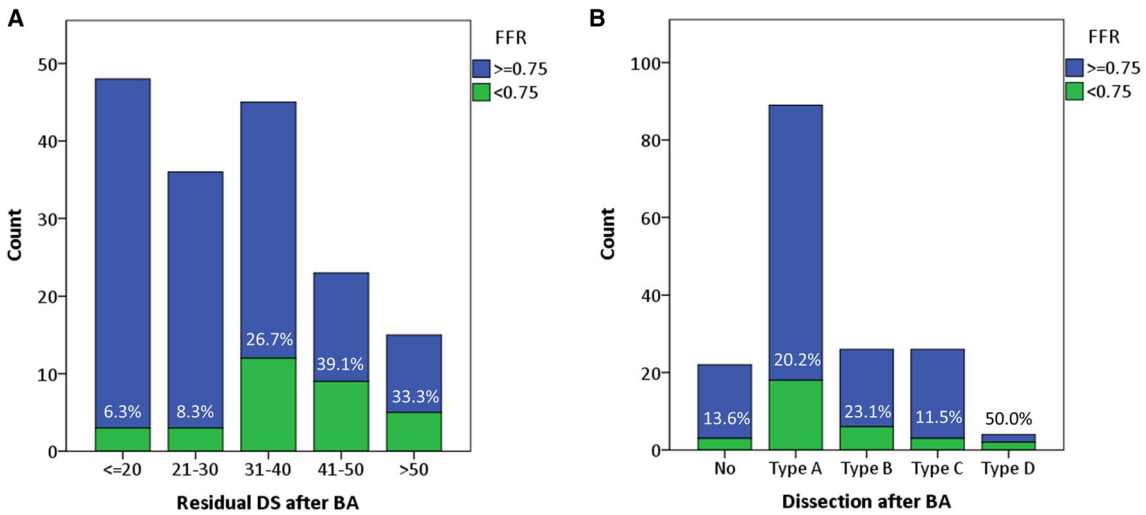

Fig. 3 Distribution of residual DS and dissection type according to post-balloon FFR cutoff value. **a** Residual DS after BA. **b** Dissection type after BA. *BA* balloon angioplasty, *DS* diameter stenosis, *FFR* fractional flow reserve

Clinical outcomes

Long term clinical follow-ups in all patients were obtained and the median duration was 40.3 months. The univariate analysis for prognosis by Kaplan–Meier method is shown in Table 3. There was one case of cardiac death in stent group and one MI in DCB group. The MI event happened 33 months after the index procedure in mid-LAD and the post-balloon FFR at the index procedure was 0.77. There was no case of target lesion thrombosis in any group. The comparison between two treatment groups showed no overall differences. In the high post-balloon FFR group, clinical outcomes (MACE) showed no difference between two groups with (p = 0.788) or without (p = 0.426) the adjustment of lesion characteristics. The included covariates for the adjustment were post-balloon DS, post-balloon FFR, reference diameter, balloon size, device size, max device pressure and max device size. The low post-balloon FFR group was treated with stents only and showed 4 (12.5%) MACE events.

Discussion

The main findings of this study are as follows; (1) there were high frequencies of mismatch between angiographic lesion characteristics and FFR values after balloon angioplasty (2) reverse mismatch population was found in LAD only.

In this study, angiographic results of residual DS and dissection type after BA were compared with post-balloon

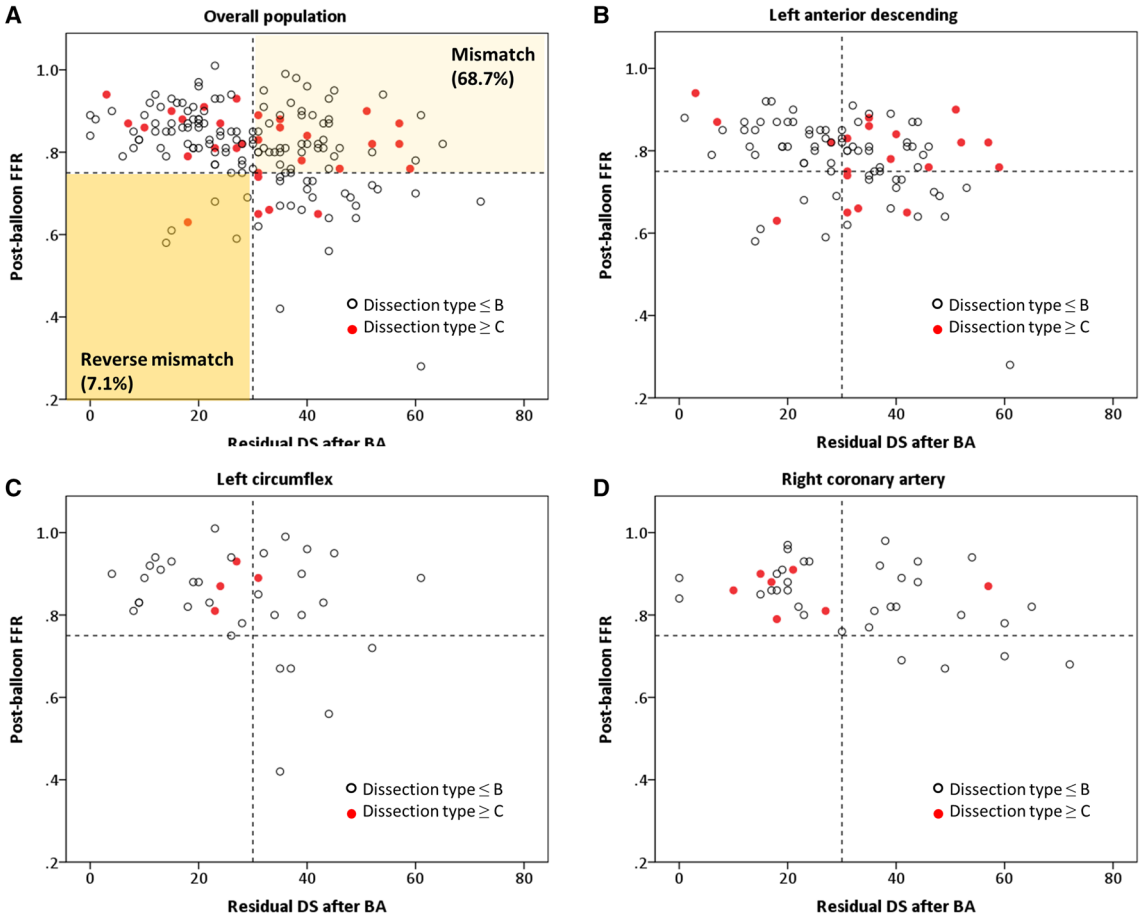

Fig. 4 Correlation between post-balloon FFR and residual DS. **a** Overall population. **b** Left anterior descending aorta. **c** Left circumflex. **d** Right coronary artery. *BA* balloon angioplasty, *DS* diameter stenosis, *FFR* fractional flow reserve

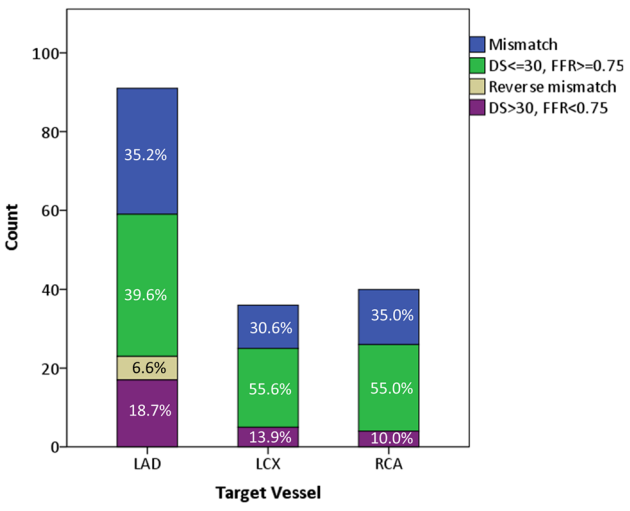

Fig. 5 Distribution of lesions according to target vessel. *DS* diameter stenosis, *FFR* fractional flow reserve, *LAD* left anterior descending aorta, *LCX* left circumflex, *RCA* right coronary artery

FFR to assess the current angiography-based and FFR-guided DCB treatment. The correlation between residual DS and post-balloon FFR showed considerable mismatch population. These lesions can be safely treated with DCBs and reduce the number of unnecessary stent implantations. Majority of lesions with severe dissection in LAD showed post-balloon FFR ≥ 0.75 and thus, increased severity of dissections did not produce decreased post-balloon FFR values. Note that all severe dissections in non-LAD lesions showed post-balloon FFR ≥ 0.75. Thus, post-balloon FFR measurements in LAD lesions could be recommended not just to reduce the number of stents in mismatch lesions but to prevent future adverse clinical events in reverse mismatch lesions, while LCX and RCA could be treated with angiography alone.

Advantages of DCB treatment on de novo coronary lesions are the potential for favorable vascular remodeling after BA in the absence of a stent, the theoretical lack of any stent thrombosis, and the option of shortening dual antiplatelet therapy to only 4 weeks. To overcome the limitations of elastic recoil and flow-limiting dissections after BA, optimal

Table 3 Clinical events at 3-year follow-up

	Total			Post-balloon FFR ≥ 0.75			Post-balloon FFR < 0.75
	DCB (n = 77)	Stent (n = 90)	p value	DCB (n = 77)	Stent (n = 58)	p value	Stent (n = 32)
Cardiac death	0	1 (1.1)	–	0	1 (1.7)	–	0
MI	1 (1.3)	0	–	1 (1.3)	0	–	0
Thrombosis	0	0	–	0	0	–	0
TLR	2 (2.6)	5 (5.6)	0.321	2 (2.6)	3 (5.2)	0.419	2 (6.3)
TVR	3 (3.9)	7 (7.8)	0.276	3 (3.9)	3 (5.2)	0.699	4 (12.5)
MACE	3 (3.9)	8 (8.9)	0.187	3 (3.9)	4 (6.9)	0.426	4 (12.5)

Values are n (%)

MACE major adverse cardiac events (composite of cardiac death, MI and TVR), *MI* myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization

lesion preparation is essential, as outlined in recommendations [10]. Therefore, in our study, rigorous lesion preparation according to established recommendations to achieve an acceptable angiographic result before the use of DCB was mandatory to avoid complications. Nevertheless, we are not free from acute complication like acute vessel occlusion or flow-limiting dissections after BA in using DCB in de novo lesions. This is especially true with larger target vessels. In the current study, there was no flow-limiting dissections and acute vessel closure after procedures, both DCB treatment and stent implantation. Our recent data evaluated the presence of these complications and confirmed that post-balloon FFR-guided DCB treatment was safe (there was no any acute complication or bail-out stenting) and effective for de novo coronary lesions with anatomical and physiological patency at 9 months follow-up [9]. Luminal and FFR gain after DCB treatment were sustained at 9 months without restenosis even though the duration of DAPT was only 4 or 6 weeks. Furthermore, intravascular ultrasound, optical coherence tomography and FFR confirmed that lesions treated with DCB showed persistent anatomical and physiological patency with plaque redistribution, healed dissection flap and vessel remodelling without chronic elastic recoil or plaque compositional changes during follow-up [6, 7].

To avoid the risk of abrupt closure of target lesions after BA, a reliable predictor of coronary flow is necessary especially in de novo coronary lesion. We therefore utilized a validated protocol from the BA era [14], which relies on the fact that reductions in the pressure gradient and the final post-balloon angioplasty pressure gradient are useful indicators of initial angiographic outcome [15]. Bech et al. suggested that an FFR > 0.90 after angioplasty was a good indicator of immediate functional improvement and reduced restenosis at 2 years follow-up [14]. These findings suggest stent-like results can be achieved with a post-balloon FFR of more than 0.90. In our previous study a post-balloon FFR > 0.85 was adopted as the cut-off value to consider DCB treatment instead of stent implantation [9]. However, the results of the DCB group were no different when compared to using a post-balloon FFR value of 0.75. We therefore adopted this latter cut-off to assess angiographic and physiologic results, together with clinical outcomes in this study.

In our study, mismatch population was 68.7% and these lesions were treated with either DCB or stent based on the operator's discretion (33.3% of DCB treatment and 66.7% of stent implantation). If these lesions were treated based on the angiography as recommend by the German consensus group [10], they would have been treated with all stent implantations, since residual DS was above 30% even if post-balloon FFR was larger than 0.75. Our previous mid-term follow-up studies for post-balloon FFR ≥ 0.75 [8, 9] and the current long-term follow-up study showed comparable clinical outcomes between DCB and stent treatments. And thus, FFR-guided DCB treatment could safely reduce the number of unnecessary stent implantations in this mismatch population.

In the population of reverse mismatch, all 6 lesions (7.1%) were treated with stents in our study. But the guideline suggests using DCB over stent, since residual DS was ≤ 30%. If we followed the guideline, one severe dissection case (type C dissection) could be treated with stent, but the rest of them (5 of 6) would receive DCB treatment. It is well known that in patients with functionally significant stenoses, FFR-guided PCI decreases the need of urgent revascularization compared with medical therapy alone [16]. And thus, these reverse mismatch lesions pose a higher clinical risk of future events and it is favorable to be treated with stent implantations. Another distinctive result from reverse mismatch population was that all these lesions were found in LAD only. A previous study reported that reverse mismatch was independently associated with LAD [17]. Among those reverse mismatch population, 4 of them (66.7%) were proximal LAD and thus, lesion location may affect the occurrence of reverse mismatch especially in a larger vessel which supplies a bigger myocardial mass. In these lesions, functional

assessment with post-balloon FFR before the decision of treatment modality could provide more clinical benefits. Also, Kim et al. reported fractional myocardial mass (FMM) in major coronary artery and its branches and showed that the median FMM was 53 g in proximal LAD, 35 g in proximal LCX, and 19 g in RCA [18]. Since LAD supplies a larger myocardial territory, a moderate stenosis can be more functionally significant compared with RCA and LCX.

PCI should be performed after having documented inducible ischemia according to current guidelines, but there are limited data if performing PCI for a functionally nonsignificant residual lesion after BA improves clinical outcomes. FFR calculated by using coronary pressure measurements is a reliable and invasive index to indicate if a stenotic lesion is causing ischemia. FFR can interrogate individual stenosis and therefore can be used for immediate decision-making in the catheterization laboratory [19, 20]. FFR-guided DCB application method may induce less stent implantations in mismatch population and conversely, more stent implantations in reverse mismatch population compared to angiography-guided strategy from German DCB consensus group. Although the post-balloon FFR-guided modality could be reliable to achieve the successful DCB treatment, the safety and efficacy of using post-balloon FFR for de novo coronary artery lesions compared to angiography-guided PCI still needs to be validated in large multi-center randomized trials.

Limitations

The limitations of this study include that it was a single center registry with a small study population and therefore, the results cannot be applied to patients beyond the inclusion criteria and study protocol. Although the results in DCB group were comparable with the stent group, this study cannot draw direct conclusions on the comparisons as the choice of treatment was left to the operator's discretion. To further confirm the efficacy of FFR-guided DCB treatment compared to stent implantation, adequately powered, multi-center randomized trials are required.

Conclusion

There were high frequencies of mismatch between angiographic lesion characteristics and FFR values after balloon angioplasty. A higher incidence of reverse mismatch was found in LAD lesions compared to non-LAD lesions. After balloon angioplasty, FFR measurements may be safe and effective compared to angiography-guided treatment if DCB only treatment is considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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