The Potential Safety of Deferring Percutaneous Coronary Intervention Based on Fractional Flow Reserve in The Ischemia-Induced Intermediate Lesions Defined by Intravascular Ultrasound

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Abstract

It has been proved that it could achieve optimal clinical outcomes by using fractional flow reserve (FFR) to guide percutaneous coronary intervention (PCI). Many studies have reported some anatomic measurements such as minimal lumen area (MLA) by intravascular ultrasound (IVUS) is associated with FFR, but there were few data in Chinese. We assessed the optimal IVUS criteria for functional significant stenosis in Chinese and then evaluated the potential safety of deferring PCI according to FFR>0.80 in those IVUS defined ischemic lesions. A total of 125 intermediate lesions (30% to 70% diameter stenosis) from 101 patients were evaluated by both FFR and IVUS, and a 12 months follow up was made. The major adverse cardiac event (MACE) was defined as a combined endpoint of all cause death, non-fatal myocardial infarction (MI) and target vessel revascularization (TVR). IVUS-MLA showed a positive correlation with FFR (r=0.483, p<0.001) and was one of the independent predictor of FFR ≤ 0.80. The best cutoff value of MLA to define the functional significance was 3.25 mm² (AUC=0.744, 95%CI=0.651-0.839, sensitivity 72.2%, specificity 66.3%). In the retrospective subgroup analysis, there were 56 lesions from 50 patients with IVUS-MLA ≤ 3.25 mm², and 26 lesions with FFR ≤ 0.80 received PCI. After review the data of 12-month follow-up, we found that there was no difference in MACE rate between 2 groups (8.3% in PCI group vs. 0.0% in deferring PCI group, p=0.225). The total events rate (MACE and angina pectoris) was also similar in 2 groups (41.6% in PCI groups vs. 23.1% deferring PCI group, p=0.159). This study indicated significant correlation between FFR and IVUS-MLA in coronary intermediate lesions. Though 3.25 mm² was the best MLA cut-off value to predict FFR ≤ 0.80 in Chinese, the positive predict value was still low. As a result, deferring PCI based on FFR in those MLA ≤ 3.25 mm² lesions was potentially safe during 12-month follow-up.

Keywords: Coronary intermediate lesions; Fractional flow reserve; Intravascular ultrasound; Clinical follow-up

Introduction

Myocardial ischemia is a predictor for clinical outcome in patients with coronary artery disease (CAD) [1]. The presence of myocardial ischemia symptoms is an important risk factor for an adverse clinical outcomes [2,3]. Revascularization of stenotic coronary lesions which induce ischemia can improve patients’ symptoms and outcome [4,5]. However, for those stenotic lesions that do not induce ischemia, deferring percutaneous coronary intervention (PCI) does not increase the incidence of major adverse cardiac events (MACE), and medical therapy alone is likely to be more effective [6,7]. It is still a challenge to assess the intermediate stenosis whether get functional significance or not only by coronary angiography (CAG) [8,9]. Fractional flow reserve (FFR) is generally known as an index to assess the physiological significance of coronary stenosis. An FFR value of 0.80 or less identifies ischemia-causing coronary stenosis with an accuracy of more than 90% [10,11]. Many studies [12-14] have proved that deferring PCI is safe based on FFR in coronary intermediate stenosis, and FFR-guided PCI compared with CAG-guided PCI get much benefit to CAD patients.

Intravascular ultrasound (IVUS) can obtain accurate anatomic measurements of the target vessel. Previous studies have proved that minimal lumen area (MLA) by IVUS is correlated with FFR and can make an estimation of functional significance of the coronary stenosis [15]. Nam’s study indicated that using 4.0mm² as the best MLA value, IVUS-guided PCI strategy for intermediate CAD was associated with favorable outcomes [16]. However, the best value of MLA is still debatable, which is from 2.4 mm² to 4.0 mm². Nowadays, there is few data about the best cutoff value of MLA to define the functional significant stenosis in Chinese people. It has not been reported about the safety of deferring PCI based on FFR in the IVUS-MLA defined ischemia lesions.

The objective of this study was to determine the best MLA criteria associated with functional significance (FFR ≤ 0.80) of intermediate coronary stenosis in Chinese, and then evaluate the potential clinical outcomes of deferring PCI based on FFR in those MLA defined ischemia-induced intermediate coronary lesions.

Methods

Study population

The patient population consisted of 101 patients (125 lesions) who undergoing both FFR and IVUS for de novo intermediate coronary lesions in Peking University 3rd Hospital between October 2010 and November 2012. An intermediate coronary lesion was defined as 30% to 70% diameter stenosis by quantitative coronary angiography (QCA). Patients were not eligible for enrollment if they: 1) had a myocardial infarction earlier than 7 days after occurred; 2) had prior coronary
artery bypass graft surgery; 3) had multiple lesions in the same epicardial artery; 4) had left main disease; 5) A major life threatening illness, a life expectancy of less than 1 year; 6) had contraindications to adenosine, aspirin, or clopidogrel. All patients signed informed consent before entry into the study.

**Study design**

The design of this prospective study has been described in (Figure 1). Firstly, FFR ≤ 0.80 was defined as the significant level of the functional stenosis. Then, the correlation between IVUS and FFR was assessed and the best cut off value of IVUS measurement was obtained. Patients who had stenosis with an FFR of 0.80 or less were to PCI plus optimal medical therapy, others were deferred PCI and to best available medical therapy alone. All patients were followed up for 12 months clinically. Furthermore, a retrospective subgroup analysis was done to the patients with functional significant stenosis defined by IVUS criteria. In this subgroup, the follow-up data was analyzed between PCI patients and deferring PCI patients.

**QCA**

CAG (AXIOM ARTIS VB21 Siemens Germany) was performed in all patients in multiple views after intracoronary injection of 0.1mg nitroglycerin. All target lesions were analyzed using standard definitions and measurements by QCA by two experienced physicians who were blinded to patients’ FFR and IVUS data. Using the guiding catheter for calibration and an edge detection system, the minimal lumen diameter (MLD), reference vascular diameter (RVD), and lesion length (LL) were measured. Percent diameter stenosis (DS%) and area stenosis percent (AS%) were calculated.

**FFR and IVUS**

FFR was defined as the ratio between mean distal coronary pressure and mean aortic pressure at maximal hyperemia. It was measured using a 0.014 - inch pressure guide wire (Radi or Volcano S5, St. Jude medical). The wire was introduced through a 6- to 7-F guiding catheter, equalized, and advanced distal to stenosis. The guide wire was advanced into the coronary artery and positioned > 3 cm distal to the target lesions. The hyperemia was induced with intravenous continuous infusion of adenosine (140 µg/kg/min, 2 min).

IVUS was performed after FFR measurement. The IVUS catheter (s5 Screenshot illustrating VH®IVUS, Volcano) was put into the distal of the lesion and pulled back automatically at a constant speed of 0.5 mm/s. MLA, MLD, and plaque burden percent (PB%) of the lesions were measured following the guidelines for IVUS measurements by American College of Cardiology. MLA was measured at the narrowest luminal cross section and the reference area at the most normal looking cross section within distal 10 mm of the lesion. PB% was calculated at the MLA site.

**Clinical follow-up**

The outcome was the rate of MACE and recurrence angina pectoris at 12 months after the procedure. MACE was defined as a composite of all cause death, non-fatal myocardial infarction and ischemia-driven target vessel revascularization (TVR). The diagnosis of myocardial infarction was based on either the development of new pathological Q waves in 2 or more contiguous leads of electrocardiogram (ECG) and/or an elevation of the cardiac enzyme level more than 3 times the upper limit of normal value. TVR included target lesion PCI and coronary artery bypass graft. Recurrence angina pectoris was defined by typical ischemia chest pain and/or subjective ischemic evidence using noninvasive test such as ECG exercise treadmill test.

**Statistical Analysis**

Data are expressed as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Normality of continuous variables was checked using the histogram and Shapiro-Wilk test. The continuous variables were compared by Student t test or Mann-Whitney U test. Categorical variables were compared using Chi-square test or Fisher exact test as appropriate. Correlations between FFR and IVUS parameters were assessed by Pearson or Spearman correlation analysis. Binary logistic regression was performed to establish the independent determinants of functional significant stenosis. Receiver-operator characteristic curve analysis was used to examine the best cutoff IVUS parameters as a predictor of the functional significance of lesion. The best cutoff value was defined as the maximum sum of sensitivity and specificity. Kaplan-Meier curves are shown for the time-to-event distributions of primary end point. A P value of less than 0.05 was considered statistically significant.
All statistical analyses were performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois).

**Results**

**Baseline characteristics**

Between October 2010 and November 2012, 101 patients with 125 intermediate lesions were enrolled. The mean age was 65.1 ± 10.1 years, and 69 patients (68.3%) were male. Based on FFR, 125 lesions were assigned to FFR ≤ 0.80 group or FFR > 0.80 group.

Baseline clinical, angiographic and IVUS characteristics were shown in (Tables 1 and 2). FFR was 0.80 or less in 36 lesions (28.8%). Besides age (61.0 ± 10.2 years in FFR≤0.80 group vs. 67.0 ± 9.5 years in FFR>0.80 group, p=0.005), there was no difference in baseline clinical characteristics between patients in these two groups.

In QCA measurements, RVD and MLD in FFR≤0.80 group were smaller than in FFR>0.80 group. Others including lesions distribution, LL, DS% and AS%, had no significant difference in both groups. For IVUS parameters, MLA was smaller in FFR≤0.80 group (3.06 ± 0.67mm² vs. 3.93 ± 1.29 mm², p<0.001). MLD in FFR≤0.80 group was also smaller than in FFR>0.80 group (1.83 ± 0.27 mm vs. 2.01 ± 0.35 mm, p=0.003). However, PB% was larger in FFR≤0.80 group (74.4% ± 7.6% vs. 66.8% ± 8.7%, p<0.001).

The correlation between FFR and IVUS measurements

FFR was positively correlated with IVUS-MLA (r=0.483, p<0.001) and IVUS-MLD (r=0.477, p<0.001). And there was a negative correlation between FFR and IVUS-PB% (r = -0.289, p=0.001) (Figure 2).

With regard to independent predictors of FFR≤0.80, logistic regression was analyzed including age, gender, diabetes, hypertension, hyperlipidemia, smoking, family history, acute coronary syndrome, old myocardial infarction, post-PCI history, LAD location, QCA...
measurements including MLD, RVD, DS%, AS%, LL, and IVUS measurements including MLD, PB%, MLA (Table 3). IVUS-MLA was one independent predictor for FFR≤0.80 (adjust OR: 0.398, 95% CI: 0.181 to 0.875, p=0.022).

Receiver operating characteristic (ROC) curve analysis was conducted to identify MLA by IVUS with the best value for predicting FFR≤0.80 (Figure 3). The best cutoff value of IVUS-MLA was 3.25 mm² (72.2% sensitivity, 66.3% specificity, AUC=0.744, 95% CI: 0.651 to 0.836). The positive predictive value was 46.4% and the negative predictive value was 85.5%. The positive predictive value using MLA≤3.25mm² to predict FFR≤0.80 was higher than that using MLA≤4.0 mm² (Figure 4).

The potential safety of deferring PCI based on FFR in the ischemia lesions defined by IVUS-MLA

According to previous result, when the lesions’ MLA was 3.25 mm² or less, PCI therapy should be done. However, the positive predict value of 3.25 mm² was still low. 56 lesions with MLA≤3.25 mm² were chosen or less, PCI therapy should be done. However, the positive predict value using MLA≤3.25 mm² to predict FFR≤0.80 was higher than that using MLA≤4.0 mm² (Figure 4).

Baseline clinical, angiographic and IVUS characteristics of subgroup was shown in (Tables 4 and 5). The mean age in deferring-PCI group was older than in PCI group (71.4 ± 7.9 years vs. 59.4 ± 11.8 years, p<0.001). There was no significant difference in other clinical baseline data between these 2 groups.

The QCA and vessel distribution had no difference between

<table>
<thead>
<tr>
<th>B</th>
<th>S.E.</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.063</td>
<td>0.027</td>
<td>0.019</td>
<td>0.938 to 0.990</td>
</tr>
<tr>
<td>QCA-MLD</td>
<td>-1.958</td>
<td>0.852</td>
<td>0.022</td>
<td>0.141 to 0.750</td>
</tr>
<tr>
<td>PB%</td>
<td>0.121</td>
<td>0.038</td>
<td>0.002</td>
<td>1.129 to 1.217</td>
</tr>
<tr>
<td>IVUS-MLA</td>
<td>-0.922</td>
<td>0.402</td>
<td>0.022</td>
<td>0.398 to 0.875</td>
</tr>
</tbody>
</table>

Other included variables : Vessel location, sex, age, diabetes, hypertension, hyperlipidemia, smoke, family history, diagnosis, previous myocardial infarction, previous PCI, QCA-DS%, QCA-AS%, QCA-LL, QCA-MLD, QCA-RVL, IVUS-MLD, IVUS-PD, IVUS-MLA

CI=confidence interval; OR=odds ratio

Table 3: Determinant of functional significant coronary artery stenosis (FFR ≤ 0.80).

![Figure 3](image3.png)  
Figure 3: ROC curve to determine the best cut-off value of IVUS-MLA to predict FFR ≤ 0.80.

![Figure 4](image4.png)  
Figure 4: The positive predictive value using MLA≤3.25 mm² to predict FFR≤0.80 was higher than using MLA≤4.0 mm².

Table 4: Clinical baseline characteristics of the patients with IVUS-MLA ≤ 3.25 mm².

<table>
<thead>
<tr>
<th></th>
<th>Total (N=50)</th>
<th>PCI group (N=24)</th>
<th>Deferring group (N=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>65.6 ± 11.1</td>
<td>59.4 ± 10.8</td>
<td>71.4 ± 7.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (58.0)</td>
<td>16 (66.7)</td>
<td>13 (50.0)</td>
<td>0.233</td>
</tr>
<tr>
<td>Female</td>
<td>21 (42.0)</td>
<td>8 (33.3)</td>
<td>13 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>21 (42.0)</td>
<td>12 (50.0)</td>
<td>9 (36.4)</td>
<td>0.271</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>33 (66.0)</td>
<td>16 (66.7)</td>
<td>17 (65.4)</td>
<td>0.924</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>31 (62.0)</td>
<td>14 (58.3)</td>
<td>17 (65.4)</td>
<td>0.608</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>23 (46.0)</td>
<td>14 (58.3)</td>
<td>9 (36.4)</td>
<td>0.093</td>
</tr>
<tr>
<td>Family history, no. (%)</td>
<td>12 (24.0)</td>
<td>8 (33.3)</td>
<td>4 (15.4)</td>
<td>0.138</td>
</tr>
<tr>
<td>Diagnosis, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.411</td>
</tr>
<tr>
<td>SAP</td>
<td>12 (24.0)</td>
<td>7 (29.2)</td>
<td>5 (19.2)</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>38 (76.0)</td>
<td>17 (70.8)</td>
<td>21 (80.8)</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction, no. (%)</td>
<td>5 (10.0)</td>
<td>4 (16.7)</td>
<td>1 (3.8)</td>
<td>0.299</td>
</tr>
<tr>
<td>Previous PCI, no. (%)</td>
<td>16 (32.0)</td>
<td>9 (37.5)</td>
<td>7 (26.9)</td>
<td>0.423</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>67.5 ± 8.0</td>
<td>67.4 ± 7.8</td>
<td>67.7 ± 8.4</td>
<td>0.914</td>
</tr>
<tr>
<td>Medication, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>27 (54.0)</td>
<td>14 (58.3)</td>
<td>13 (50.0)</td>
<td>0.555</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>12 (24.0)</td>
<td>6 (25.0)</td>
<td>6 (23.1)</td>
<td>0.674</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>24 (48.0)</td>
<td>13 (54.2)</td>
<td>11 (42.3)</td>
<td>0.402</td>
</tr>
<tr>
<td>β-blocker</td>
<td>18 (36.0)</td>
<td>9 (37.5)</td>
<td>9 (34.6)</td>
<td>0.832</td>
</tr>
<tr>
<td>Statin</td>
<td>26 (52.0)</td>
<td>15 (62.5)</td>
<td>11 (42.3)</td>
<td>0.153</td>
</tr>
</tbody>
</table>

deferring-PCI group and PCI group. In IVUS measurements, PB% in PCI group was higher than in deferring-PCI group (74.5% ± 8.4% vs. 67.5% ± 6.5%, p<0.001). There was no difference in MLD and MLA.

Complete 12-month follow-up data of the patients in subgroup was reviewed and analyzed. 92% of patients accomplished the clinical follow-up (3 patients were lost in deferring-PCI group and 1 patient was lost in PCI group, p=0.661). The 12-month clinical outcomes were summarized in (Figure 5). MACE occurred in 2 patients in PCI group and 0 in deferring-PCI group (8.3% vs. 0.0%, p=0.225). 1 patient in PCI group occurred myocardial infarction 2-month after the procedure and 1 patient in PCI group occurred ischemia-induced target vessel revascularization. No death was observed in both groups. Recurrence angina pectoris occurred in 8 patients in PCI group and in 6 patients in
accurate anatomic information of the stenosis vessel, and previous studies revealed that a MLA could accurately assess the physiological significance of lesion. In present study, IVUS measurements including MLA, MLD and PB% were correlated with FFR, which was similar with previous study. Only MLA was the independent predictor to reveal FFR≤0.80. The result was consistent with the study by Kang [18]. Some studies [15,19] had reported that MLD and vessel location were independent factors to predict FFR too. Although there was controversy on IVUS measurements about predicting FFR, MLA was proved to be the independent predictor and best correlation with FFR in all studies. As a result, we chose MLA as the standard to perform the subgroup analysis further. In this study, the best cutoff value of MLA was 3.25 mm². The sensitivity and specificity was 72.2% and 66.3% respectively, the positive predict value was 46.4% and the negative predict value was 85.5%. This result was consistent with some previous studies which showed MLA had low specificity to predict functional stenosis. It would over-estimate the severity of the lesions. Notably, the specificity of MLA≤4.0 mm² was only 36.6% as in our analysis. It means many patients with whichever MLA≤4.0 mm² or MLA≤3.25 mm² were not ischemic. Bruno R’s meta-analysis [20] showed that a best cut-off value of MLA in non-LM trials was 2.61 mm², and IVUS-MLA may misclassify in up to 20% of the lesions which was similar with our study. Some recent studies showed that MLA was affected by RVD and lesion location, so that the value of MLA was diversity in different researches. FIRST study showed that the accuracy of MLA for identifying FFR<0.80 would be improve when reference vessel-specific analyses were performed [21]. And some studies had reported that the accuracy of MLA to predict FFR was higher in the vessels which had a larger RVD [19,22]. The probable reason was that the deficiency of the vascular lumen was correlation with RVD. For example, in the vessel with RVD ≤ 2.5 mm, little deficiency of lumen would lead to MLA less than the cutoff value; however, in the vessel with RVD>3.5 mm, severe loss of lumen would result significant MLA value [18,22]. Therefore, many studies including present study showed that IVUS measurements such as MLA could not predict physiological significance of a lesion accurately, because the presence of myocardial ischemia is determined by not only the lesion anatomic severity but also the amount of myocardium supplied.

Survival free from MACE and total events were shown by means of Kaplan-Meier curve (Figure 6). There was no differences between these 2 groups both in survival free from MACE and total events.

**Table 5:** Angiographic and intravascular ultrasound parameters of the ivus-mla ≤ 3.25 mm² lesions.

<table>
<thead>
<tr>
<th>Angiographic parameters</th>
<th>Total (N=56)</th>
<th>PCI group (N=26)</th>
<th>Deferring group (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>35 (62.5)</td>
<td>17 (65.4)</td>
<td>18 (60.0)</td>
<td>0.741</td>
</tr>
<tr>
<td>LCX</td>
<td>10 (17.9)</td>
<td>3 (11.5)</td>
<td>7 (23.3)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>9 (16.1)</td>
<td>5 (19.2)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>2 (3.6)</td>
<td>1 (3.8)</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>QCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The major findings in the study are: 1) in coronary intermediate lesions, MLA≤3.25 mm² was the best cutoff value to predict FFR≤0.80 in Chinese people. However, the specificity and positive predict value were not optimal. 2) The retrospective subgroup analysis showed that deferring PCI based on FFR in those IVUS-MLA defined ischemia lesions (MLA≤3.25 mm²) was safe during 12-month follow-up potentially.

In the recent years, FFR was considered to be an accurate method to estimate the functional significant of a stenosis lesion. Park et al. had reported that there were some mismatch between FFR and angiographic diameter stenosis percent [17]. IVUS could obtain

![Figure 5: The 12-month follow-up data of the subgroup analysis.](image-url)
COURAGE study\textsuperscript{6} and other Meta-analysis\textsuperscript{23} have showed that PCI therapy based on CAG was not better than optimal medical therapy alone in decreasing MACE. The aim of FAME study\textsuperscript{12} was to compare the influence to patients’ outcomes between different PCI-guiding procedures. It has proved that the clinical outcome of patients with FFR-guided functional vascularization was significantly better than patients with CAG-guided anatomic vascularization. In those FFR defined non-functional lesions, deferring PCI was proved to be safe. The death and non-fatal myocardial infarction rate was less than 1\%\textsubscript{13} and revascularization rate was less than 2\% in 2 years\textsuperscript{24}. Furthermore, FAME II study\textsuperscript{14} had showed that PCI plus optimal medical therapy in those FFR defined functional significant lesions could get more clinical benefit. Recently, a meta-analysis showed that FFR-guided drug eluting stent (DES) implantation was associated with superior long-term clinical outcomes compared with CAG-based strategy\textsuperscript{25}. As a result, FFR-guided functional vascularization could bring more benefits to CAD patients.

In a long period, IVUS was thought to be another method to assess lesions’ function and guide functional vascularization. According to present study, 3.25mm\textsuperscript{2} was the best cutoff value of IVUS-MLA to predict FFR$\leq$0.80 in Chinese. It means that lesions with MLA$\leq$3.25 mm\textsuperscript{2} would cause myocardial ischemia and should accept PCI therapy. However, the specificity of IVUS-MLA was still low in this study. It would cause over-estimation the functional significance of some stenosis and lead to over-PCI therapy. In order to assess the safety of deferring-PCI in IVUS-MLA defined ischemic lesions, we did the retrospective subgroup analysis. After 12-month follow-up, we found in those IVUS-MLA defined ischemic lesions, making clinical procedure based on FFR was still safe potentially. Both the MACE rate and total events rate have no significant difference between PCI group and deferring-PCI group. Nam’s\textsuperscript{16} had done a non-random study to 177 intermediate lesions. 83 of them was guided by FFR ($<0.80$) to make the procedure, and 94 of them was guided by IVUS (MLA$<4.0$ mm\textsuperscript{2}). 33.7\% lesions in FFR group and 95.3\% lesions in IVUS group received PCI therapy, but the MACE rate had no significant difference in those 2 groups. This result was consisting with our study. We also found that IVUS could over-estimate the severity of stenosis and cause more than 50\% lesions received unnecessary PCI therapy. To those FFR defined non-functional stenosis, although IVUS-MLA indicated ischemia, deferring-PCI in those lesions maybe was still safe.

Besides MACE, improving the symptom was another important goal in CAD patients. Many studies have showed PCI therapy was better than medical therapy alone in relieving angina pectoris. However, in subgroup analysis of our study, we found the rate of recurrent angina was higher in PCI group than deferring-PCI group during the follow-up. It also indicated that deferring-PCI in those non-functional lesions was not only safe but also get much benefit in improving life quality. This result was similar with DEFER study.

There were still some limitations about our study. First, this was a single center, small sample, non-random study, and the recruit of the patients was not continuous. As a result, we could not exclude selection bias. Secondly, the subgroup analysis was a retrospective research. Because the number of patients was too small, the results of the subgroup analysis just indicate a potential possibility, it should be proved significantly after enlarge the sample sizes. Besides, during the follow-up, we could not get the CAG follow-up data.

In conclusion, we found that IVUS-MLA could predict FFR. The best-cutoff value was 3.25mm\textsuperscript{2}, but the positive value was less than 50\%. It indicated that IVUS would over-estimate the functional significance in more than a half intermediate lesions and cause overtreatment. Furthermore, we found that deferring PCI based on FFR$>0.80$ in those IVUS-MLA defined ischemic lesions could still get favorable clinical outcomes potentially. Thus, we suggest using FFR to guide whether did PCI therapy or not in the intermediate lesions in CAD patients. However, if the hospital had no condition to measure FFR, IVUS-MLA$\leq$3.25 mm\textsuperscript{2} could be a relative good substitution to guide functional estimation and revascularization.

References

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