Fractional Flow Reserve Compared With Intravascular Ultrasound Guidance for Optimizing Stent Deployment

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Background—Determination of fractional flow reserve (FFR) has been proposed as a means to assess stent deployment. In this prospective, multicenter trial, we evaluate the use of FFR to optimize stenting by comparing it with standard intravascular ultrasound (IVUS) criteria.

Methods and Results—Eighty-four stable patients with isolated coronary lesions underwent coronary stent deployment starting at 10 atm and increased serially by 2 atm until the FFR was ≥0.94 or 16 atm was achieved. IVUS was then performed. FFR was measured with a coronary pressure wire with intracoronary adenosine to induce hyperemia. The diagnostic characteristics of an FFR <0.94 to predict suboptimal stent expansion by IVUS, defined in both absolute and relative terms, were calculated. Over a range of IVUS criteria, the highest sensitivity, specificity, and predictive accuracy of FFR were 80%, 30%, and 42%, respectively. Receiver operator characteristic analysis defined an optimal FFR cut point at ≥0.96; at this threshold, the sensitivity, specificity, and predictive accuracy of FFR were 75%, 58%, and 62%, respectively (P<0.03 for comparison of predictive accuracy, P<0.01 for concordance between FFR and IVUS). The negative predictive value was 88%. Significantly better diagnostic performance was achieved in a subgroup that received higher doses (>30 μg) of intracoronary adenosine during pressure measurements, suggesting that FFR might be overestimated in the other group.

Conclusions—A fractional flow reserve <0.96, measured after stent deployment, predicts a suboptimal result based on validated intravascular ultrasound criteria; however, an FFR ≥0.96 does not reliably predict an optimal stent result. Higher doses of intracoronary adenosine than previously used to measure FFR improve these results. (Circulation. 2001;104:1917-1922.)

Key Words: angioplasty • stents • adenosine • pressure

An important criterion of optimal stent deployment is maximum expansion throughout the length of the stent. Angiography alone is not a precise technique to detect local areas of incomplete stent expansion. In 40% to 70% of stents that appear well deployed by angiography, intravascular ultrasound (IVUS) imaging reveals a region of the stent that is underexpanded compared with the remainder of the stent and with the reference segments. A number of studies have shown that the IVUS-determined absolute and relative minimum stent areas are more powerful predictors of freedom from restenosis than any angiographic variable. However, the time required to perform a careful IVUS examination, the expense of the catheters, and the expertise required to interpret the images represent practical barriers for many operators.

Recently, the availability of accurate pressure-sensing guide wires and the development of the fractional flow reserve (FFR) index have offered a new and convenient method for measuring the physiological impact of epicardial coronary stenoses, including those remaining after suboptimal stent deployment. FFR is defined as the maximum blood flow to the myocardium achieved in the presence of a narrowing compared with the theoretical maximum blood flow possible in the absence of the narrowing. It is calculated by comparing the mean coronary pressure distal to a stenosis, as measured by a coronary pressure wire, with the mean
proximal coronary pressure, as measured by a guiding catheter, at maximal hyperemia. FFR was originally introduced as an index for evaluating angiographically intermediate coronary lesions, where a value of ≤0.75 has been shown to correlate with stress-induced ischemia and a value ≥0.75 with low event rates during the ensuing year.

Because FFR indicates the status of epicardial conductance, it has also been evaluated as an aid in gauging the success of coronary interventions. In the setting of balloon angioplasty, an FFR ≥0.90 has been shown to predict freedom from restenosis, particularly when combined with a favorable angiographic result. Recently, in a small single-center study evaluating coil stents, an FFR ≥0.94 was identified as the appropriate threshold defining optimal stent deployment. This finding has not been evaluated in a broader trial with current generation stents. The aim of the current study was to investigate the application of FFR to stent optimization in a prospective, multicenter trial format, by comparing the FFR after stenting with standard IVUS criteria for optimal stent deployment.

Methods

Patients
Patients older than 18 years of age who were undergoing stenting of a native coronary artery were eligible for this study. Patients with multivessel disease were included; however, the target vessel could not have a second lesion >50% on angiography. Major exclusion criteria included primary stenting for acute myocardial infarction (MI), Braunwald class III unstable angina, or MI within the past month. All patients provided informed written consent; the protocol was approved by the Institutional Review Board for Human Subjects at each of the 11 participating US centers.

Procedure
Each patient underwent stent deployment at a starting pressure of 10 atm. FFR was measured, and if ≥0.94, IVUS was performed. To monitor the effect of graded expansion on FFR, serial balloon inflations were performed at 12, 14, and 16 atm. Once the FFR was ≥0.94 or a pressure of 16 atm was achieved, IVUS was performed. Balloon and stent type and size were left to the operator’s discretion. Figures 1 and 2 outline case examples.

FFR Measurements
FFR was measured with a 0.014-inch miniaturized pressure monitoring guide wire system, PressureWire (Radi Medical Systems), to record the coronary pressure distal to the stented segment. FFR was calculated by dividing the mean distal coronary pressure by the mean proximal coronary pressure, measured by the guiding catheter, during maximal hyperemia. In most cases, only a single measurement was made. Hyperemia was induced with intracoronary adenosine. The recommended dosage for intracoronary adenosine was 15 to 30 μg for the right coronary artery and 20 to 40 μg for the left coronary system, but the exact dosage was left to the operator’s discretion. Guiding catheters with side holes were not used. FFR calculations were reviewed in a core laboratory by investigators who were blinded to the IVUS results.

IVUS Measurements
IVUS was performed with either a Cardiovascular Imaging Systems/Boston Scientific Corp or an Endosonics Corp ultrasound imaging system. IVUS measurements were made off-line (Tape Measure, Indec Inc.), at end diastole, in a core laboratory, blinded to the FFR results. They included minimum stent diameter and area, proximal and distal stent edge diameters and areas, and proximal and distal reference diameters and areas. Reference vessel measurements were made before a major branch, 5 to 10 mm proximal to or distal to the stented region, in the least diseased section. Stent expansion, apposition, and lumen ratio were also assessed. The percent area expansion was defined as the minimum stent area (MSA) divided by the average of the proximal and distal reference areas. Incomplete apposition was defined as at least one stent strut not apposed to the vessel wall, with clear blood flow behind it.

Figure 1. Example of case demonstrating poor correlation between FFR and IVUS. Images: A, Preintervention angiogram demonstrating tight lesion in left circumflex coronary artery (arrow); B, postintervention angiogram demonstrating residual stenosis of 5% by QCA; C, pressure tracing showing phasic and mean pressures recorded simultaneously from guiding catheter and pressure wire after balloon inflation at 10 atm with FFR of 0.96 (recording from pressure wire is lower pressure tracing); D, IVUS image of MSA, which is 4.8 mm², providing percent area expansion of 68%.
Quantitative Coronary Angiography
A core angiographic laboratory performed quantitative coronary angiography (QCA) with QCAPlus (Sanders Data Systems), blinded to the FFR and IVUS results. With the guiding catheter used as a scaling device, analysis of the reference diameter, minimum lumen diameter, percent diameter stenosis, and lesion length were calculated, both before and after stenting.

Analysis
The sensitivity, specificity, positive and negative predictive values, predictive accuracy, and likelihood ratio (sensitivity/1 – specificity) for an FFR < 0.94 to predict a suboptimal IVUS result based on a variety of absolute and relative criteria were calculated. In addition, a receiver operator characteristic curve was created to determine the most accurate cut point for defining an optimal FFR result. A retrospective subset analysis comparing the effect of adenosine dosage on the correlation between FFR and IVUS was performed.

Single proportions were averaged and listed as mean ± SD. Two proportions were compared by means of a 2-tailed Fisher’s exact test. A significant difference was defined as a value of P < 0.05.

Analyses were performed with Number Crunching Systems Software.

Results
Patient and Procedural Characteristics
Characteristics of the 84 patients enrolled in the study are outlined in Table 1. Their average age was 62 years; 79% were men. The average percent diameter stenosis by QCA before intervention was 70%, with an average lesion length of 7 mm and an average reference diameter of 3.1 mm. All of the stents deployed were slotted tube stents [Guidant, (Duet, 15, Multilink, 15, Tristar, 11); Boston Scientific (Nir, 32); AVE/Medtronic (S670 = 8); Cordis Corp, (Crossflex, 2; Bx Velocity, 1)], with an average diameter of 3.3 mm, length of 18 mm, and maximal deployment pressure of 12.4 atm. The average maximal dosage of intracoronary adenosine was 32 μg. The average final FFR was 0.95; the average MSA by IVUS was 6.1 mm²; and the average residual stenosis by QCA was 8.7%. Incomplete apposition was noted in 19% and incomplete expansion in 70%. In 8 of the patients with

Data are listed as mean ± SD or percent.
incomplete apposition, the FFR was ≥0.96 and in 13 it was ≥0.94.

Comparison of FFR With IVUS
Table 2 and Table 3 depict the correlation between FFR and IVUS for assessing optimal stent deployment with various cut points used to define optimal FFR and IVUS results. For example, using a cut point of ≥0.94 to define an optimal FFR result and an MSA ≥7 mm² to define an optimal IVUS result, the diagnostic characteristics of FFR to predict the IVUS result were sensitivity, 80%; specificity, 30%; negative predictive value, 83%; positive predictive value, 26%; predictive accuracy, 42%; and likelihood ratio, 1.1 (P=NS for concordance between FFR and IVUS). Receiver operator characteristic curve analysis showed that an FFR cut point of ≥0.96 provided the best concordance (ie, highest predictive accuracy) with the IVUS result (Figure 3). There was a significant correlation between FFR and IVUS with the FFR cut point ≥0.96 and IVUS cut point of MSA ≥7 mm² (P=0.01 for concordance between FFR and IVUS). The diagnostic characteristics were sensitivity, 75%; specificity, 58%; negative predictive value, 88%; positive predictive value, 36%; predictive accuracy, 62%; and likelihood ratio, 1.8. This predictive accuracy was significantly better than the predictive accuracy of 42% with an FFR cut point of ≥0.94 (P=0.01).

The data were also analyzed with the use of relative IVUS criteria (ie, percent area expansion) to define an optimal IVUS result. The diagnostic characteristics of FFR in this setting are also displayed in Tables 2 and 3. Including other IVUS characteristics in the definition of an optimal result (eg, apposition, expansion, or lumen ratio) did not improve the correlation between FFR and IVUS.

Comparison of QCA With IVUS
With the use of a residual stenosis of ≤10% by QCA to define an optimal stent result and an MSA ≥7 mm² to define and optimal IVUS result, the diagnostic characteristics of QCA to predict the IVUS result were as follows: sensitivity, 60%; specificity, 30%; negative predictive value, 71%; positive predictive value, 21%; predictive accuracy, 38%; and likelihood ratio, 0.9 (P=NS for concordance between QCA and IVUS). The combination of a FFR ≥0.96 and an optimal QCA result did not correlate better with an optimal IVUS result than the FFR result alone.

### Table 2. Diagnostic Characteristics of FFR ≥0.94 to Predict an Optimal IVUS Result With Various IVUS Cut Points

<table>
<thead>
<tr>
<th>IVUS Cut Point</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
<th>Predictive Accuracy, %</th>
<th>Likelihood Ratio</th>
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<tr>
<td>MSA ≥6 mm²</td>
<td>77</td>
<td>31</td>
<td>61</td>
<td>49</td>
<td>52</td>
<td>1.1</td>
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<tr>
<td>MSA ≥7 mm²</td>
<td>80</td>
<td>30</td>
<td>83</td>
<td>26</td>
<td>42*</td>
<td>1.1</td>
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<tr>
<td>MSA ≥8 mm²</td>
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<td>28</td>
<td>83</td>
<td>18</td>
<td>36</td>
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<tr>
<td>% AE ≥70</td>
<td>68</td>
<td>19</td>
<td>26</td>
<td>59</td>
<td>50</td>
<td>0.84</td>
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<tr>
<td>% AE ≥80</td>
<td>63</td>
<td>21</td>
<td>48</td>
<td>33</td>
<td>37</td>
<td>0.80</td>
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<tr>
<td>% AE ≥90</td>
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<td>26</td>
<td>74</td>
<td>20</td>
<td>35</td>
<td>0.90</td>
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<tr>
<td>MSA≥6 or %AE≥70</td>
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<td>74</td>
<td>22</td>
<td>60</td>
<td>0.93</td>
</tr>
<tr>
<td>MSA≥7 or %AE≥90</td>
<td>76</td>
<td>29</td>
<td>70</td>
<td>36</td>
<td>45†</td>
<td>1.1</td>
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</table>

%AE indicates percentage area expansion (MSA/average reference area); NPV and PPV, negative and positive predictive values.

*P=0.01 for comparison with predictive accuracy in Table 3; †P=0.01 for comparison with predictive accuracy in Table 3.

### Table 3. Diagnostic Characteristics of FFR ≥0.96 to Predict an Optimal IVUS Result With Various IVUS Cut Points

<table>
<thead>
<tr>
<th>IVUS Cut Point</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
<th>Predictive Accuracy, %</th>
<th>Likelihood Ratio</th>
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<tr>
<td>MSA ≥6 mm²</td>
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<td>56</td>
<td>60</td>
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<tr>
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<td>55</td>
<td>90</td>
<td>26</td>
<td>58</td>
<td>1.6</td>
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<td>% AE ≥70</td>
<td>49</td>
<td>48</td>
<td>62</td>
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<td>49</td>
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<tr>
<td>% AE ≥80</td>
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<td>48</td>
<td>60</td>
<td>36</td>
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<td>0.90</td>
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<tr>
<td>% AE ≥90</td>
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<td>83</td>
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<td>1.3</td>
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<tr>
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<tr>
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<td>60</td>
<td>79</td>
<td>48</td>
<td>63†</td>
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</tbody>
</table>

%AE indicates percent area expansion; NPV and PPV, negative and positive predictive values.

*P=0.01 for comparison with predictive accuracy in Table 2; †P=0.01 for comparison with predictive accuracy in Table 2.
Area expansion cut point of 0.96, with IVUS criteria of MSA ≥7 mm² or percent area expansion ≥90.

Figure 3. Sensitivity-specificity plot demonstrating optimal FFR cut point of 0.96, with IVUS criteria of MSA ≥7 mm² or percent area expansion ≥90.

Impact of Intracoronary Adenosine Dosage

Subgroup analysis was performed to assess whether the dosage of intracoronary adenosine affected the results (Figure 4). The sensitivity, specificity, and predictive accuracy of FFR in patients who received ≤30 μg of intracoronary adenosine were 54%, 53%, and 53%, respectively. In those who received >30 μg of intracoronary adenosine, the sensitivity, specificity, and predictive accuracy improved to 81%, 71%, and 76%, respectively. The predictive accuracy was significantly better in the high-dose adenosine group (P=0.04). An FFR cut point of 0.96 continued to provide the highest predictive accuracy.

Discussion

The main finding in this multicenter study performed with FFR in patients who received 4). The sensitivity, specificity, and predictive accuracy of dosing intracoronary adenosine affected the results (Figure 4). The sensitivity, specificity, and predictive accuracy of FFR in patients who received ≤30 μg of intracoronary adenosine were 54%, 53%, and 53%, respectively. In those who received >30 μg of intracoronary adenosine, the sensitivity, specificity, and predictive accuracy improved to 81%, 71%, and 76%, respectively. The predictive accuracy was significantly better in the high-dose adenosine group (P=0.04). An FFR cut point of 0.96 continued to provide the highest predictive accuracy.

On the other hand, our results also demonstrate that FFR does not reliably predict an optimal result defined by IVUS measurements. In fact, in using the predefined cut point of FFR ≥0.94 to define an optimal stent result, FFR did not correlate with the absolute or relative IVUS measurements of stent area. An FFR threshold of 0.96, although only slightly higher than 0.94 (a difference that is close to the resolution of the pressure measurement system), improved the predictive accuracy to 62% (P=0.01 for concordance between FFR and IVUS). There remained, however, a proportion of patients in whom the FFR result was optimal, but the IVUS result remained suboptimal, giving a specificity of 58%.

Our analysis suggests several possible reasons why FFR did not correspond more closely to the IVUS-determined stent dimensions. First, in this study, the decision was made prospectively to induce hyperemia with intracoronary adenosine, with the expectation that intracoronary is likely to be favored over intravenous administration in the United States because it is a less expensive and more convenient technique. Intravenous administration, however, may be a more reliable hyperemic stimulus. If full hyperemia is not achieved in a given intracoronary injection, the apparent FFR is increased—that is, made to appear falsely normal. Maximizing hyperemia is especially important when measuring FFR after stenting because detection of very small gradients is necessary to distinguish an optimally deployed stent from a suboptimally deployed stent.

Traditionally, the recommended dose of intracoronary adenosine for measuring FFR has been 15 to 20 μg. An important practical observation of the current study is that higher doses of intracoronary adenosine (30 to 40 μg) substantially improved the correlation of FFR with IVUS (predictive accuracy of 76% versus 53% in the traditional dose group, P=0.04). No complications were seen in the higher-dose group.

A second reason for the lack of a closer correlation between FFR and IVUS is the potential for significant— but angiographically undetected—stenoses occurring outside of the stent. Unless a slow pullback of the pressure wire is performed under continuous intravenous adenosine infusion to search for occult pressure drops occurring outside of the stent, the cause of an abnormally low FFR may be falsely attributed to the stented segment. Alternatively, measuring FFR immediately distal to and immediately proximal to the stent with intracoronary adenosine isolates the contribution of the stented segment to the FFR; this adds time and complexity to the recording and analysis and was performed in only a minority of patients in this study.

A third reason for a lack of correlation between the FFR and IVUS findings is based on the sensitivity of FFR in discriminating subtle changes in flow obstruction in the nearly normal range (ie, the range of stent optimization). Once a reasonable initial expansion of a stent is achieved, small increases in the MSA may not consistently alter FFR because the lumen has already expanded to a degree that physiological obstruction is minimal and changes are difficult to detect. Further increases in stent area—beyond the point where the FFR has become normal—may still be clinically important in cases in which subsequent intimal proliferation occurs. The greater the initial MSA, the less likely it is that intimal proliferation will lead to a functionally significant stenosis in follow-up.

![Figure 4. Comparison of diagnostic characteristics of FFR ≥0.96 to predict optimal stent result by IVUS (MSA ≥7 mm² or percent area expansion ≥90%) depending on dosage of intracoronary adenosine administered (low-dose adenosine, ≤30 μg; high dose >30 μg). *P < 0.04 for comparison. NPV and PPV indicate negative and positive predictive values.](image-url)
Comparison With the Literature

In the only other study evaluating the use of FFR to assess stent deployment, Hanekamp et al\(^\text{15}\) demonstrated a strong correlation between the FFR and IVUS results after stenting. The design of that study differed in important ways from this one. Hanekamp et al deployed each stent at a much lower initial pressure of 6 atm and per protocol correlated FFR and IVUS over a wide range of deployment conditions ranging from clearly suboptimal to optimal. In the present study, IVUS was performed once only, after the FFR was ≥0.94 or a 16-atm inflation pressure was reached. In this way, the ability of FFR to predict an optimal IVUS result was more rigorously tested. It is also important to note that Hanekamp et al used the Wiktor-i stent, a coil stent, which, because of its design, probably has a greater chance of affecting blood flow and the coronary pressure if underdeployed. In the present study, only current-generation, slotted-tube stents were implanted, which are less likely to affect coronary flow if underexpanded. Finally, all of the measurements of FFR in the study by Hanekamp et al were made using intravenous adenosine, a more consistent means of inducing hyperemia.\(^\text{9}\)

Limitations

In retrospect, the decision to use intracoronary adenosine at traditional doses was a limitation of this study. However, the subgroup analysis of higher-dose adenosine indicates that the specificity of FFR for stent optimization is still not high. Intravenous adenosine might provide a better specificity than intracoronary adenosine, but it is more time consuming and, in the United States, considerably more expensive. In general, FFR measurements were made only once in this study. Repeating all FFR measurements and averaging the two values probably would not have had a dramatic impact, given that the variability in repeat FFR measurements is in the range of only 0.01.\(^\text{17}\)

In this study, IVUS served as the reference standard for optimal stent deployment; of course, IVUS has its own limitations in accuracy and provides anatomic information only. Clinical follow-up of patients in whom FFR was measured after stenting will be necessary in future studies to validate these findings and to investigate how optimal IVUS (anatomy) or optimal FFR (physiology) results affect the clinical outcome.

Conclusions

In this multicenter study, a fractional flow reserve <0.96 after stenting predicted a suboptimally deployed stent based on IVUS criteria. On the contrary, an FFR ≥0.96 measured with intracoronary adenosine did not reliably predict an optimal result. Higher doses of intracoronary adenosine than previously used are important to optimize the value of fractional flow reserve measurements after stenting.

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