Influence of the Amount of Myocardium Subtended by a Stenosis on Fractional Flow Reserve

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Background—Fractional flow reserve (FFR) specifically relates to the severity of a stenosis to the mass of tissue to be perfused. Accordingly, the larger the territory to be perfused, the greater the flow and the pressure gradient induced by maximal hyperemia. Although this notion may be considered intuitive, its unequivocal demonstration is still lacking. The aim of our study was to evaluate the influence of the amount of myocardium subtended to an intermediate stenosis on FFR, especially in relation to quantitative coronary angiography.

Methods and Results—The severity of each lesion was assessed by FFR and 2-dimensional quantitative coronary angiography. The amount of jeopardized myocardium was evaluated using 3 validated scores specifically adapted to this aim: the Duke Jeopardy Score (DJS), the Myocardial Jeopardy Index (MJI), and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Lesion Score (ALS). The presence of a concomitant collateralized chronic total occlusion was also reported. A total of 213 intermediate coronary stenoses in 184 patients were enrolled. FFR values were correlated to minimal lumen diameter (r=0.34; P<0.0001) and diameter stenosis (r=-0.28; P<0.0001). FFR was inversely correlated with DJS, MJI, and ALS (r=-0.28, P<0.0001; r=-0.40, P<0.0001; and r=-0.34, P<0.0001). Lesions localized on proximal left anterior descending were related to significantly lower FFR values and to a higher rate of a positive FFR compared with those in distal left anterior descending, left circumflex, and right coronary arteries (0.80±0.09 versus 0.84±0.08 versus 0.88±0.09 versus 0.91±0.04; P<0.0001). The presence of a collateralized chronic total occlusion was associated with significantly lower FFR values (0.80±0.07 versus 0.85±0.09; P<0.005). At multivariate analysis MJI, minimal lumen diameter, and presence of a collateralized chronic total occlusion were confirmed as significant predictors of FFR.

Conclusions—A larger amount of perfused myocardium subtended by a stenosis is associated with a higher probability that an angiographically intermediate coronary stenosis is functionally significant. (Circ Cardiovasc Interv. 2013;6:00-00.)

Key Words: coronary angiography ■ coronary heart disease ■ myocardial fractional flow reserve

The accuracy of coronary angiography in correctly assessing the severity and, more importantly, the hemodynamic relevance of angiographically intermediate coronary stenoses is largely debated. This is attributed not only to the inter- and intraobserver variability in the interpretation of coronary angiograms, which could be reduced by the systematic use of 2-dimensional and 3-dimensional quantitative coronary angiography (QCA),1 or to the limited spatial resolution of conventional angiography, which could be easily overcome by endovascular imaging, but also to the evidence that lumen narrowing is only 1 of the multiple determinants of the functional significance of a stenosis.2 To this regard, the use of the pressure wire to calculate fractional flow reserve (FFR) has emerged as a powerful tool not only to correctly diagnose a hemodynamically significant stenosis but also to guide a safe and cost-effective percutaneous coronary intervention.3

Among many favorable characteristics that have contributed to the success of FFR, one is the ability of FFR to specifically relate the severity of a stenosis to the mass of tissue to be perfused.4 Accordingly, the larger the amount of perfused tissue, the greater the flow and the pressure gradient induced by maximal hyperemia. Although this notion is intuitive and is suggested by few indirect data,5-8 its unequivocal demonstration is still lacking. Thus, the aim of the present study was to assess the influence of the amount of myocardium subtended to an index lesion on FFR, also in relation to lesion-specific characteristics assessed by QCA. The amount of perfused myocardium subtended by a stenosis was assessed using 3 well-validated scores specifically

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WHAT IS KNOWN

• Fractional flow reserve is moderately and inversely correlated to minimal lumen diameter, minimal lumen area, and percentage diameter stenosis.

• It is widely accepted that fractional flow reserve is dependent on the amount of tissue to be perfused. Nevertheless, this assumption has never been formally demonstrated.

WHAT THE STUDY ADDS

• We demonstrate, for the first time, that a hemodynamically significant stenosis is associated not just to the anatomic severity of the lesion but also to the amount of myocardial tissue subtended by the stenosis itself.

• We confirm that coronary angiography, even when used with a well-validated quantitative software has a mild, although significant, ability to predict functionally significant stenoses, especially when they appear intermediate at visual estimation.

Intermediate coronary stenoses were defined on the basis of visual estimation as those determining a reduction of vessel diameter between 30% and 80%. Lesions in coronary arteries with diffuse coronary artery disease as well localized on left main or coronary artery by-pass grafts or supporting an area of infarcted myocardium were excluded (Figure 1).

Coronary Angiography and Measurement of FFR

Diagnostic coronary angiography was performed through radial or femoral percutaneous approach. Nonionic contrast medium was used for all patients. At least 2 different projections differing >30° were recorded for each assessed lesion. Coronary stenoses were visually assessed by the operator and, when clinically indicated, FFR was performed. After administration of heparin 100 IU/kg IV, a 0.014-inch pressure monitoring guide wire (Pressure Wire Certus, St. Jude Medical, St. Paul, MN, or Prime Wire Volcano Therapeutics, Inc, Rancho Cordova, CA) was calibrated and introduced into the guiding catheter. The wire was advanced into the guiding catheter until the pressure transducer was just outside its tip, and the pressure measured by the sensor was then equalized to that of the guiding catheter. The wire was then advanced into the vessel distally to the target coronary stenosis. Special attention was paid to avoid arterial pressure wave damping, nonselective cannulation of coronary ostia and variations in the position of the pressure wire tip. FFR was calculated as the lowest ratio of distal coronary pressure divided by aortic pressure after achievement of maximal hyperemia, obtained using intravenous or intracoronary adenosine. Femoral or brachial vein was used for intravenous 140 μg Kg-1 minute-1 adenosine administration, and maximal hyperemia was assumed at least after 60 seconds in the presence of stable systemic blood pressure decrease compared with baseline remaining for at least 10 beats. For intracoronary adenosine, incremental bolus of intracoronary adenosine (60 μg, 300 μg, and 600 μg) were administered with each next dose given at least 60 seconds apart from the previous or after returning to baseline hemodynamic conditions. Each administration was performed in 5 to 10 seconds and rapidly flushed by saline solution. Next higher dose was not administered in case of atrioventricular block lasting >5 seconds and intravenous adenosine was used to induce maximal hyperemia. Similarly in case of FFR values between 0.81 and 0.83 with 600 μg intracoronary adenosine, FFR was retested using intravenous adenosine according to our internal protocol. Finally, an FFR value of <0.80 was considered abnormal. When >1 stenosis was present in the same artery, we used a pull-back maneuver under maximal hyperemia to appreciate the exact location and physiological significance of sequential stenoses.

Assessment of Coronary Angiography

Localization on the coronary tree and quantitative assessment of stenosis severity at coronary angiography was performed offline independently by 2 expert interventional cardiologists blinded to clinical and FFR data. In particular, for the LAD, the lesion was considered proximal if localized before a well-developed (≥ 2 mm) first diagonal branch or within the proximal third of the vessel, whereas the remaining lesions were considered distal. The presence of a collateralized CTO in another vessel was also reported.

Two-dimensional QCA was performed offline using the cardiovascular angiography analysis II system (Pie Medical Imaging, Maastricht, the Netherlands). Automated distance calibration was used to determine pixel size. All analyses were performed during the ECG-gated end-diastolic frame. Angiographic views with the least foreshortening and yielding the best depiction of the stenoses were used. Edge detection correction was performed if required. Reference vessel diameter (RVD), lesion length (LL), minimal lumen diameter (MLD), and diameter stenosis (DS) were calculated.

Calculation of the Amount of Myocardium Subtended by the Stenosis

The Duke Jeopardy Score

The DJS was developed by Dash et al and validated by Califf et al. The coronary tree is divided into 6 segments: the LAD,
diagonal branches of the LAD, septal perforating branches, the circumflex coronary artery, obtuse marginal branches, and the posterior descending coronary artery. Two points are assigned to each of these segments. All segments distal to the index stenosis are considered to be at risk. The maximum possible score is 12 for all myocardial mass and, for example, 6 for the proximal LAD.

The Myocardial Jeopardy Index

The MJI is a well-validated method, coming from the Bypass Angioplasty Revascularization Investigation group,11 to calculate jeopardized myocardium based on the size and the distribution of the coronary arteries. In this score, LAD, left circumflex, and right coronary arteries, as well as the ramus, diagonals, obtuse marginals, posterior descending, and posterolateral branches are graded based on vessel length and size according to specific criteria. In particular, a score of 0 indicates an insignificant or inconspicuous artery, and a score of 3 represents a large artery extending more than two thirds of the distance from base to apex. Septal branches are arbitrarily assigned a maximum total score of 3. Right-ventricular marginals and posterior descending artery septal branches are not scored. All scores of branches distal to the index lesion are summed and divided by the global score, supplying the entire left ventricle to calculate the jeopardized myocardium as a percentage of left-ventricular myocardial volume.15

APPROACH Lesion Score

The ALS was initially developed at the Green Lane Hospital,16 with subsequent modifications from pathological data as reported by Kalbfleish and Hort17 and Lee et al.14 Specifically, to calculate the ALS in our study, the amount of myocardium jeopardized by the index lesion was calculated taking into account the downstream area, expressed as a percentage of the left ventricle, according to pathological data, and the location of the stenosis.12 When the stenosis was not located in the proximal part of the vessel, the amount of jeopardized myocardium was reduced to two thirds of the region if the lesion was located in the middle part of the vessel and to one third when placed in the distal segment.

Statistical Analysis

Categorical variables were expressed as percentages and analyzed by Fisher exact test. Continuous variables were expressed as mean±SD and compared by the t test. Correlation was performed using r Pearson test. Intra- and interobserver reproducibility of the different jeopardy scores was tested on the first 50 patients by the 2 expert interventional cardiologists involved in the quantitative assessment of stenosis severity at coronary angiography. Multivariable analysis to identify predictors of FFR was performed including in the model all the variables correlated to FFR with a P value ≤0.1 chosen among the following: age, sex, major cardiovascular risk factors (diabetes mellitus, active smoking, hypertension, dyslipidemia, familiarity for coronary artery disease), history of previous myocardial infarction in myocardial territory remote from that of target lesion and indication of coronary angiography, medical therapy, QCA parameters, and the amount of jeopardized myocardium. In case of evident collinearity between 1 variable and another similar, only the most significant was included in the model. All statistical analyses were performed using Statistica 5.5 (Stat Soft Inc, Tulsa, OK) and Prism 5.0 (Graphpad Software Inc, La Jolla, CA). A P value of 0.05 was considered significant.

Results

Clinical and Procedural Characteristics

FFR was performed in 213 intermediate coronary stenoses in 184 consecutive patients (Figure 1). Patients’ characteristics of the final population are summarized in Table 1. The mean age was 65±10 years and 78% were males. They were referred for coronary angiography for chronic stable angina (43%), atypical chest pain (20%), previous acute coronary syndrome (30%), or silent ischemia (7%). Seventy-eight patients (42%) had a previous percutaneous coronary intervention, 60 (33%) a previous myocardial infarction in a remote area, and 33 (18%) a collateralized CTO. The visually estimated average angiographic percentage stenosis was 60±11%. The target lesion was located on proximal LAD artery in 54 (25%) cases, on distal LAD artery in 100 (47%), on circumflex artery in 40 (19%), and on right coronary artery in 19 (9%). Mean FFR was 0.85±0.09 with 67 lesions on 213 (31%) with an FFR <0.80. All QCA parameters (Table 1) were in agreement with the enrollment of intermediate coronary stenoses. Mean DJS, MJI, and ALS were 3.47±1.56, 29.77±11.34%, and 31.86±12.84%, respectively. Reproducibility for the assessment of the different jeopardy score was very good for both intra- (r=0.99; P<0.001 for DJS and r=0.98; P<0.001 for

Figure 1. Lesions enrolled after exclusion criteria (see text for details). CAD indicates coronary artery disease.
Among the different clinical characteristics, FFR was significantly correlated to age only (r=0.18; P=0.008) and was significantly (or with a borderline significance) lower in lesions from current smokers (0.80±0.07 versus 0.86±0.09; P<0.001), or male patients (0.84±0.09 versus 0.86±0.08; P=0.09). No other clinical characteristic was associated or correlated to FFR values (data not showed).

### Correlation Between Clinical Characteristics and FFR Values

Among the different clinical characteristics, FFR was significantly correlated to QCA parameters of stenosis severity (MLD: r=0.34; P<0.0001; DS: r=−0.28; P<0.0001). No significant correlation was found neither with LL (r=0.07; P=0.31) nor RVD (r=0.10; P=0.13) (Figure 2). More importantly, FFR was inversely correlated also with DJS, MJI, and ALS (r=−0.28; P<0.0001; r=−0.40; P<0.0001; r=−0.34; P<0.0001) (Figure 3).

Lesions with an FFR ≤0.80 had not only a mean MLD significantly lower or a DS significantly higher than lesions with an FFR >0.80 (1.31±0.32 versus 1.53±0.35; P<0.0001 for MLD and 54.54±10.20 versus 50.00±9.34; P=0.0016 for DS), but also significantly lower values of DJS (4.21±0.19 versus 3.14±0.19; P<0.0001), MJI (36.52±1.45 versus 26.67±0.80; P<0.0001), and ALS (38.81±1.44 versus 28.67±1.00; P<0.0001; Table 2). Notably, none of lesions’ characteristics, with the exception of RVD, was significantly correlated to the amount of jeopardized myocardium, thereby confirming that the severity of lumen narrowing and the amount of jeopardized myocardium play independent roles on the functional significance of a stenosis (Table 3).

Lesions localized on proximal LAD were associated to significantly lower FFR values and to a higher rate of a positive FFR compared with those in distal LAD, left circumflex, and right coronary arteries (0.80±0.09 versus 0.84±0.08 versus 0.88±0.09 versus 0.91±0.04; P<0.0001, P<0.05 for trend; 28/54, 51.8% versus 32/100, 32% versus 7/40, 17.5% versus 0/19 0%; P<0.05; Figure 4). Again and interestingly, the lower FFR values of proximal LAD were not explained by more severe stenoses, considering that DS and MLD were not significantly different compared with lesions localized on other coronary segments (Table 4). Not surprisingly, lesions located on proximal LAD were associated with significantly higher indices of jeopardized myocardium (5.00±1.39 versus 2.96±1.25; P<0.0001 for DJS; 41.22±9.68 versus 25.88±9.01, P<0.0001 for MJI; and 44.66±9.74 versus 27.51±10.69, P<0.0001 for ALS).

The presence of a collateralized CTO was associated to significantly lower FFR values and to a significantly higher rate of positive FFRs (0.80±0.07 versus 0.85±0.09, P<0.005; 18/35, 54.5% versus 49/180, 27.2%, P=0.0015; Figure 5). However, presence of a collateralized CTO was associated to a significantly higher mean DS despite similar values of MLD and RVD or indices of jeopardized myocardium (Table 5). On the contrary, in the subgroup of patients without a collateralized CTO, FFR was significantly correlated to DJS (r=−0.25; P=0.0006), MJI (r=−0.35; P<0.0001), ALS (r=−0.30; P=0.0001), DJS (r=−0.24; P=0.0011), and MLD (r=−0.32; P<0.0001) but not to RVD (r=0.12; P=0.09) and LL (r=−0.06; P=0.40), similarly to overall population.

To identify the predictors of FFR, we built a significant multivariate model (P<0.0001; R²=0.35) including the following variables: MJI, MLD, presence of a collateralized CTO, current smoking habit, male gender, and age. Interestingly, in this model MJI was the strongest predictor of FFR (beta=−0.38; P<0.0001) followed by MLD (beta=0.32; P<0.0001), CTO (beta=−0.14; P=0.02) and current smoking (beta=−0.12;
Age and male gender did not significantly predict FFR in this multivariate analysis (Table 6).

In the attempt to exclude a significant influence of the disparity between number of patients and of lesions, we repeated analysis randomly excluding lesions in patients with >1 lesion tested with FFR and excluding all patients with >1 lesion tested and we found similar results.

**Discussion**

Our study demonstrates that a hemodynamically significant stenosis is associated not just to the anatomic severity of the lesion but also to the amount of myocardial tissue subtended by the stenosis itself. This is clearly showed by the significant inverse correlation between the amount of jeopardized myocardium and the FFR values and further supported by the significantly higher FFR values observed in lesions located on proximal LAD or with a concomitant collateralized CTO.

Several studies have investigated the relationship between lumen narrowing and hemodynamic significance of a given stenosis. A large consensus has been reached on the notion that FFR is moderately and inversely correlated to MLD, minimal lumen area, and percentage DS. Nevertheless, rather...
than a linear correlation, a curvilinear trend better describes this relationship. In particular for mild or intermediate stenoses, the correlation between FFR and stenosis severity is even weaker. This suggests that even considering the important role of LL, other factors contribute to determine the functional significance of a coronary stenosis.2 Our study shows that one of these factors is the amount of perfused myocardium.

FFR is a reproducible measurement, because pressure in all epicardial coronary artery branches in the absence of a stenosis is virtually identical to aortic pressure, differently from flow, lumen area, and perfused myocardial mass, which decrease moving from proximal to distal coronary segments. Nevertheless, in the assessment of stenosis severity, FFR is influenced by the amount of perfused myocardium; for a given stenosis the larger the territory, the higher the flow and the pressure gradient induced by maximal hyperemia.4 This notion is supported by the observation that FFR could be hemodynamically not significant even in the presence of an angiographically significant stenosis in a coronary branch supplying infarcted myocardium.5,6 Although this could be considered an indirect evidence of the impact of the amount of myocardial mass on FFR, this argument cannot be generalized to lesions which subtend a normal viable myocardium.5

Another argument in favor of the potential contribution of the extent of myocardium at risk the worse the prognosis, our data could help explaining the important prognostic value of FFR in guiding percutaneous coronary intervention.3,4

Myocardial jeopardy scores were developed several years ago to predict the outcome of acute coronary syndromes on the basis of coronary angiography.9–12 More recently they were demonstrated to correlate well with the area at risk and with the infarct size measured by cardiac magnetic resonance.13 In our study, we used DJS, MJI, and ALS to assess jeopardized myocardium subtended by the index stenosis in stable patients. We found that, in particular for angiographically intermediate stenoses, the larger the amount of jeopardized myocardium, the lower the FFR and the higher the rate of an abnormal FFR. For example, an FFR value ≤0.80 is significantly more likely in a 50% stenosis on the proximal LAD than on the second marginal branch. Thus, considering that the greater the extent of myocardium at risk the worse the prognosis, our data could help explaining the important prognostic value of FFR in guiding percutaneous coronary intervention.3,4

### Table 2. Comparison of Angiographic Findings Between Lesions With FFR > 0.80 and FFR ≤ 0.80

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FFR &gt; 0.80</th>
<th>FFR ≤ 0.80</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>0.89±0.05</td>
<td>0.74±0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVD, mm</td>
<td>3.12±0.71</td>
<td>2.96±0.69</td>
<td>0.12</td>
</tr>
<tr>
<td>LL, mm</td>
<td>17.42±9.56</td>
<td>18.07±8.60</td>
<td>0.65</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.53±0.35</td>
<td>1.32±0.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DS, mm</td>
<td>50.00±9.34</td>
<td>54.55±10.20</td>
<td>0.0016</td>
</tr>
<tr>
<td>DJS</td>
<td>3.14±0.12</td>
<td>4.21±0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MJI, %</td>
<td>26.67±0.80</td>
<td>36.52±1.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALS, %</td>
<td>28.67±1.00</td>
<td>38.81±1.44</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ALS indicates Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Lesion Score; DJS, Duke Jeopardy Score; DS, Diameter Stenosis; LL, Lesion Length; MJI, Myocardial Jeopardy Index; MLD, Minimal Lumen Diameter; and RVD, Reference Vessel Diameter.

### Table 3. Correlation Between the Amount of Jeopardized Myocardium and Lesions’ Characteristics at QCA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DJS</th>
<th>MJI</th>
<th>ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>0.14*</td>
<td>0.20†</td>
<td>0.16*</td>
</tr>
<tr>
<td>LL</td>
<td>−0.04</td>
<td>−0.10</td>
<td>−0.06</td>
</tr>
<tr>
<td>MLD</td>
<td>0.03</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>DS</td>
<td>0.08</td>
<td>0.13</td>
<td>0.05</td>
</tr>
</tbody>
</table>

ALS indicates Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Lesion Score; DJS, Duke Jeopardy Score; DS, Diameter Stenosis; LL, Lesion Length; MJI, Myocardial Jeopardy Index; MLD, Minimal Lumen Diameter; QCA, quantitative coronary angiography; and RVD, Reference Vessel Diameter.

### Table 4. Comparison of FFR and of Angiographic Findings at QCA Between Lesions Located on Proximal LAD vs Lesions Located on Other Coronary Segments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lesion on Proximal LAD (n=54)</th>
<th>Lesion on Other Coronary Segment (n=159)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>0.80±0.09</td>
<td>0.86±0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVD</td>
<td>3.37±0.84</td>
<td>2.97±0.63</td>
<td>0.0002</td>
</tr>
<tr>
<td>LL</td>
<td>16.88±8.55</td>
<td>17.87±9.50</td>
<td>0.50</td>
</tr>
<tr>
<td>MLD</td>
<td>1.54±0.41</td>
<td>1.44±0.33</td>
<td>0.07</td>
</tr>
<tr>
<td>DS</td>
<td>53.14±11.09</td>
<td>50.85±9.32</td>
<td>0.14</td>
</tr>
<tr>
<td>DJS</td>
<td>5.00±1.39</td>
<td>2.96±1.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MJI</td>
<td>41.22±9.68</td>
<td>25.88±9.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALS</td>
<td>44.66±9.74</td>
<td>27.51±10.69</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ALS indicates Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Lesion Score; DJS, Duke Jeopardy Score; DS, Diameter Stenosis; FFR, fractional flow reserve; LAD, left anterior descending; LL, Lesion Length; MJI, Myocardial Jeopardy Index; MLD, Minimal Lumen Diameter; QCA, quantitative coronary angiography; and RVD, Reference Vessel Diameter.
This observation has been confirmed in our study and helps explaining the important negative impact of proximal LAD stenosis on prognosis and the efficacy of its revascularization. Moreover, no systematic data but only anecdotal case reports have suggested that collateralized CTO might influence FFR by increasing the amount of perfused myocardium: our study provides the first formal demonstration that collateralized CTO is indeed associated with a significantly lower FFR. Taken together, these data suggest the importance of the functional assessment of stenoses in particular when located in proximal LAD, in the presence of collateralized CTO or in general when a large amount of myocardium is subtended by the index stenosis. From a practical point of view, this does not imply that we should not perform FFR in distal lesions, rather that we should also be aware that even a moderate stenosis might be associated with a significant inducible ischemia when a large myocardium is subtended and, consequently, that we have to interrogate it with FFR.

Moreover, our study confirms that coronary angiography, even when used with a well-validated quantitative software has a mild, although significant, ability to predict functionally significant stenoses, especially when they appear intermediate at visual estimation. In this particular setting of lesions, the degree of narrowing and the extent of jeopardized myocardium play separate independent roles in determining the functional significance of a stenosis. Nevertheless, the $R^2$ demonstrates that only a limited part of the variability of FFR values can be effectively predicted using the available clinical and angiographic data. This strongly suggests again the need to always interrogate an intermediate stenosis by a pressure wire to correctly estimate its functional significance in the absence of a clear evidence of ischemia at noninvasive stress tests.

Finally, our study shows that FFR might be influenced by smoking habit. This association adds some complexity to the functional assessment of coronary stenoses but it does not substantially limit its clinical utility. Nevertheless, this result that is in agreement with a similar collateral finding of Kang et al7 deserves further specifically designed studies to be confirmed.

**Limitations**

Despite intravenous adenosine being considered the gold standard to induce maximal hyperemia, in our study, we used prevalent intracoronary adenosine. However, the systematic adoption of our previously validated protocol14 should have minimized this potential limitation.

In the present study, we included intermediate coronary stenoses only, and this could have reduced the potential impact of narrowing severity on FFR. Indeed, as clearly depicted in Figure 2, the wider variability in the correlation between lumen narrowing and FFR is observed in real intermediate stenoses (40%–60% DS). In these cases, the role of the amount of subtended myocardium could be prevalent on stenosis severity. On the other hand, these lesions precisely represent the clinical scenario in which FFR was proven to be mostly helpful23 and for this purpose is widely used both in our and in worldwide catheterization laboratories.

As we included in the present study 213 lesions in 184 patients, there is a small disparity in the number of patients and lesions potentially influencing our results, especially considering correlations between lesion- and patient-specific characteristics, such as smoking and presence of a CTO. However, further analysis including 1 lesion per patient only confirmed our results.

The presence of a moderate diffuse disease, which can lead to an underestimation of stenosis severity by visual estimation or by QCA, could have also influenced correlation between FFR and the amount of jeopardized myocardium. For example, in the case of a very long lesion from proximal to mid-distal LAD,
FFR would be calculated distally and correlated with an exces-
sively large amount of myocardium. However, the a priori exclu-
sion of patients with significant diffuse disease, the mean LL, 
and the evidence that only 16 lesions exceeded 30 mm suggest 
that, at least in this series of lesions, moderate diffuse disease has 
not significantly influenced the conclusions of our study. 

The amount of myocardium at risk subtended by the 
lesions, which were interrogated by FFR, was estimated by 
the DJS, the MJI, and the ALS. Unfortunately, in our popula-
tions, which were interrogated by FFR, was estimated by 
that, at least in this series of lesions, moderate diffuse disease has 
and the evidence that only 16 lesions exceeded 30 mm suggest 
especially large amount of myocardium. However, the a priori exclu-
sively large amount of myocardium. 

Conclusion 
The study demonstrates that a larger amount of 
perfused myocardium subtended by a stenosis is associated 
with a higher probability that an angiographically 
intermediate coronary stenosis is functionally significant. 

Disclosures 
None. 

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Influence of the Amount of Myocardium Subtended by a Stenosis on Fractional Flow Reserve

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