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When should fractional flow reserve be performed to assess the significance of borderline coronary artery lesions: Derivation of a simplified scoring system

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ABSTRACT

Objectives: To derive a simplified scoring system (SSS) that can assist in selecting patients who would benefit from the application of fractional flow reserve (FFR).

Background: Angiographers base decisions to perform FFR on their interpretation of % diameter stenosis (DS), which is subject to variability. Recent studies have shown that the amount of myocardium at jeopardy is an important factor in determining the degree of hemodynamic compromise.

Methods: We conducted a retrospective multivariable analysis to identify independent predictors of hemodynamic compromise in 289 patients with 317 coronary vessels undergoing FFR. A SSS was derived using the odds ratios as a weighted factor. The receiver operator characteristics curve was used to identify the optimal cutoff (≥3) to discern a functionally significant lesion (FFR ≤ 0.8).

Results: Male gender, left anterior descending artery apical wrap, disease proximal to lesion, minimal lumen diameter and % DS predicted abnormal FFR (≤0.8) and lesion location in the left circumflex predicted a normal FFR. Using a cutoff score of ≥3 on the SSS, a specificity of 90.4% (95% CI: 83.0–95.3) and a sensitivity of 38.0% (95% CI: 31.5–44.9) was generated with a positive predictive value of 89.0% (95% CI: 80.7%–94.6%) and negative predictive value of 41.6% (95% CI: 35.1%–48.3%).

Conclusions: The decision to use FFR should be based not only on the % DS but also the size of the myocardial mass jeopardized. A score of ≥3 on the SSS should prompt further investigation with a pressure wire.

1. Introduction

Fractional flow reserve (FFR) is increasingly being used to assess the hemodynamic significance of borderline coronary artery stenosis at the time of angiography. FFR-guided percutaneous coronary intervention (PCI) has been associated with reduced major adverse cardiac events and to yield enhanced clinical outcomes in patients presenting with multi-vessel coronary artery disease (CAD) [1]. Since the publication of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial [2], there has been an increased use of FFR. However, data from U.S. Medicare beneficiaries in 2012 reported that the percent of diagnostic catheterizations undergoing FFR remained low (4%) [3].

A strategy of routine FFR measurement of all vessels with any degree of luminal narrowing in patients with stable angina at the time of diagnostic coronary angiography can change the number deemed significant and required revascularization in 26% of patients [4]. Operators may not deem that FFR of all diseased vessels to be feasible in routine daily practice environment given its impact on cost, procedure time, excess contrast load and reduced but definite procedural complication risk [4].

During coronary angiography, the operator is often faced with deciding if a lesion is ischemic and whether hemodynamic severity assessment with FFR is warranted. These decisions are usually based on the operator's subjective interpretation of angiographic percent diameter stenosis (% DS) which is subject to wide inter and intra-observer variability [5,6]. Recent studies have shown that angiographic factors relating to the amount of myocardium at jeopardy, such as left anterior descending (LAD) artery apical wrap and proximal lesion location, may also be important factors affecting the hemodynamic impact of a stenosis [7–10].

The purpose of this study is to identify demographic/clinical and angiographic predictors of hemodynamically significant lesions which can assist in targeted selection of patients who are more likely to benefit from the application of FFR assessment during cardiac catheterization.

Abbreviations: AUC, area under the curve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; MLD, minimum lumen diameter; NPV, negative predictive value; PCI, percutaneous coronary intervention; PPV, positive predictive value; RCA, right coronary artery; SSS, simplified scoring system.

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Moreover, to develop a simplified scoring system (SSS) for the identification of vessels warranting FFR assessment.

2. Methods

2.1. Study population

From 2007 to 2012, 14,021 patients underwent diagnostic coronary angiography at a single center, of which 9728 were performed by faculty members of the University of South Florida, Morsani College of Medicine. From this cohort, 645 patients underwent clinically driven, FFR assessment. Excluded from this group were patients (n = 356) who had one or more of the following: left main lesion (≥50%), chronic total coronary artery occlusion anywhere in the coronary circulation, sequential lesions (two or more discrete and separate lesions 30% in diameter stenosis in the same vessel by visual assessment), a history of coronary artery bypass grafting, the presence of hemodynamically significant valvular stenosis or regurgitation, history of acute or prior myocardial infarction or abnormal ventricular ejection fraction (<50%). The final study population consisted of 289 patients with 317 single and multiple vessels undergoing FFR assessment. The study was approved by the Institutional Review Board and a written waiver of informed consent was granted.

2.2. Study procedures

Following informed consent, coronary angiography was performed through radial or femoral access based on patient suitability and operator discretion. A 6 Fr. Guiding catheter was used for the initial angiography prior to FFR assessment. If the systolic blood pressure was over 100 mm Hg, 100 to 200 microgram intracoronary nitroglycerine was generally administered prior to FFR measurement. Intravenous anticoagulants with either heparin or bivalirudin were also administered prior to the introduction of the pressure wire. Maximum hyperemia was achieved by intravenous adenosine infusion at 140 μg/kg/min. The St. Jude Radi wire (St. Jude Medical Inc., Saint Paul, MN, USA) was used for FFR measurement in all patients. FFR was defined as the ratio between the mean coronary pressure distal to an observed coronary artery stenosis and the mean aortic pressure at maximum hyperemia. An FFR cutoff of ≤0.8 was used to determine myocardial ischemia and generally in need of revascularization.

2.3. Angiographic analysis

Coronary angiograms were retrospectively subjected to qualitative and quantitative analysis using computerized automated edge detection (QAngio XA, Leiden, Netherlands) with the contrast-filled guiding catheter as a calibration reference. A lesion was identified to be in a main branch if it was located in a major epicardial vessel such as the LAD, right coronary artery (RCA) or left circumflex artery (LCX); or in a side branch if located in a diagonal, obtuse marginal, posterior descending or posterolateral branch.

Lesions were considered proximal if present in the main vessel proximal to the first major diagonal in the LAD, prior to the first major acute marginal in the RCA or prior to the first obtuse marginal in the LCX. LAD apical wrap was defined as one that terminated more than one-third of the way on the diaphragmatic surface. Disease proximal to the lesion included moderate, non-discrete luminal irregularities (30–50% DS) proximal to the lesion being investigated.

2.4. Simplified scoring system for predicting FFR (≤0.8)

A simplified scoring system (FFR-SSS) was devised to assist the operator in determining the need for FFR, based on selected demographic/clinical variables. The scoring scheme was based on the results of a multivariable model designed to predict the probability of a functionally significant lesion (FFR ≤ 0.8). Each significant demographic/clinical factor generated from the multivariable analysis was assigned a value of “2”. An LAD apical wrap and a lesion in a non-LCX vessel were assigned a value of “1”. The final score for a given lesion was based on the sum of the values assigned to each of the significant variables (odds ratio > 1) and ranged from “0” to “10”. The higher the final score, the greater the likelihood of a functionally significant lesion.

2.5. Statistical analysis

Data analyses were performed on a per-patient basis for demographic/clinical variables and on a per-lesion characteristic for the remainder of the calculations. Demographic, clinical and lesion-specific data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean ± the standard deviation. Two-sample unpaired Student's t-tests were used to assess the equality of means in continuous variables.

To identify independent determinants of FFR ≤0.8, univariable analyses were performed using 18 demographic/clinical variables. Those with a probability value ≤0.10 were included in a multivariable logistic regression model, with flow limitation (FFR ≤ 0.8) as the dependent variable. The final multivariable logistic regression model included six covariates.

The area under the curve (AUC) was determined by a receiver operator characteristic curve with 95% confidence interval (CI) to detect FFR ≤0.8 from the value generated by the SSS. The results of this analysis was used to identify the optimal cut-off point of the scoring scheme to determine sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% CI.

All probability values reported are two-sided and not adjusted for multiple testing. A probability value of 0.05 or less indicated a significant difference between measures. All analyses were performed using the Number Cruncher Statistical Systems software (Version 9; NCSS, Kaysville, UT, USA).

3. Results

There were 289 patients with 317 single and multiple vessels assessed with FFR of which 81 (28.0%) underwent revascularization. Among those 289 patients, 32 (11.1%) underwent PCI of additional vessels (n = 35) without FFR assessment. In the study group (N = 289), 175 (60.6%) were male and the mean age was 62.6 ± 10.9 years (range, 34 to 87). There were 97 (33.6%) patients who had diabetes mellitus, 226 (78.2%) hypertension and 147 (50.9%) a history of known coronary artery disease. Pre-procedure stress testing was performed in 144 (49.8%) patients. The patient baseline demographic/clinical characteristics are summarized in Table 1 and were similar to previously reported FFR studies [1–11].

The information in Table 2 presents the angiographic lesion characteristics of the study group. Of the 317 lesions that underwent FFR assessment, 91 (28.7%) were abnormal (≤0.8) and 226 (71.3%) normal. Fig. 1 shows the distribution of % DS in the normal and abnormal FFR groups. Although the mean % DS in the abnormal FFR group was higher than in the normal FFR group (53.3 ± 11.5 versus 47.5 ± 9.6; p < 0.001), there was significant overlap in the two cohorts. There were 36 of 173 (20.7%) lesions with <50% DS that had an abnormal FFR and 88 of 143 (61.5%) with ≥50% DS with a normal FFR.

The information in Table 3 displays the univariable and multivariable predictors of abnormal FFR in the 317 lesions subjected to pressure wire assessment as deemed by the operator to be angiographically indeterminate. Of the demographic/clinical, lesion/vessel and luminal dimension variables included in the multivariable model, six were found to be significant: male gender (p = 0.002), disease proximal to the lesion (p = 0.014), LAD apical wrap (p < 0.001), MLD (p = 0.015) and % DS (p < 0.001). Lesion location in the LCX was independently predictive of a normal FFR (p = 0.024).