JACC: CARDIOVASCULAR IMAGING
VOL. 11, NO. 4, 2018

ORIGINAL RESEARCH

Lesion-Specific and Vessel-Related Determinants of Fractional Flow Reserve Beyond Coronary Artery Stenosis

Amir Ahmadi, MD,[a,b] Jonathon Leipsic, MD,[b] Kristian A. Øvrehus, MD,[c] Sara Gaur, MD,[c] Emilia Bagiella, PhD,[a] Brian Ko, MD,[d] Damini Dey, PhD,[e] Gina LaRocca, MD,[a] Jesper M. Jensen, MD,[c] Hans Erik Bøtker, MD,[c] Stephan Achenbach, MD,[f] Bernard De Bruyne, MD, PhD,[g] Bjarne L. Nørgaard, MD, PhD,[c] Jagat Narula, MD, PhD[a]

ABSTRACT

OBJECTIVES The aims of the present study were: 1) to investigate the contribution of the extent of luminal stenosis and other lesion composition-related factors in predicting invasive fractional flow reserve (FFR); and 2) to explore the distribution of various combinations of morphological characteristics and the severity of stenosis among lesions demonstrating normal and abnormal FFR.

BACKGROUND In patients with stable ischemic heart disease, FFR-guided revascularization, as compared with medical therapy alone, is reported to improve outcomes. Because morphological characteristics are the basis of plaque rupture and acute coronary events, a relationship between FFR and lesion characteristics may exist.

METHODS This is a subanalysis of NXT (HeartFlowNXT: HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography), a prospective, multicenter study of 254 patients (age 64 ± 10 years, 64% male) with suspected stable ischemic heart disease; coronary computed tomography angiography including plaque morphology assessment, invasive angiography, and FFR were obtained for 383 lesions. Ischemia was defined by invasive FFR ≤0.80. Computed tomography angiography–defined morphological characteristics of plaques and their vascular location were used in univariate and multivariate analyses to examine their predictive value for invasive FFR. The distribution of various combinations of plaque morphological characteristics and the severity of stenosis among lesions demonstrating normal and abnormal FFR were examined.

RESULTS The percentage of luminal stenosis, low-attenuation plaque (LAP) or necrotic core volume, left anterior descending coronary artery territory, and the presence of multiple lesions per vessel were the predictors of FFR. When grouped on the basis of degree of luminal stenosis, FFR-negative lesions had consistently smaller LAP volumes compared with FFR-positive lesions. The distribution of plaque characteristics in lesions with normal and abnormal FFR demonstrated that whereas FFR-negative lesions excluded likelihood of stenotic plaques with moderate to high LAP volumes, only one-third of FFR-positive lesions demonstrated obstructive plaques with moderate to high LAP volumes.

CONCLUSIONS In addition to the severity of luminal stenosis, necrotic core volume is an independent predictor of FFR. The distribution of plaque characteristics among lesions with varying luminal stenosis and normal and abnormal FFR may explain the outcomes associated with FFR-guided therapy. (J Am Coll Cardiol Img 2018;11:521–30)

From the [a]Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Division of Cardiology, Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada; [c]Division of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [d]Division of Cardiology, Monash University, Melbourne, Australia; [e]Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California; [f]Division of Cardiology, University of Erlangen-Nuremberg, Erlangen, Germany; and the [g]Division of Cardiology, Cardiovascular Center Aalst, Aalst, Belgium. Dr. Leipsic is a consultant for and has received stock options from Circle CVI and HeartFlow; and has received fellowship support from GE Healthcare. Dr. Ko has received speaker fees from St. Jude Medical, Merck Sharpe & Dohme, Novartis, Bristol-Myers Squibb, and Specialised Therapeutics. Dr. Dey may receive royalties for software licenses from Cedars-Sinai Medical Center. Dr. Jensen has received a speaker honorarium from

ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2017.11.020

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

ICA = invasive coronary angiography

FFR = fractional flow reserve

HRP = high-risk plaque

LAD = left anterior descending coronary artery

LAP = low-attenuation plaque

LCx = left circumflex coronary artery

RCA = right coronary artery

On the basis of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) family of studies (1,2), fractional flow reserve (FFR)-guided therapy has become the current standard for treatment of patients with stable ischemic heart disease. However, what continues to be intriguing is how a marker describing the functional significance of an anatomic lesion would identify plaque behavior and clinical outcomes. The prognostic outcome has traditionally been linked to the morphological features of high-risk plaques (HRPs) vulnerable to rupture. Therefore, it is important to address whether plaque morphology could influence the FFR abnormality, and if so, whether a normal FFR would predict relatively stable plaque morphology and hence a lower rate of future major adverse cardiovascular events. It may also be interesting to inquire whether an abnormal FFR would predict a higher likelihood of major adverse cardiovascular events.

SEE PAGE 531

Luminal stenosis is an established predictor of FFR (3). However, the relationship between the 2 is far from perfect (4–6), and there are a considerable number of stenotic lesions without ischemia and ischemic lesions without stenosis (7,8). The imperfect relationship between luminal stenosis and FFR has been attributed to the limitations of 2-dimensional interpretation of luminal stenosis on invasive coronary angiography (ICA), even though more accurate measures of luminal narrowing (e.g., minimal luminal diameter and minimal luminal area with intravascular ultrasound) have not helped improve the relationship between the degree of stenosis and FFR (9). Other anatomic characteristics such as the lesion length, entrance and exit angles, and size of the reference vessel have been proposed to explain the discrepancy, but without convincing evidence (10).

Coronary computed tomography angiography (CTA) is well placed to evaluate HRP characteristics and correlate them with the FFR-based hemodynamic relevance of the coronary artery lesions. On the basis of a multivariable analysis of various CTA-defined vessel factors, including quantitative percentage of luminal stenosis, minimal luminal area, minimal luminal diameter, and total lesion length in vessel, as well as the total plaque volume within the vessel, it was reported that total low-attenuation plaque (LAP) volume >30 mm^3 in the culprit vessel was an independent predictor of FFR and additive to the CTA-verified degree of luminal stenosis of the most stenotic lesion (11). Because the lesion-specific large LAP volume is known to be associated with short- and intermediate-term outcomes (12,13) and because vessel-specific LAP correlates with FFR (11), it is logical that FFR may be a marker of severely stenotic lesions, large LAP volume, or a combination thereof (8). Conversely, a normal FFR should define a plaque with a lack of these features and hence with a benign prognostic outcome.

In the present study, we focused on the most stenotic lesion of the vessel and explored: 1) the contribution of various lesion-related and vessel-related factors to the invasive FFR value; and 2) the distribution of various combinations of plaque characteristics (morphology) and the severity of stenosis (anatomy) among lesions demonstrating normal and abnormal FFR.

METHODS

STUDY POPULATION AND PROTOCOL. This is a subanalysis of NXT (HeartFlowNXT: HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography; NCT01757678) comprising patients suspected of stable coronary artery disease (CAD) (14). Coronary CTA was performed within 60 days before clinically indicated nonemergency ICA. Excluded were patients with prior stent implantation or coronary bypass surgery; contraindications to beta-blockers, nitrates, or adenosine; suspicion of acute coronary syndrome; significant arrhythmia; and body mass index $\geq$35 kg/m^2 (15,16).

In 254 patients, 484 vessels were evaluated by CTA, ICA, and FFR. Vessels without stenosis noted on coronary CTA (n = 81) and vessels with complete occlusion on ICA (n = 20) were excluded from the analyses (**Figure 1**). The study complied with the Declaration of Helsinki, and the local ethics committees approved the study protocol. All patients provided written informed consent.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY ACQUISITION. Coronary CTA was performed using computed tomography (CT) scanners with 64 or more

Bracco Imaging. Dr. De Bruyne has served as an institutional consultant for Abbott, Boston Scientific Corporation, and Opsens. Dr. Nørgaard's institution has received unrestricted research grants from HeartFlow and Siemens. Dr. Botker's institution has received an unrestricted research grant from HeartFlow.

Manuscript received September 21, 2017; revised manuscript received November 7, 2017, accepted November 8, 2017.

detector rows, as previously described (15,16). Beta-blockers were administered if necessary, targeting a heart rate of 60 beats/min. Sublingual nitrates were administered before scanning in all patients (14).

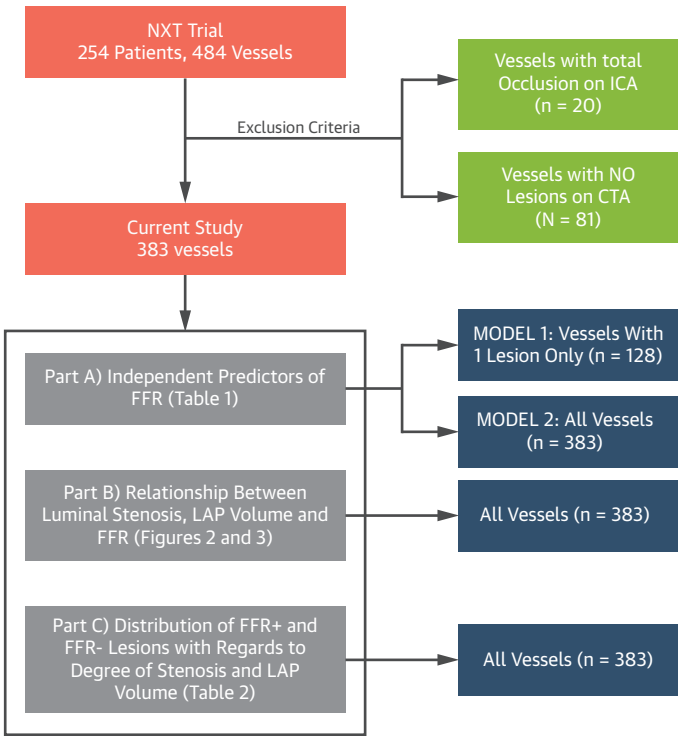
CORONARY PLAQUE ANALYSIS. The coronary plaque analysis strategy has previously been described (11). In short, coronary segments ≥2 mm with plaque were analyzed using semiautomated software (AutoPlaq version 9.7, Los Angeles, California). Two readers (S.G. and K.A.Ø.) who were blinded to ICA and invasive FFR results performed the analyses using multiplanar coronary CTA images. Scan-specific thresholds for noncalcified plaque and calcified plaque were automatically generated (17). Plaque components were quantified within the manually designated area by using adaptive algorithms (17); adjustments were made if necessary. LAP volume was defined by the volume of part of the plaque with attenuation <30 Hounsfield units. The remodeling index was obtained by dividing the maximum vessel area within the lesion by the area of a proximal normal reference point. Positive remodeling was defined by the presence of a remodeling index ≥1.1. The most stenotic lesion in each vessel was identified, and various plaque components specific to that lesion were used in the analysis (14).

INVASIVE CORONARY ANGIOGRAPHY AND FRACTIONAL FLOW RESERVE MEASUREMENTS. ICA and invasive FFR were performed according to standard practice (15,16). The FFR pressure wire was positioned a minimum of 20 mm distal to the stenosis in vessel segments ≥2 mm. Hyperemia was induced by intravenous adenosine (140 to 180 mg/kg/min). FFR ≤0.80 was defined as the presence of lesion-specific ischemia.

STATISTICAL ANALYSIS. The following statistical analyses were performed. 1) Various vessel- and lesion-related factors were investigated as independent predictors of FFR by using univariate and multivariate analyses in 2 models: in model 1, vessels with only 1 lesion per vessel were identified, and the analysis was performed on this subset; in model 2, the analysis was expanded to all vessels in the study. 2) The relationship between LAP volume and the degree of luminal stenosis for the most obstructive lesions with normal and abnormal FFR was explored for all vessels (n = 383). 3) The distribution of various combinations of the degree of luminal stenosis and the extent of LAP volume was investigated for all lesions with normal and abnormal FFR (**Figure 1**).

The CTA-verified most stenotic lesions of each vessel were identified. Descriptive analyses of lesion characteristics of the most stenotic lesion in the vessel together with various vessel-related variables for prediction of invasive FFR were conducted using means and SDs, or medians and interquartile ranges for continuous data and frequency and proportion for binary and categorical data. The lesion-related variables used in this analysis were total plaque volume, noncalcified plaque volume, calcified plaque volume, LAP volume, lesion length, CT-based diameter stenosis (quantitative coronary angiography), and remodeling index. The vessel-related variables were epicardial vessel territory (left anterior descending coronary artery [LAD], right coronary artery [RCA], left circumflex coronary artery [LCx]), location of the

FIGURE 1 The Study Protocol



This study analyzed the data from the NXT (HeartFlowNXT: HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography) database, which included information from 254 patients and 484 vessels. For the purpose of this report, 81 computed tomography angiography (CTA)-verified normal coronary vessels and 20 invasive coronary angiography (ICA)-verified completely occluded vessels were excluded. The statistical analyses were performed in 3 different parts. Part A explored various vessel-related and lesion-related factors as independent predictors of fractional flow reserve (FFR) by using univariate and multivariate analysis in 2 models; model 1 included vessels with only 1 lesion per vessel (n = 128), and model 2 included all vessels (n = 383). Part B explored the relationship between low-attenuation plaque (LAP) volume and degree of luminal stenosis (emerging as independent predictors of fractional flow reserve in part A) and fractional flow reserve (n = 383) of the most stenotic lesions. Part C explored the distribution of lesions with normal and abnormal fractional flow reserve with regard to their degree of luminal stenosis and low-attenuation plaque volume (n = 383).

TABLE 1 Lesion-Specific and Vessel-Related Determinants of FFR*

Effect	Model 1: Vessel With 1 Lesion Only (n = 128)			Model 2: All Vessels (≥1 Lesion per Vessel) (n = 383)		
	Estimate	SE	p Value	Estimate	SE	p Value
Intercept	1.006	0.020	<0.0001	1.044	0.020	<0.0001
% Luminal stenosis by CTA-QCA	−0.001	0.0003	<0.0353	−0.002	0.0002	<0.0001
LAP volume	−0.002	0.0003	<0.0001	−0.001	0.0003	0.0006
Vessel territory (LAD vs. RCA/LCx)	−0.076	0.0158	<0.0001	−0.065	0.011	<0.0001
Lesion location (proximal vs. middle/distal)	−0.0206	0.0129	0.1152	−0.024	0.010	0.0174
Number of segments	–	–	–	−0.019	0.006	0.0020
Lesion length, mm	−0.0011	0.001	0.2771	0.0002	0.001	0.7762

*On the basis of the univariate analysis comparing various lesion-related (total plaque volume, noncalcified plaque volume, calcified plaque volume, LAP volume, lesion length, CT-based diameter stenosis [QCA], and remodeling index) and vessel-related factors (epicardial vessel territory [LAD, RCA, LCx], location of the lesion within the vessel [proximal, middle, distal], and number of lesions per vessel), a multivariable model was constructed to identify independent contributors to FFR. In 128 vessels with 1 lesion only (model 1), LAP volume and percentage of luminal stenosis were independent lesion-related predictors of FFR; lesion length was not an independent determinant of FFR. In this group LAP volume was a stronger predictor of FFR as compared with the degree of luminal stenosis. Among various vessel-related factors, the presence of the lesion in the LAD as opposed to the RCA and LCx was the only independent predictor of FFR. Similarly, among all vessels considered with 1 or more lesions per vessel (model 2), LAP volume and the degree of luminal stenosis were again independent predictors of FFR. In this group the presence of the lesion in the LAD, the proximal location of the lesions, and the number of involved vessel segments were the vessel-related independent predictors of FFR. Therefore, in both models, from the lesion standpoint, percentage of luminal stenosis and LAP volume were the most important lesion-related predictors of FFR, both of which can be conveniently assessed by routine CTA.

CTA = computed tomography angiography; FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LAP = low-attenuation plaque; LCx = left circumflex coronary artery; QCA = quantitative coronary angiography; RCA = right coronary artery; SE = standard error.

lesion within the vessel (proximal, middle, distal), and number of lesions per vessel.

Univariate analyses were conducted to determine the relationship between variables of interest and FFR. On the basis of these analyses, multivariate models were built to identify independent contributors of FFR. The analysis was conducted on vessels with only 1 lesion (model 1) and all vessels (model 2) separately. The analysis of the vessels with only 1 lesion (model 1) was conducted using linear regression models. For the analysis of all vessels (model 2), linear models with generalized estimating equations were used to correct for the correlation among vessels on the same patient. All analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina). All tests were 2-sided at the 0.05 significance level.

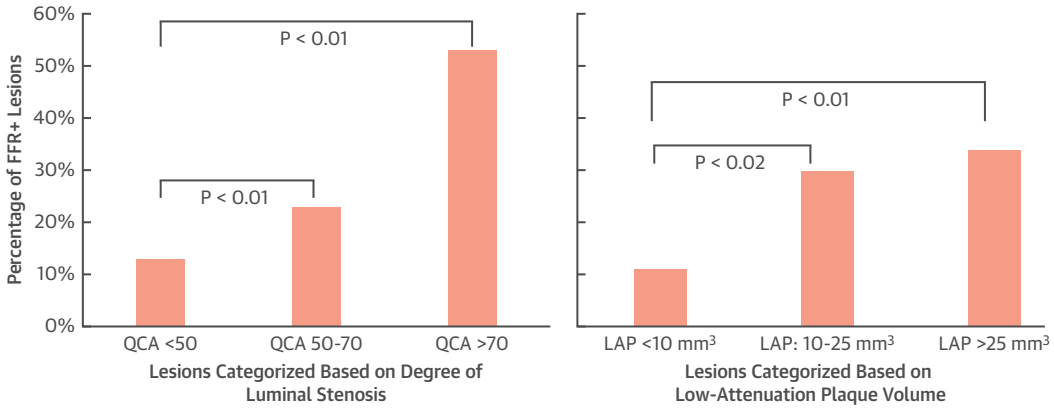
RESULTS

From the NXT study database of 254 patients and 484 vessels, after the exclusion of 81 CTA-verified normal vessels and 20 ICA-verified totally occluded vessels, analysis was performed on 383 vessels for exploring relationship between FFR and morphological composition of the lesion (Figure 1). Of these vessels, 128 showed only 1 lesion, and these vessels were also analyzed separately. Baseline characteristics of the NXT study population have been reported earlier (14). Briefly, the mean age of NXT patients was 64 ± 10 years, 162 (64%) of the patients were male, and 220 (87%) of the patients demonstrated an intermediate pre-test risk of significant CAD at 20% to 80% on the updated Diamond-Forrester risk scale.

INDEPENDENT PREDICTORS OF FFR. Model 1: vessels with 1 lesion only. Of the 383 vessels, 128 demonstrated a single lesion (32% LAD, 41% LCx, 27% RCA). Of these, 15 vessels demonstrated FFR ≤0.8 (12%); 23% of LAD lesions were FFR-positive (FFR[+]) as compared with 8% LCx and 6% RCA lesions. The determinants of invasive FFR were explored in a multivariable model including CTA-verified lesion-specific variables (degree of stenosis, lesion length, and LAP volume) and vessel-related variables (vessel territory, location of the lesion on the vessel, and number of involved segments per vessel) (Table 1). Only LAP volume and degree of luminal stenosis by CTA emerged as the independent lesion-related predictors of invasive FFR (Table 1). In this model, LAP volume (estimate −0.002; $p < 0.0001$) was a superior predictor as compared with the degree of luminal stenosis (estimate −0.001; $p < 0.04$). The lesion length was not a predictor of FFR (estimate −0.001; $p = 0.3$). In addition, location of the lesion in the LAD was the only independent vessel-related predictor of FFR (estimate −0.08; $p < 0.0001$).

Model 2: all vessels. The analyses of all 383 vessels (49% LAD, 28% RCA, and 23% LCx) demonstrated invasive FFR of ≤0.8 in 83 (22%) vessels; 33% of LADs were FFR(+) compared with 10% of RCAs and 13% of LCxs ($p < 0.001$). As described earlier, multivariable analysis of lesion- and vessel-related variables revealed the degree of stenosis and LAP volume to be the independent predictors of invasive FFR. Notably, the lesion length, similar to model 1, was not a predictor of FFR. With regard to vessel-related factors, localization of the lesion in the LAD (as opposed to RCA or LCx), the

FIGURE 2 **Independent Increase in Percentage of FFR(+) Lesion With an Increase in the Degree of Luminal Stenosis or LAP Volume**



(Left) Lesions were divided into 3 groups on the basis of the computed tomography angiography–verified degree of stenosis (<50%, 50% to 70%, >70%). The percentage of fractional flow reserve-positive (FFR[+]) lesions increased with worsening degree of luminal stenosis. **(Right)** Conversely, when lesions were divided into 3 groups on the basis of the low-attenuation plaque (LAP) volume tertiles of the fractional flow reserve-positive lesions (low-attenuation plaque <10 mm^3, 10 to 25 mm^3, >25 mm^3), there was an increase in the percentage of fractional flow reserve-positive lesions with increasing low-attenuation plaque volume, regardless of luminal stenosis. QCA = quantitative coronary angiography.

number of vessel segments involved, and the proximal location of the lesion within the vessel emerged as the independent predictors of FFR (Table 1).

RELATIONSHIP BETWEEN THE SEVERITY OF STENOSIS AND LAP VOLUME IN FFR-NEGATIVE AND FFR-POSITIVE LESIONS. All lesions were divided into 3 groups on the basis of the CTA-verified degree of luminal stenosis: <50%, 50% to 70%, and >70%. The percentage of FFR(+) lesions increased with the increase in degree of luminal stenosis (Figure 2). Similarly, on classifying the lesions into 3 categories on the basis of the LAP volume, the proportion of FFR(+) lesions increased significantly with the increase in LAP volume (Figure 2), independent of the degree of luminal stenosis.

When lesions were grouped together on the basis of the degree of luminal stenosis, there were FFR(+) and FFR-negative (FFR[−]) lesions within each group. There were no significant differences between the degree of stenosis of FFR(+) and FFR(−) lesions within each subgroup. However, statistically significant differences were noted between the LAP volumes of FFR(+) and FFR(−) lesions within each subgroup (Figures 3A and 3B).

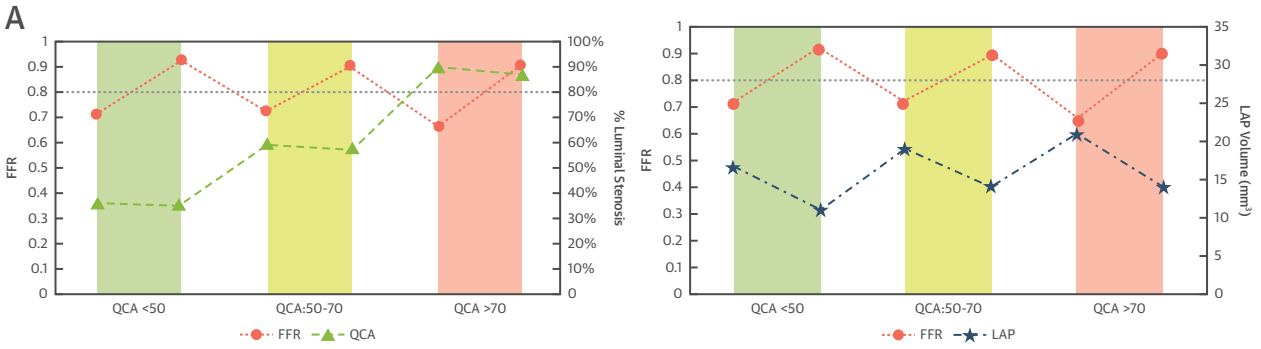
DISTRIBUTION OF THE SEVERITY OF STENOSIS AND LAP VOLUMES IN LESIONS WITH NORMAL AND ABNORMAL FFR. The LAP volume of each lesion and the degree of luminal stenosis were compared between lesions with normal and abnormal FFR. For this purpose, 50% ICA-verified luminal stenosis was used as the cutoff value to differentiate obstructive from nonobstructive lesions, and small, moderate, and large LAP volumes were defined by cutoff values of <10 mm^3, 10 to 25 mm^3, and >25 mm^3, respectively. The cutoff values for LAP were determined on the basis of LAP volume tertiles of the FFR(+) lesions.

Of 300 lesions with FFR >0.80, 53% were nonobstructive with small LAP volumes, whereas 4% of lesions were obstructive with moderate LAP, and 2% were obstructive with large LAP volumes. Interestingly, among lesions with FFR ≤0.80, 54% were nonobstructive; 30% of lesions were obstructive with moderate or large LAP volumes, and 28% had small LAP volumes (Table 2).

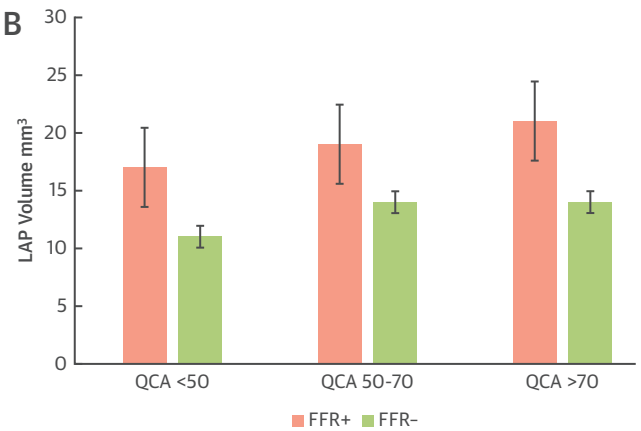
DISCUSSION

It has been previously proposed that the presence of a large necrotic core may somehow contribute to lesion-specific ischemia expressed by abnormal FFR, independent of the degree of stenosis (7,8). It has also been reported that the total LAP volume within the entire vessel and the degree of luminal stenosis were the independent predictors of FFR (11). Unlike earlier studies (11) wherein vessel-level characteristics were observed to be predictors of normal or abnormal FFR, the present study focused on the most stenotic lesion,

FIGURE 3 LAP Volume Can Describe the Difference Between FFR(−) and FFR(+) Lesions With the Same Degree of Luminal Stenosis



	FFR			QCA%			LAP Volume (mm³)		
Stenosis Category	FFR-	FFR+	P Value	FFR-	FFR+	P Value	FFR-	FFR+	P Value
<50%	0.92	0.72	<0.0001	35%	36%	0.3	11	17	0.05
50-70%	0.90	0.72	<0.0001	57%	59%	0.3	14	19	0.04
>70%	0.90	0.66	<0.0001	87%	89%	0.2	14	21	0.05



(A) (Left) At each degree of luminal stenosis, there were fractional flow reserve-positive (FFR[+]) and fractional flow reserve-negative (FFR[−]) lesions. Fractional flow reserve is treated as a continuous variable in this graph. For each group of quantitative coronary angiography results (QCA) (<50%, 50% to 70%, >70%; **green triangles**), the difference in fractional flow reserve is not explained by the difference in the degree of luminal stenosis because they are not significantly different. **(Right)** However, within each group of quantitative coronary angiography results, the fractional flow reserve-negative lesions (**dark pink solid circle** >0.8) were associated with a smaller low-attenuation plaque (LAP) volume **(blue star),** and the fractional flow reserve-positive lesions (**dark pink solid circle** <0.8) were associated with a larger low-attenuation plaque volume **(blue star).** Therefore, the difference in low-attenuation plaque volume can explain, at least in some cases, why lesions with similar degrees of stenosis have a substantially different fractional flow reserve. The **inset table below** summarizes the findings of the figure and demonstrates that there is statically significant difference between the low-attenuation plaque volume of fractional flow reserve-positive and fractional flow reserve-negative lesions in each stenosis category. There is no statistically significant difference in the quantitative coronary angiography results between fractional flow reserve-positive and fractional flow reserve-negative lesions of each stenosis category. **(B)** This figure presents a concept similar to that demonstrated in **(A)** by using fractional flow reserve as a dichotomous variable. Here, for each group of luminal stenosis category (i.e., <50%, 50% to 70%, >70%), the **pink bars** represent fractional flow reserve-positive and the **green bars** represent fractional flow reserve-negative lesions. The difference between the low-attenuation plaque volume (y-axis) of fractional flow reserve-positive and fractional flow reserve-negative lesions is statistically significant for all 3 groups ($p < 0.05$).

which is clinically more relevant. We used CTA as a tool that allowed identification and quantification of morphological characteristics of the most stenotic lesion, as well as the degree of luminal stenosis, to explore their relationship with lesion-specific ischemia by FFR. The degree of luminal stenosis and the LAP volume of the most stenotic lesion were the independent predictors of FFR. In addition to the lesion-specific characteristics, the presence of the lesion in the LAD artery, the location of the lesion in the proximal part of the vessel, and multiple lesions within the same vessel were also the independent predictors of invasive FFR. Importantly, lesion length, usually considered an important determinant of FFR, was found not to be related to ischemia. Moreover, we observed that among the lesions with a similar degree of luminal stenosis, the lesions with FFR ≤0.80 had significantly larger LAP volumes compared with the lesions with FFR >0.80. Therefore, it is conceivable that the difference in LAP volume could explain the stenosis-FFR mismatch in some cases, whereas in others, vascular territory and the additive effect of multiple lesions in the same vessel may contribute to the mismatch. We observed that most FFR(−) lesions were either nonobstructive or had small LAP volumes, findings that most likely explain the favorable prognosis associated with FFR(−) lesions reported in the DEFER and FAME studies (1). Conversely, the abnormal FFR may result from variable combinations of plaque stenosis and morphological traits of the lesion. In the current study, more than one-half of lesions with an FFR value ≤0.80 had <50% luminal stenosis, and only one-third of FFR(+) lesions demonstrated obstructive plaques with moderate to large LAP volumes. This finding could explain why adverse cardiovascular events occur in a relatively small portion of lesions with abnormal FFR when these patients are treated with medical therapy only (8.6%) compared with revascularization (7.2%) (2). Therefore, FFR could be accepted as a sensitive but not a specific marker of obstructive lesions associated with moderate to large LAP volumes or HRPs.

LAP VOLUME AND SEVERITY OF LUMINAL STENOSIS ARE INDEPENDENT PREDICTORS OF FFR. The imperfect relationship between stenosis and FFR is well documented (4,5), and large numbers of lesions with stenosis-ischemia mismatch have been described. Importantly, among lesions with intermediate degrees of luminal stenosis, the ratio of FFR(+) to FFR(−) lesions is almost 50:50 (8), and it has been attributed to possible limitations of 2-dimensional angiography, lesion length, and other factors (9,10,18). The present study, in a multivariable model, did not find lesion length to be important and instead suggested that in addition to luminal stenosis LAP volume is an independent lesion-related predictor of FFR. There were FFR(+) and FFR(−) lesions in all lumen stenosis categories wherein the FFR(+) lesions demonstrated significantly larger LAP volumes. This relationship suggests that the addition of the lesion-specific LAP volume may enhance the prognostic importance of luminal obstruction and stenosis-related ischemia in stable CAD. The importance of the LAP volume may be more pronounced in mildly to moderately stenotic lesions because lesion-specific ischemia in such patients is not likely to result from anatomic stenosis but rather from development of functionally significant stenosis at the time of maximum hyperemia, as described later (8).

During FFR measurement, the infusion of adenosine dilates the distal arteriolar bed with a drop in the resistance in the distal coronary bed that leads to development of an increased gradient between the aorta and distal coronary bed to drive increased coronary blood flow through the stenotic lesion or a maximally hyperemic state. Epicardial coronary artery autoregulatory mechanisms also respond to the state of maximal hyperemia by further dilatation, which, in addition, is exacerbated by nitroglycerin administration (a standard component of FFR

TABLE 2 FFR Is a Sensitive But Not Specific Predictor of Lesions at High Risk of Developing Major Adverse Events*

Type of Lesion	FFR-Negative Lesions (%)	FFR-Positive Lesions (%)
Nonobstructive with small LAP	53	12
Obstructive with small LAP	4	16
Nonobstructive with moderate LAP	26	28
Obstructive with moderate LAP	4	18
Nonobstructive with large LAP	11	14
Obstructive with large LAP	2	12

Values are %. *The distribution of various lesion types on the basis of the degree of luminal stenosis and LAP volume was examined in lesions with normal and abnormal FFR. For this purpose, obstructive and nonobstructive lesions were defined on the basis of 50% luminal stenosis by invasive angiography as the cutoff point. Conversely, small, moderate, and large LAP volumes were defined on the basis of tertiles of LAP volume of FFR(+) lesions (small <10 mm^3, moderate 10 to 25 mm^3, large >25 mm^3). Although most FFR(−) lesions were nonobstructive with a small LAP volume, there was a small portion (6%) with obstructive luminal stenosis and moderate to large LAP plaques. If we assume that this 6% of lesions has a high risk of future events as a result of their obstructive nature and a moderate to large LAP volume, FFR has a reasonable sensitivity for detecting such lesions. In contrast, 30% of FFR(+) lesions were obstructive with a moderate to large LAP volume (high risk), and 28% had a small LAP volume (low risk), thus making FFR not a specific detector of potentially high-risk plaques. Therefore, it can be concluded that FFR is a sensitive but not specific detector of high-risk lesions.

Abbreviations as in Table 1.

protocol). In the case of severe and fixed luminal stenosis, because the vessel at the level of stenosis cannot dilate any further, a post-stenotic pressure drop occurs. Conversely, in the case of mild to moderate luminal stenosis with a large necrotic core, it is proposed (8) that the epicardial vessel likely develops dynamic stenosis with an inability to dilate at the lesion site. With the rest of the vessel dilating during maximal hyperemia, the once mild to moderate stenosis may become functionally significant. The reason for the local inability of the vessel to dilate at the site of a large necrotic core is not clear, but this inability could be caused by significant positive remodeling at that level. The maximally stretched smooth muscle layer (or maximal positive remodeling) would restrict further dilatation analogous to the limits of Glagov phenomenon, after which the lipid-rich lesions encroach on the luminal diameter (19). Furthermore, the large, lipid-rich necrotic core should add inflammatory insult, oxidative stress, and hence local endothelial dysfunction (7,20–22). FFR is not a direct measure of ischemia, but rather is a surrogate that measures a ratio in pressure drop across the lesion. The transstenotic pressure decay is inversely proportional to the fourth power of the lumen radius, and it contributes significantly to the specific curvilinear pressure-flow relationship and defines the physiological importance of a fixed or dynamic narrowing (23). As a consequence, a change in luminal diameter relative to other segments of the same vessel, caused by local vasodilatory impairment at the time of maximal hyperemia, produces a marked hemodynamic effect, leading to abnormal FFR measurement. It is also reasonable to presume that the impairment in vasodilatation may vary depending on the size of the necrotic core, the volume of the reference vessel, and the vessel's overall ability to dilate.

COMBINATION PLAQUE MORPHOLOGY AND THE DEGREE OF LUMINAL STENOSIS MAY EXPLAIN OUTCOMES IN LESIONS WITH NORMAL AND ABNORMAL FFR. Analyses of the DEFER and FAME trial results (1,2,8) suggest that: 1) the benefit of FFR-guided therapy predominantly results from the safe deferral of FFR(−) lesions to medical therapy only, thereby avoiding the complications of unnecessary revascularization; and 2) only a small portion of FFR(+) lesions (8.6%) will result in future myocardial infarction if they are not revascularized (8,24,25). It is not clear why relatively normal post-stenotic pressure (normal FFR) would strongly predict freedom from subsequent events known to be caused by HRP morphology and plaque rupture.

From numerous intravascular ultrasound and CTA studies (12,13,26,27), it is known that obstructive lesions with high-risk features (large necrotic core and thin fibrous cap) portend a maximum likelihood of future events, ranging up to 22%, and nonobstructive lesions with high-risk features often undergo rapid plaque progression to become increasingly prone to rupture (28). More importantly, the absence of a large necrotic core or a thin fibrous cap, even in obstructive plaques, renders these lesions at low risk for future events; the negative predictive value for future events ranges from 96% to 100% for non-HRPs (12,13,26,27,29–32). It could thus be surmised that: 1) obstructive lesions with a large necrotic core should be at high risk of plaque rupture and an acute event; 2) nonobstructive lesions with a moderate to large necrotic core may result in unstable symptoms or subsequent events on plaque progression; and 3) lesions with a small or absent necrotic core, regardless of the degree of stenosis, should remain at a relatively low risk for future events.

Exploring the distribution of various lesion types (the plaque characteristics and severity of luminal stenosis) in FFR(−) and FFR(+) cohorts may explain the event rates in both groups. In the FFR(−) cohort, only 2% of lesions were obstructive by ICA and had a large LAP volume; the rest of the lesions were either nonobstructive or had smaller LAP volumes. This could explain why lesions with normal FFR could safely be treated with medical therapy alone and only a minority may result in future events including revascularization. Conversely, among FFR(+) lesions, only 30% were obstructive, with moderate to large LAP volume, and hence at high risk of future events; 29% had a small LAP volume and were therefore at low risk for future events. These observations can perhaps explain why only a relatively small portion of FFR(+) plaques would result in events if these lesions were left to medical therapy alone (24). These observations also beg to question the validity of revascularization recommendations for all FFR(+) lesions when only 8.6% of FFR(+) lesions in patients randomized to medical therapy alone in the FAME 2 trial resulted in death or myocardial infarction (2). These findings question the necessity of revascularization in all abnormal FFR lesions and bring up the possibility of the use of CTA plaque characterization as a means to stratify the lesions with normal and abnormal FFR further.

STUDY LIMITATIONS. This was a post hoc analysis of data from the NXT trial. The pre-specified selection criteria for inclusion in this study resulted in a higher proportion of patients with obstructive CAD than in a

nonselected coronary CTA population. Patients with acute coronary syndromes or previous revascularization were excluded in this study. Thus, applicability of results to those patient categories needs further study.

CONCLUSIONS

The current study demonstrated that the CT-defined LAP volume (a surrogate for necrotic core) of the most stenotic lesion in the vessel and the degree of luminal stenosis were the independent predictors of FFR. We also observed that in the plaques with a similar degree of stenosis, the presence of greater LAP volume was associated with lesion-specific ischemia or abnormal FFR. Further, most lesions with normal FFR did not demonstrate HRP characteristics, and only a small subset of FFR(+) lesions had these characteristics, thereby making FFR a more sensitive but less specific predictor of high-risk coronary lesions. Additional information about plaque morphological features, such as LAP volume, may offer a logical next step beyond FFR measurement in therapeutic decision making. This proposal would need to be tested in a randomized prospective fashion in patients presenting with stable CAD.

ADDRESS FOR CORRESPONDENCE: Dr. Jagat Narula, Icahn School of Medicine at Mount Sinai, 1190 Fifth Avenue, GP-1 West, N-125, New York, New York 10029. E-mail: narula@mountsinai.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The ischemia-stenosis mismatch could probably be explained in many cases by the lesion's morphological composition. The relationship of lesion morphology and FFR may also help explain superior outcomes associated with FFR-guided therapy.

TRANSLATIONAL OUTLOOK: The links among luminal obstruction, plaque morphology, and functional characteristics of the plaque can open a new door for future studies to investigate the value of combining these features in lesion stratification and guiding revascularization.

REFERENCES

1. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

2. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

3. Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. Circulation 1975;51:1085–94.

4. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. J Am Coll Cardiol Intv 2012;5:1029–36.

5. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study Fractional Flow Reserve Versus Angiography for Multivessel Evaluation. J Am Coll Cardiol 2010;55:2816–21.

6. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J 2015;36:100–11.

7. Ahmadi A, Kini A, Narula J. Discordance between ischemia and stenosis, or PINSS and NIPSS: are we ready for new vocabulary? J Am Coll Cardiol Img 2015;8:111–4.

8. Ahmadi A, Stone GW, Leipsic J, et al. Association of coronary stenosis and plaque morphology with fractional flow reserve and outcomes. JAMA Cardiol 2016;1:350–7.

9. Johnson NP, Kirkeeide RL, Gould KL. Coronary anatomy to predict physiology: fundamental limits. Circ Cardiovasc Imaging 2013;6:817–32.

10. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol 2010;55:173–85.

11. Gaur S, Ovrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. Eur Heart J 2016;13:1220–7.

12. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.

13. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

14. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 2009;3:122–36.

15. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145–55.

16. Gaur S, Achenbach S, Leipsic J, et al. Rationale and design of the HeartFlowNXT (HeartFlow Analysis of Coronary Blood Flow Using CT Angiography: NeXt sTeps) study. J Cardiovasc Comput Tomogr 2013;7:279–88.

17. Dey D, Schepis T, Marwan M, Slomka PJ, Berman DS, Achenbach S. Automated three-dimensional quantification of noncalcified coronary plaque from coronary CT angiography: comparison with intravascular US. Radiology 2010;257:516–22.

18. Nakazato R, Shalev A, Doh JH, et al. Aggregate plaque volume by coronary computed tomography angiography is superior and incremental to luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. J Am Coll Cardiol 2013;62:460–7.

19. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.

20. Lavi S, Bae JH, Rihal CS, et al. Segmental coronary endothelial dysfunction in patients with minimal atherosclerosis is associated with necrotic core plaques. Heart 2009;95:1525–30.

21. Lavi S, McConnell JP, Rihal CS, et al. Local production of lipoprotein-associated phospholipase A2 and lysophosphatidylcholine in the coronary circulation: association with early coronary atherosclerosis and endothelial dysfunction in humans. Circulation 2007;115:2715–21.

22. Lavi S, Yang EH, Prasad A, et al. The interaction between coronary endothelial dysfunction, local oxidative stress, and endogenous nitric oxide in humans. Hypertension 2008;51:127–33.

23. Spaan JA, Piek JJ, Hoffman JI, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. Circulation 2006;113:446–55.

24. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208–17.

25. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–84.

26. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319–26.

27. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

28. Ahmadi A, Leipsic J, Blankstein R, et al. Do plaques rapidly progress prior to myocardial infarction? The interplay between plaque vulnerability and progression. Circ Res 2015;117:99–104.

29. Kaul S, Narula J. In search of the vulnerable plaque: is there any light at the end of the catheter? J Am Coll Cardiol 2014;64:2519–24.

30. Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041–51.

31. Oemrawsingh RM, Cheng JM, Garcia-Garcia HM, et al. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol 2014;64:2510–8.

32. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. J Am Coll Cardiol Img 2011;4:894–901.

KEY WORDS coronary artery stenosis, myocardial ischemia, percutaneous coronary intervention, revascularization, stable ischemic heart disease, vulnerable plaque