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

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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 2017;■:■–■) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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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.

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 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 $\geq$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

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