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Noninvasive Fractional Flow Reserve Derived From Coronary CT Angiography

Clinical Data and Scientific Principles

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ABSTRACT

Fractional flow reserve derived from coronary computed tomography angiography enables noninvasive assessment of the hemodynamic significance of coronary artery lesions and coupling of the anatomic severity of a coronary stenosis with its physiological effects. Since its initial demonstration of feasibility of use in humans in 2011, a significant body of clinical evidence has developed to evaluate the diagnostic performance of coronary computed tomography angiography–derived fractional flow reserve compared with an invasive fractional flow reserve reference standard. The purpose of this paper was to describe the scientific principles and to review the clinical data of this technology recently approved by the U.S. Food and Drug Administration. (J Am Coll Cardiol Img 2015;8:1209–22) © 2015 by the American College of Cardiology Foundation.

STRENGTHS AND LIMITATIONS OF CURRENT METHODS OF NONINVASIVE CORONARY ARTERY DISEASE IMAGING

For several decades, stress testing has served as the cornerstone for assessment of symptomatic individuals with suspected or known coronary artery disease (CAD) (1). When stress testing is performed in conjunction with noninvasive imaging, an array of methods are used, including stress echocardiography and myocardial perfusion imaging (MPI) by single-photon emission computed tomography (SPECT), positron emission tomography, and cardiac magnetic resonance. These tests identify stress-induced regional wall motion abnormalities or reductions in coronary flow reserve (CFR) as a surrogate marker for flow-limiting epicardial coronary artery stenosis (2,3). Among these methods, MPI by SPECT remains the most commonly used technique for noninvasive CAD evaluation in the United States, and it accounts for approximately three-fourths of the 10 million stress imaging tests performed in the United States annually.

The rationale for the use of CFR for diagnosing CAD stems from the pioneering research of Gould and Lipscomb (4), who demonstrated compromise of flow with progressive narrowing of the coronary luminal diameter. Importantly, this reduced CFR is used simply as a surrogate for myocardial ischemia

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ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver-operating characteristic curve

CABG = coronary artery bypass graft

CAD = coronary artery disease

CFD = computational fluid dynamics

CFR = coronary flow reserve

CT = computed tomography

CTA = computed tomography angiography

FFR = fractional flow reserve

FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve

MPI = myocardial perfusion imaging

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

(an inadequacy of myocardial oxygen for a given metabolic state) and has never been validated in a human model. Although reductions in CFR manifest generally predictable reductions at hyperemic flow states for coronary stenosis ≥70%, the relationship between coronary stenosis and myocardial ischemia is nevertheless complex. Approximately 1 in 5 high-grade lesions with ≥70% stenosis do not cause ischemia, and diminution of coronary flow can begin as early as 40% diameter stenosis or in the context of diffuse or serial "nonobstructive" stenosis (5). Furthermore, CFR accounts for abnormalities across the entirety of the coronary vascular bed, which includes not only the epicardial coronary arteries but also the intramyocardial pre-arteriolar, arteriolar, and capillary circulations (6). Precise localization of CFR abnormalities to the epicardial versus nonepicardial vessels is vital, given that effective treatments exist for the former (including both medical therapy and revascularization), but no known effective treatments exist for the latter.

Recent clinical data have assessed the diagnostic specificity of MPI for patients undergoing invasive coronary angiography (ICA). In the nuclear substudy of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, only 32% of patients with ≥70% stenosis exhibited severe ischemia and 40% manifested no or mild ischemia according to MPI (7). Similarly, among >650,000 patients undergoing nonemergent ICA recorded in the National Cardiovascular Data Registry, noninvasive stress test findings offered minimal discriminatory value for identifying and excluding anatomically "obstructive" coronary stenosis (C index 0.75 vs. 0.74 for clinical evaluation vs. noninvasive testing) (8). Similar findings were observed in a 47-center study in Michigan: among 6,198 patients, stress imaging test results were not predictive of high-grade coronary lesions at the time of ICA (odds ratio: 0.79; 95% confidence interval: 0.56 to 1.11; $p = 0.17$) (9). Collectively, nearly two-thirds of patients undergoing nonemergent ICA do not have anatomically obstructive CAD.

Recently, coronary computed tomography angiography (CTA) has been offered as an anatomic alternative to stress imaging testing (1). Based on several prospective multicenter studies, coronary CTA exhibits high diagnostic performance for the identification and exclusion of anatomically obstructive coronary stenosis compared with an ICA reference standard. Coronary CTA findings are prognostically important and serve as effective guides toward medical and invasive management. However, similar to limitations of CFR that manifest a generally weak association with ischemia, and further emphasizing the complex relationship between stenosis and flow, coronary CTA has exhibited low specificity for identification of ischemia-causing coronary stenosis (10). Indeed, >50% of lesions considered anatomically obstructive according to coronary CTA do not cause ischemia. These findings are not singular to coronary CTA but are observed uniformly for all anatomic methods of coronary imaging, including ICA and intravascular ultrasound.

INVASIVE FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) performed at the time of ICA for combined anatomic-physiological evaluation represents the current gold standard for determining whether a coronary artery stenosis causes ischemia (11). FFR is defined as the ratio of maximal hyperemic flow to part of the myocardium in the presence of a stenosis in the supplying epicardial artery to the maximum hyperemic flow to the same myocardial territory in the hypothetical case in which the supplying artery is normal. An FFR ≤0.80 (i.e., when the distal coronary pressure is 80% of the aortic pressure under conditions of maximal hyperemia) is commonly accepted as the threshold below which a lesion is considered ischemia causing. Deferral of percutaneous coronary intervention (PCI) for vessels with an FFR >0.80 is associated with improved clinical outcomes and reduced costs compared with an ICA alone-guided intervention (12). Conversely, coronary revascularization in vessels with a measured FFR ≤0.80 is associated with reduced risk of death, myocardial infarction, or urgent revascularization compared with an ICA alone-guided revascularization or optimal medical therapy (OMT) alone (13,14). Based on these and other data, current guidelines regarding myocardial revascularization assign a Class IA recommendation to FFR for the assessment of coronary artery stenoses with a diameter reduction ranging from 50% to 90% unless there is noninvasive proof of ischemia (15).

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY–DERIVED FRACTIONAL FLOW RESERVE

Coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) is a novel noninvasive approach for precise localization of ischemia-causing coronary stenoses (**Central Illustration**). It applies