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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)

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Objectives The goal of this study was to determine the diagnostic performance of noninvasive fractional flow reserve (FFR) derived from standard acquired coronary computed tomography angiography (CTA) datasets (FFR_{CT}) for the diagnosis of myocardial ischemia in patients with suspected stable coronary artery disease (CAD).

Background FFR measured during invasive coronary angiography (ICA) is the gold standard for lesion-specific coronary revascularization decisions in patients with stable CAD. The potential for FFR_{CT} to noninvasively identify ischemia in patients with suspected CAD has not been sufficiently investigated.

Methods This prospective multicenter trial included 254 patients scheduled to undergo clinically indicated ICA for suspected CAD. Coronary CTA was performed before ICA. Evaluation of stenosis (>50% lumen reduction) in coronary CTA was performed by local investigators and in ICA by an independent core laboratory. FFR_{CT} was calculated and interpreted in a blinded fashion by an independent core laboratory. Results were compared with invasively measured FFR, with ischemia defined as FFR_{CT} or FFR ≤0.80.

Results The area under the receiver-operating characteristic curve for FFR_{CT} was 0.90 (95% confidence interval [CI]: 0.87 to 0.94) versus 0.81 (95% CI: 0.76 to 0.87) for coronary CTA ($p = 0.0008$). Per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia were 86% (95% CI: 77% to 92%) and 79% (95% CI: 72% to 84%) for FFR_{CT} versus 94% (86 to 97) and 34% (95% CI: 27% to 41%) for coronary CTA, and 64% (95% CI: 53% to 74%) and 83% (95% CI: 77% to 88%) for ICA, respectively. In patients ($n = 235$) with intermediate stenosis (95% CI: 30% to 70%), the diagnostic accuracy of FFR_{CT} remained high.

Conclusions FFR_{CT} provides high diagnostic accuracy and discrimination for the diagnosis of hemodynamically significant CAD with invasive FFR as the reference standard. When compared with anatomic testing by using coronary CTA, FFR_{CT} led to a marked increase in specificity. (HeartFlowNXT–HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography [HFNXT]; NCT01757678) (J Am Coll Cardiol 2014;63:1145–55) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AUC = area under the receiver-operating characteristic curve

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

CTA = computed tomography angiography

cMR = cardiac magnetic resonance

FFR = fractional flow reserve

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

ICA = invasive coronary angiography

NPV = negative predictive value

PPV = positive predictive value

Invasive coronary angiography (ICA) is the established clinical standard for detecting coronary artery disease (CAD). The correlation between angiographic and physiological stenosis severity, however, is poor (1,2). Because coronary physiology trumps anatomy for clinical outcome (3,4), current guidelines for the management of stable CAD recommend documenting ischemia by using a noninvasive functional test (e.g., single photon emission computed tomography, stress echocardiography, cardiac magnetic resonance [cMR]) before considering ICA or coronary revascularization (4,5). Shortcomings of current noninvasive diagnostic strategies in CAD, however, are apparent from the frequently inaccurate selection of patients for ICA (6). Fractional flow reserve (FFR), which assesses the ratio of flow across a stenosis to putative flow in the absence of a stenosis, has been shown to be a powerful tool for detecting lesion-specific myocardial ischemia. Several randomized trials have shown that an FFR threshold of 0.80 distinguishes patients and coronary lesions that will benefit from coronary revascularization (7) from those that will not (8). Consequently, FFR is the accepted reference standard for assessing the functional significance of CAD in a lesion-specific manner (4). Noninvasive anatomic assessment by coronary computed tomography angiography (CTA) is being increasingly used as an accurate tool for detecting or excluding CAD (9–12). Although the absence of coronary stenoses according to coronary CTA is associated with an excellent prognosis and obviates the need for any further diagnostic evaluation (11), the correlation of stenoses detected by using coronary CTA to downstream myocardial ischemia is poor (13). Recently, a method using computational fluid dynamics to calculate coronary blood flow, pressure, and FFR based on routinely acquired coronary CTA datasets at rest (FFR_{CT}) has been described (14–16). FFR_{CT} combines anatomic and functional information to enable appropriate therapeutic decision making. This method has tremendous potential because noninvasive determination of FFR may be a unique, useful test to differentiate individuals who will or will not benefit from revascularization, and thus FFR_{CT} has the potential of being a reliable gatekeeper to the pathway of ICA.

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The aim of the present study was to assess the diagnostic performance of FFR_{CT} by using invasive FFR as the reference standard. Compared with previous studies (15,16), a substantially refined version of the FFR_{CT} technology was used, and the emphasis on coronary CTA acquisition quality was strengthened.

Methods

Study design. The rationale and design of the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) study have been described previously (17). The study was designed to characterize FFR_{CT} diagnostic accuracy in patients suspected of having CAD by using invasive FFR as the reference standard, and it reflects improvements in FFR_{CT} technology (updated proprietary software with quantitative image quality analysis, improved image segmentation, refined physiological models, and increased automation), as well as emphasis on the coronary CTA image acquisition protocol to reflect current guidelines (18). The study protocol was approved at each of the 10 participating centers (Online Appendix) by the local institutional review board. All study subjects provided written informed consent.

Study population. Coronary CTA performed <60 days before scheduled nonemergent ICA was required for inclusion. As pre-specified (17), the first 100 patients included in the study had no requirements with regard to coronary stenosis severity. Beginning with patient 101, at least 1 stenosis with luminal diameter reduction between 30% and 90% in a vessel segment ≥2 mm in diameter according to coronary CTA was required. Exclusion criteria included previous coronary intervention or coronary bypass surgery; contraindications to beta-blocking agents, nitroglycerin, or adenosine; suspected acute coronary syndrome; previous myocardial infarction <30 days before coronary CTA or between coronary CTA and ICA; and body mass index >35 kg/m^2.

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