Title

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EDITORIAL COMMENT

FFR Derived From Coronary CT Angiography

Solving the Calcification Dilemma of Coronary CT Angiography*

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Since its emergence in 2005, coronary computed tomography angiography (CTA) has matured into a robust method for direct visualization of the coronary arteries and atherosclerotic plaque. Early prospective multicenter studies reported high diagnostic performance for coronary CTA in the identification and exclusion of high-grade coronary stenoses compared with the reference standard of invasive coronary angiography (ICA) (1–3). Both direct and historical comparison data have established the superiority of coronary CTA over functional stress testing for identification of anatomically obstructive coronary artery disease.

Despite diagnostic sensitivities of coronary CTA that approached 100% for coronary artery disease, specificities were markedly lower, ranging between 64% and 90% for coronary CTA-determined stenosis severity and reflecting a non-negligible rate of false-positive findings wherein coronary CTA diagnoses overestimate the severity of the luminal narrowing. This reduced performance has been attributed to limitations mainly caused by motion and calcium artifacts; the former has largely been overcome with the use of pre-procedural beta-blockers and higher temporal resolution CT scanners.

However, coronary calcification, which occurs from partial volume effects, has remained problematic. The magnitude of the adverse diagnostic effects of coronary calcification on coronary CTA was highlighted in a recent meta-analysis of 1,634 patients from 19 studies that examined the performance of coronary CTA across different thresholds of coronary artery calcium (CAC) scores (4). Subgroups at CAC scores <10 and <100 demonstrated high specificities of 90% (94% to 100%) and 88.5% (81% to 91.5%), respectively, whereas at CAC scores >400, the specificity declined significantly to 42% (28% to 56%) while retaining a high sensitivity of 97.5% (94% to 99%). These may, in part, explain the equally concerning findings that among stenoses considered high-grade according to coronary CTA, nearly 75% are not ischemia-causing compared with invasive fractional flow reserve (FFR).

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The study by Nørgaard et al. (5) in this issue of *iJACC* represents findings from the prospective, international, multicenter NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial, which evaluated the diagnostic performance of fractional flow reserve derived from coronary computed tomography angiography (FFR_{CT}), a novel method approved by the US Food and Drug Administration that uses computational fluid dynamics applied to typical coronary CTA images for calculation of FFR (6). Importantly, FFR_{CT} enables calculation of "3-vessel" FFR because it can interrogate any point within the coronary vascular bed for its hemodynamic significance. In NXT, the primary endpoint was 1 of discrimination (i.e., the area under the receiver-operating characteristic curve [AUC]) because this metric allows identification of the optimal sensitivity and specificity for any given test. On a per-patient basis, the AUC was 0.90 for FFR_{CT},

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with a >2-fold increase in diagnostic specificity for ischemia-causing coronary lesions by FFR. These data evoked optimism for a technique that allows for direct visualization of coronary artery anatomy (by coronary CTA) and precise identification of the coronary artery stenoses that cause ischemia (by FFR_{CT}). Notably, the average CAC score in NXT was 302 Agatston units, which places the study population in the prognostically worst risk category when defined according to the Multi-Ethnic Study of Atherosclerosis (7).

However, the detailed breakdown of FFR_{CT} accuracies across coronary calcium score ranges was not detailed in the original NXT paper (6) and is the subject of the paper by Nørgaard et al. (5). For 214 patients who underwent CAC scoring in NXT, with 333 vessels directly examined by using FFR, the diagnostic performance of FFR_{CT} was evaluated for study-specific quartiles of CAC scoring. Interestingly, the investigators observed no differences in diagnostic accuracy, sensitivity, or specificity of FFR_{CT} across any CAC score quartiles, including no differences at even the highest quartile of patients with Agatston CAC scores ranging from 416 to 3,599. For these patients, FFR_{CT} showed marked improved discrimination of ischemia compared with coronary CTA alone (AUC: 0.91 vs. 0.71; $p = 0.0004$). Indeed, in this highest quartile, FFR_{CT} reclassified 60% of cases, leading to a significant reduction in false-positive findings. These results emphasize the immunity of FFR_{CT} to the largest imaging limitation of coronary CTA and demonstrate that the test is not affected by even the most severe calcifications.

Before the introduction of FFR_{CT}, there was no noninvasive method for simultaneous detection of coronary stenosis and determination of whether that stenosis causes ischemia. This ability to precisely locate a lesion that may benefit from coronary revascularization represents a significant advancement in diagnostic imaging. Added to the visualization of atherosclerotic plaque features that augment the diagnosis of coronary lesion-specific ischemia, the use of FFR_{CT} may enable pre-procedural planning in a manner that other modalities do not. In addition, its general immunity to coronary calcification represents a major advance compared with coronary CTA imaging.

These data (5), although from a substudy of a larger parent trial, are of considerable import in today's health care milieu, in which false-positive noninvasive imaging test results commonly beget unnecessary ICA for subjects who are subsequently found not to have disease. In a recent report from the National Cardiovascular Data Registry of 661,063 patients undergoing elective ICA after functional stress testing, more than one-half of patients did not have any actionable coronary stenosis, with the majority of patients having normal coronary arteries, confirming the low diagnostic accuracy of stress testing that is observed in current clinical practice (8). Among the 302,651 patients who underwent myocardial perfusion imaging (the most commonly used test in the United States today), only 134,670 (44.4%) had obstructive disease at ICA. Exercise treadmill testing, stress echocardiography, and magnetic resonance imaging yielded similarly low rates of obstructive disease. These findings are in direct accordance with a recent 47-center study of the Advanced Cardiovascular Imaging Consortium by Chinnaiyan et al. (9), in which stress test results did not predict the presence of anatomically obstructive coronary artery disease at ICA.

Numerous other clinical and economic assessment studies for FFR_{CT} are ongoing. In the recently reported RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain) study, which was presented in abstract form at the 2015 EuroPCR Scientific Sessions, FFR_{CT} was evaluated for its ability to influence clinical decision making in salutary fashion (10). In 200 consecutive patients in stable condition with chest pain, cardiologists' decision making was tested when using standard coronary CTA versus coronary CTA plus FFR_{CT}. In this study by Curzen et al., 12% of patients who would have been treated with medical therapy alone would have been sent for ICA with intended revascularization if the FFR_{CT} results were known. Conversely, 30% of patients who would have been referred to ICA were reassigned to medical therapy alone when using FFR_{CT} added to coronary CTA. Nearly 20% of patients who were chosen for coronary revascularization were found to have different vessels needed for treatment, a finding highlighting the ability of FFR_{CT} to perform 3-vessel evaluation.

Two additional ongoing FFR_{CT} trials are notable. The multicenter PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts [NCT01943903]) trial of nearly 600 patients (whose enrollment is completed; results are expected to be reported in 2015) is a 2-period prospective evaluation of current practice versus FFR_{CT}-based practice. It has a 90-day primary endpoint of ICA normalcy; secondary endpoints will include major adverse cardiac events, quality of life, medical radiation, and resource consumption. Finally, the multinational CREDENCE (Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia [NCT02173275]) trial of >600 patients is comparing

coronary CTA and FFR_{CT} head-to-head against stress testing for definitive determination of which methods are best for the diagnosis of ischemia. These trials will further inform the clinical cardiovascular imaging community on the use of FFR_{CT}. At present, however, the technology seems to have taken 1 large step closer to a "1-stop shop" of anatomic identification of coronary stenoses as well as determination of their physiologic significance.

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