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EDITORIAL COMMENT

# Incremental Benefit of CT Perfusion to CT Coronary Angiography

## Another Step to the One-Stop-Shop?*

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Cardiac computed tomography (CT) assessment of both anatomic coronary artery disease (CAD) and myocardial ischemia has been a goal since the advent of electron beam CT imaging >30 years ago (1). Since then, however, attention has been primarily focused on optimizing coronary CT angiographic technology to achieve diagnostic accuracy similar to invasive coronary angiography. The result was a robust, highly sensitive technology to rule out epicardial CAD (2). Investigations also reconfirmed that anatomic assessment of coronary anatomy by using CT or invasive angiography was insufficient to predict myocardial ischemia, resulting in only fair specificity and positive predictive values (3). CT angiography would have to be combined with additional information to "rule in" ischemia at the same rates of "ruling out" CAD.

To be a viable alternative to existing nuclear and echocardiographic stress testing, CT myocardial perfusion required high-fidelity myocardial enhancement, rapid cardiac coverage during myocardial contrast transit, and acquisitions performed at a reasonable radiation dose (4). Incremental improvements in spatial resolution and longer detector coverage or dual head scanners largely achieved these goals. However, the transition of CT myocardial perfusion into clinical care has been slow owing to confusion from differing CT perfusion techniques, variable comparators to CT perfusion by various studies, and differing patient populations (5). In the largest multicenter study to date, the CORE320 (Coronary Artery Evaluation Using 320-Row Multidetector CT Angiography) trial, the diagnostic specificity of 74% and positive predictive value of 86% of combined CT angiography and perfusion were not compelling enough to adopt CT perfusion over other stress testing techniques (6). Thus, questions remained for CT perfusion, some simple and some more complex. Whether to use static CT myocardial perfusion (obtained at a single time point) or dynamic CT perfusion (obtained with multiple scans over time and capable of quantitative myocardial flow) has not been established. Implementation in general cardiology practice was also not clear because many previous CT perfusion studies tested lower risk patients or those without known CAD or previous arterial revascularization (5). Finally, competing technologies to CT myocardial perfusion, specifically CT fractional flow reserve ($FFR_{CT}$), have been topics of special interest (7,8), but it is unclear if these are direct competitors or complementary techniques (9).

The current study by Pontone et al. (10) in this issue of *iJACC* is an important advance in the long history of CT myocardial perfusion. This multicenter study describes the diagnostic advantage of contemporary CT perfusion techniques versus CT angiography alone in a high ischemia risk cohort (69% CAD prevalence of >50% stenosis in at least 1 artery). This paper is part of a series of investigations (11) from this multicenter group that evaluates combined CT angiography with static stress CT perfusion using the latest generation CT scanner and advanced image processing. The current scanner tested utilizes long z axis coverage, spatial resolution nearing that of invasive coronary angiography, and software imaging enhancements, including iterative reconstruction and coronary motion correction (12). Compared with invasive angiography and FFR, the physiological gold standard for functional assessment of coronary stenoses, CT angiography sensitivity and "ruling out"

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ischemia were very high, similar to many other CT technologies (2). More importantly, the addition of stress CT perfusion to this CT angiography increased the modest per-patient and per-vessel specificity by 18% and 29%, respectively. Compared with less contemporary CT perfusion technologies, there seemed to be numerical improvements in accuracy measures and nearing that of the noninvasive standard of magnetic resonance imaging and quantitative positron emission tomography myocardial perfusion imaging (13). In addition, the full heart coverage in 1 CT gantry and other imaging enhancements provided very rapid imaging and combined CT angiography and perfusion at a reasonable mean radiation dose of 5.3 mSv. This dose is incrementally lower than in previous studies (6) and well within the range of current nuclear stress testing (14). The current paper is an important advance toward the comprehensive, one-stop-shop myocardial evaluation envisioned by the CT designers so many decades ago.

There were some additional insights of this study (10) that are worth noting. First, the study used both the beta-blocker metoprolol and sublingual nitroglycerin to slow the heart rate and dilate the epicardial arteries, respectively. Although standard for CT angiography, these medications also function as anti-ischemia agents with the potential to diminish the specificity of stress CT perfusion, as previously shown in pharmacological nuclear stress imaging (15-17). Fortunately, the diagnostic accuracy measures did not appear to be substantially decreased with these medications in the current study. Second, a concern in scanning high-risk patients who have CAD is that the higher prevalence of coronary calcium or stents will lead to a higher false-positive rate of significant coronary stenosis and result in additional unnecessary testing (18). In the high-risk group, calcium blooming artifacts were present in >20% of coronary segments, although only 2% of coronary segments were not evaluable at study conclusion. The latter is typical for most current scanners but may speak to the expertise of the readers as well as the technology. Regardless, although the effects of calcium were not specifically assessed, the reclassification of "significant" CAD by CT angiography to no ischemia and no further testing with CT angiography and perfusion was 78%. This outcome is both a payer and patient opportunity cost savings as well as a safety advantage to patients. Finally, the current protocol allowed reasonable time (approximately 15 min) to decide on further testing based on the CT angiographic data. If the CT angiogram did not show significant coronary stenosis, this outcome was highly predictive of normal FFR and, thus, no additional testing would be required. In practice, having a CT reader available during a 15-min interval between CT scans may be a limitation to workflows in some centers. However, the findings by Pontone et al. (10) support this type of judicious protocol.

As with any advance, residual questions remain. The authors (10) did not include resting CT perfusion in their paradigm. Because stress CT perfusion abnormalities are evident in both ischemia and infarction, differentiation of these in a high-risk population is important to prevent evaluation and possibly revascularization of nonviable myocardium. Whether resting CT perfusion (possibly as part of the CT angiogram) or adding a late enhancement scan would answer this question is a topic of additional study. Similarly, this approach may identify what appear to be suspicious lesions, but intervention on these may not resolve ischemia if the primary origin of ischemia is from microvascular disease (19). In addition, whether the use of dynamic CT (multiple CT images during contrast myocardial transit) would improve specificity further is not known. Dynamic CT imaging has the potential to provide quantitative blood flow information that could improve specificity further as well as identify the subset of patients with ischemia from small vessel coronary disease that may or may not have epicardial stenosis (20-23). Pontone et al. (11). and others are studying dynamic CT perfusion to this end.

Finally, FFR using computed flow patterns based on the CT angiographic images ($FFR_{CT}$) has emerged as another modality to improve CT angiographic specificity (7,8). $FFR_{CT}$ data are encouraging and resulted in recommendations for coverage by the National Institute for Clinical Excellence medical technology guidance, as well as a recent Centers for Medicare & Medicaid Services billing code. $FFR_{CT}$ is numerically not as robust as the findings from the current study (10). Small studies have suggested that the combination of $FFR_{CT}$ with CT angiography and CT perfusion may provide even more robust diagnostic accuracy (9). This idea will be further tested with the PERFECTION (Comparison Between Stress Cardiac Computed Tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography in the Evaluation of Suspected Coronary Artery Disease) study by Pontone et al. (11). As with so many other technologies, future CT interpretation will amalgamate all available information, which may include CT angiography, CT perfusion, $FFR_{CT}$, CT myocardial appearance, and/or cardiac function, to construct a vector of data to enhance diagnosis and treatment decisions.

To achieve the mainstream acceptance and reimbursement of other types of stress testing, larger multicenter CT perfusion trials with cardiac outcomes as the final arbiter are needed, similar to the landmark cardiac CT trials in acute chest pain and in chronic chest pain. In the interim, the current study (10) is another important step toward the comprehensive one-stop-shop for coronary and cardiac anatomy as well as myocardial blood flow evaluation.

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