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EDITORIAL COMMENT

A New Decade of Old Questions

Steps Toward Demonstrating the Efficacy of Physiologic CAD Evaluation by CT*

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At the time of its introduction in 2005, coronary computed tomography angiography (CCTA) of ≥64 detector rows was broadly evaluated in single and, subsequently, multicenter clinical trials for its diagnostic performance against an invasive coronary angiography (ICA) reference standard (1). The majority of these studies observed similar results, with CCTA exhibiting very high sensitivities and generally moderate specificities for identification and exclusion of a ≥50% luminal diameter stenosis by ICA. Despite its similar specificity to stress imaging tests, such as those performed with single-photon emission computed tomography or stress echocardiography, CCTA was and is still considered by many to be a method that excels at exclusion of high-grade coronary stenosis, but not a method that excels at its specific and reliable identification.

Even though proponents of CCTA contended that the performance measures were sufficient to justify its routine use in clinical care based on its negative predictive value, large-scale clinical outcomes trials with CCTA-guided strategies were lacking, and prior randomized controlled trials such as COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) that used ICA stenosis to guide clinical decision making for revascularization did not observe improved mortality with revascularization (2–4). Furthermore, given the traditional approach to employ stress testing to guide physiologic-based treatment decisions of revascularization and medical therapy for coronary artery disease (CAD), discussion ensued as to which was the noninvasive "superior" approach for CAD assessment—CCTA or stress imaging. This disagreement and equipoise among the scientific community set the stage for the performance of 2 large-scale multisite randomized controlled trials assessing the performance of CCTA: PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) (n = 10,003) and SCOT-HEART (Scottish Computed Tomography of the Heart) (n = 4,146) (5,6). In PROMISE, CCTA was tested against any method of functional stress testing, and no differences were observed in major adverse cardiac events between groups at a 25-month follow-up. In contrast, SCOT-HEART evaluated patients undergoing a standard of care that often but not always included stress electrocardiographic testing versus that standard plus CCTA. At a 1.7-year follow-up, the CCTA group experienced a near significant 38% reduction in fatal and nonfatal myocardial infarction ($p = 0.0527$) that increased to a significant 50% reduction at 3 years ($p = 0.02$) (7). Germane to the latter study, the rates of ICA were similar among randomized groups, with no significant differences in coronary revascularization rates. Rather, the most notable difference between the CCTA and non-CCTA arm that appeared to drive the benefit in the CCTA arm was a 4-fold increased use of CAD preventive medical therapies in patients that underwent CCTA.

Since these seminal publications, the field of CCTA has evolved additional tools that now enable physiologic evaluation of CAD beyond anatomical CCTA detail, including vasodilator-mediated stress testing by computed tomography perfusion (CTP) by static,

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dual energy, or dynamic approaches; modeling of hyperemia for computation of fractional flow reserve from computed tomography (FFRCT) through computational fluid dynamics; and quantification of the contrast opacity before and after a stenosis at a resting state to further understand the hemodynamic significance of a particular coronary lesion (transluminal attenuation gradient [TAG]) (8).

Each of these methods, as well as the different approaches within each method, differs significantly, and have important advantages and limitations: 1) CTP by static methods is subject to the same limitations as perfusion assessed by single-photon emission computed tomography, in that it is a relative technique that may be subject to false negative results in the setting of balanced ischemia (9,10). Dual energy CTP suffers from higher radiation doses if performed in the projection domain, whereas dual energy computed tomography in the image domain does not offer the ability to perform actual material decomposition. Dynamic CTP offers an understanding of absolute blood flow at the myocardial level, but may be associated with higher radiation exposure. 2) FFRCT aims to evaluate decrements in hyperemic coronary pressure across a given coronary lesion and, in this regard, does not allow for determination of the effects of a coronary lesion on myocardial blood flow. Two computational fluid dynamic methods currently exist that enable estimation of FFR by CT, including a software-as-a-service method that employs 3-dimensional modeling and on-site solutions that use reduced order computational fluid dynamic methods to allow for calculations to be achievable on a traditional standalone computer (11). One major limitation to both of these approaches is their reliance solely on the luminal geometry, which alone is insufficient to reliably determine the lesion-causing nature of a coronary stenosis. 3) TAG contrasts with both CTP and FFRCT in that it can be performed on a resting CCTA and is represented by a linear regression coefficient between the opacification and axial distance of any given location within a coronary artery. Early studies have demonstrated a positive relationship of TAG to high-grade coronary stenosis, which represented a surrogate of coronary ischemia, with limited subsequent studies observing a similar relationship to hyperemia-induced FFR (12,13). Notably, the capability of assessing resting differences in coronary flow across the entire cardiac cycle in intermediate stenoses is generally antithetical to observations in preclinical and clinical models that demonstrate that resting flow disturbances occur only in severe stenoses.

In this issue of *iJACC*, Celeng et al. (14) report a summary meta-analysis of these techniques—both alone as well as in combination with CCTA—to diagnose ischemia. This well-performed study evaluated 54 studies, wherein 5,330 patients were included with a focus on per-vessel performance against an invasive FFR reference standard. For any physiologic measure alone, CTP was demonstrated to exhibit the highest accuracy and specificity (86%) and was superior to TAG and FFRCT, which performed nearly identically (77% and 78%, respectively). These findings were similar on a per-patient level, with CTP demonstrating the highest specificity (79%) compared with TAG (39%) and FFRCT (76%). Interestingly, the addition of CCTA information yielded mild improvements to CTP (sensitivity 81% to >82%, specificity 86% to >88%), whereas this addition of CCTA information to FFRCT reduced its sensitivity (85% to 76%) and increased its specificity (78% to 80%). Compared with static CTP methods, dynamic CTP demonstrated higher sensitivity (85% vs. 72%) with lower specificity (81% vs. 90%). For different methods of FFRCT, offsite versus on-site performed similarly (85% vs. 84%). Importantly, the investigators also presented an illustration of the high diagnostic performance of FFRCT when the values are very low or very high, but modest performance between the range of 0.74 and 0.82 when the invasive FFR was in the intermediate range.

Celeng et al. (14) should be commended for an analysis that summarizes the current state of physiologic CAD evaluation by CCTA and their study, as most high-quality studies do, evoke numerous additional questions. This meta-analysis emphasizes what we currently know about physiologic CAD evaluation by CCTA but, more importantly, emphasizes how early on we are in fully understanding the potential of CCTA and its associated tools for physiologic CAD evaluation, as has been described by Celeng et al. (14). Recently, novel methods of computing FFR using deep neural networks and machine learning have been developed to calculate FFR from CT using coronary luminal topographies and geometries for calculation of FFR (15,16). Beyond the use of luminal measures alone, Dey et al. (17) have integrated the entirety of coronary luminal and atherosclerotic plaque features considering plaque burden, composition, and location with outputs of coronary vessel ischemia determined by a machine learning algorithm.

In their seminal paper, Fryback and Thornbury (18) describe a multistep process demonstrating the efficacy of diagnostic imaging wherein technical

evaluation and diagnostic accuracy—the current state of physiologic CAD evaluation by CCTA—are followed by evaluation of the effect of the imaging test to influence diagnostic work-up, patient management, and ultimately patient-centered and societal outcomes of improved event-free survival and cost-effectiveness. Based on this foundation, an important question is whether it is possible to employ these techniques to assess the salutary effects of medical therapy; for example, for a symptomatic patient with myocardial ischemia who is successfully treated with antianginal medications, will the perfusion abnormalities on CTP normalize as they do with such techniques as single-photon emission computed tomography and positron emission tomography? The same question is important to understand for FFRCT, which by all methods relies on luminal geometry alone that is expectedly unaffected by medical therapy. Although seemingly poor performing for diagnosis of ischemia, it is nevertheless curious whether the accuracy of TAG is affected in the setting of reduced chronotropy, as might be expected for a patient chronically treated with beta blockers.

For mainstream use of these techniques, however, clinical outcomes-based trials remain needed. To date, no large-scale CT study has evaluated CAD outcomes when knowing both coronary "anatomy" and "physiology." Though historical debate has defined these terms at a binary threshold of stenosis severity or with the presence or absence of a perfusion abnormality, the present study data by Celeng et al. (14), as well as that related to atherosclerosis information offered by CCTA, highlight the oversimplification that comes from such categorizations wherein "physiology" can represent resting differences in contrast opacification, differences in rest-stress myocardial perfusion, absolute myocardial blood flow, or modeled differences in hyperemic pressure differences along a vessel. As the field awaits the performance of well-performed clinical trials that address these issues, including the highly awaited ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial (NCT01471522), wherein patients with moderate-to-severe ischemia by stress testing underwent CCTA, with one-half assigned to medical therapy and the other one-half to medical therapy plus early invasive angiography with intended revascularization. This study, though not using CT alone to provide both anatomic and physiologic information, will nevertheless offer significant information gain as to the ideal approaches to CAD treatment in the setting of abnormal anatomy and/or physiology. The field of CT would do well to consider the ISCHEMIA trial as an example of high-quality research based on patient-centered outcomes. Rather than simply identifying small differences in the areas under receiver-operating characteristics curve for discrimination of ischemia, assessment of these newer CCTA tools to guide therapy in a manner that improves clinical CAD outcomes and cost-effectiveness likely represents the next era of research required to substantively advance the field of diagnostic imaging.

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