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EDITORIAL COMMENT

Stress Myocardial Perfusion Imaging by Computed Tomography

A Dynamic Road Is Ahead*

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The recent adoption of cardiac computed tomography (CCT) into clinical practice has invigorated the debate regarding the strengths and limitations of directly imaging coronary atherosclerosis (i.e., anatomy) versus imaging myocardial perfusion (i.e., physiology). Although proponents of CCT point to its excellent negative predictive value and thus the ability to exclude the presence of coronary artery disease (CAD), critics, who tend to advocate perfusion-based techniques, point to the somewhat limited positive predictive value for detecting coronary stenosis (as detected by invasive angiography) and mainly the low positive predictive value for ischemia (as detected by myocardial perfusion imaging [MPI]). In actuality, both anatomic imaging and the assessment of perfusion are potentially useful approaches when applied to appropriately selected patients, although each has unique strengths and limitations (1).

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The recognition that these 2 diagnostic strategies are often complementary has led to a search for the ideal method for integrating CCT and MPI. This will typically involve the use of multiple modalities, but the recent recognition that CCT can be used to evaluate stress and rest myocardial perfusion offers the potential of acquiring data on coronary anatomy and perfusion using a single examination that can be performed with 1 modality (2,3) The possible advantages of such a single-modality comprehensive examination include lower cost, increased availability, lower radiation, and intrinsic coregistration of anatomy and physiology. The implicit assumption underlying the superiority of this approach is that CCT must be able to provide data on MPI at least as well as currently used techniques.

Although the field of computed tomography perfusion (CTP) is still in its infancy, initial reports indicate that the information provided by CTP may be comparable to single-photon emission computed tomography (SPECT) MPI for the detection of angiographic stenosis and expose patients to an equal amount of radiation (2). Moreover, Rocha-Filho et al. (4) showed that the data provided by CTP is complementary to CTA and can thus enhance the diagnostic accuracy for detecting stenosis. Despite these favorable initial reports, larger studies are needed to establish the diagnostic accuracy of CTP. Although CTP has excellent spatial resolution, it has relatively poor contrast compared with nuclear or cardiac magnetic resonance techniques. CTP is further limited by artifacts resulting from motion and beam hardening, and the requirement to inject iodinated contrast limits its application in patients who have impaired renal function.

Initial CTP investigations used qualitative methods to distinguish areas of hypoperfused myocardium from normal myocardium. More recently, several animal (5,6) and human (7) studies attempted to quantify myocardial perfusion using milliliters per gram per minute, analogous to quantification, which is now possible with positron emission tomography or, more recently, with cardiac magnetic resonance. Before discussing potential approaches to quantitative CTP, it is important

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to review potential advantages of myocardial blood flow (MBF) quantification that have been proposed in cardiovascular imaging: 1) identification of subclinical CAD; 2) improved detection of stenosis, particularly when using nuclear techniques when a balanced reduction in blood flow may result in an apparently "negative" MPI; 3) improved assessment of the extent of CAD, which may be underestimated by visual assessment of SPECT MPI (8); 4) ability to monitor response to therapy; 5) improved overall risk assessment, likely as a result of the first 3 reasons. Notable, however, is that in the case of CCT, the benefits outlined in 1), 2), and 3) may no longer be relevant because CCT offers the ability to detect subclinical atherosclerosis, can identify the presence of multivessel or left main obstructive CAD, and provides an accurate assessment of the extent of CAD. Thus, when added to computed tomography angiography, the most important advantage of CTP, whether by qualitative, semiquantitative, or using absolute MBF quantification, would be the assessment of the hemodynamic significance of anatomic lesions. With this objective in mind, future investigations will need to determine whether a visual assessment of CTP (as is currently clinically performed for most modalities evaluating MPI) could be improved by semiquantitative or absolute quantification. Such studies will need to use an appropriate gold standard for MBF (quantitative positron emission tomography or cardiac magnetic resonance or microspheres for animal studies).

In this issue of *iJACC*, Ho et al. (9) present the results of one of the first human studies that used a dynamic CTP protocol to quantify MBF. This study used the latest generation dual-source CCT to estimate MBF during rest and stress among 35 patients with a fixed or reversible perfusion defect on SPECT. The protocol consisted of serial imaging of the entire myocardium during stress and rest to construct time attenuation curves of the aorta and left ventricle. Perfusion defects were subsequently defined as areas of decreased blood flow compared with surrounding tissue. Among the 30 patients who also underwent invasive angiography, CTP demonstrated a high sensitivity (95%) but a lower specificity (65%) for the detection of stenosis. Compared with SPECT MPI, quantitative CTP had a sensitivity of 83% and a specificity of 78%. The average radiation dose was 18 mSv for the combined stress and rest CTP and 2 mSv for computed tomography angiography (which, due to issues related to coverage and the lower resolution used for CTP, required a separate dedicated scan).

Although the study by Ho et al. (9) is intriguing, there are several notable limitations. First, although MBF was estimated using CTP, there was no reference standard available for comparison. Qualitative SPECT is a suboptimal reference, as evident by the finding that many segments that had abnormal stress CTP but normal SPECT had stenosis on computed tomography angiography. Second, the radiation dose of the entire protocol (~20 mSV) is higher than the dose observed from nonquantitative CTP techniques (~12 mSv) (2). Given the novel dose-saving capabilities of the scanner used in this study, it is likely that, if replicated on other scanners, dynamic CTP would yield even higher radiation doses.

It is noteworthy that the method used to quantify MBF in this study represents an unproven approach to determine absolute MBF. Although the rate of contrast enhancement (up slope of the myocardial time attenuation curve) increases approximately linearly with flow, the normalization of this parameter by the amplitude of the arterial input function does not yield an estimate of absolute blood flow, as suggested by the units (i.e., ml/ml/min) used in this study. Even if the question of absolute versus relative flows is disregarded, the flow reserve ratios that are established using this method (6) are lower than anticipated based on physiological studies. The slope integral parameter (5) is an alternative approach that is validated against microsphere measurements and yields a more accurate flow reserve estimate. Still, any of the above semiquantitative parameters do not provide absolute MBF. Tracer kinetic modeling or the central volume principle would be preferable.

Another limitation of the dual-source dynamic CTP protocol is the limited temporal resolution as datasets were acquired every 2 or 4 heartbeats. This limitation could result in an underestimation of blood flow, particularly during stress as temporal resolution requirements for MBF quantification become more critical with increasing MBF (10). In the present study, this limitation was offset by the fact that the arterial input function could be sampled with relatively higher temporal resolution and was then used to interpolate the tissue time attenuation curves using a 2-compartment model with the measured arterial input function as constraining input.

Despite initial optimism regarding CTP, many questions need to be answered before this technique

can be adopted into clinical use. The diagnostic accuracy of CTP needs to be demonstrated in larger, ideally multicenter, studies. Although the potential ability to quantify MBF is exciting, quantitative or semiquantitative techniques will require validation against methods that can measure MBF. Furthermore, future studies will need to demonstrate whether there is added value for such quantitative CTP techniques beyond static CTP, especially in light of the higher radiation exposure associated with dynamic imaging. Ultimately, should a validated, optimized, and accurate CTP protocol be available, randomized trials will be needed to compare the clinical effectiveness of the CCT/CTP examination with other modalities. One thing seems certain for now—a dynamic road is ahead!

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