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EDITORIAL COMMENT

Understanding Coronary Physiology Through Dynamic CT Perfusion Imaging*

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The introduction of fractional flow reserve (FFR) through the results of several randomized trials has led to a paradigm shift away from a revascularization strategy guided by anatomy alone to one that bridges the anatomy with the physiology (1,2). Two commonly used techniques to assess coronary physiology include pressure assessment through FFR and myocardial perfusion, expressed by myocardial blood flow (MBF); importantly, they are not interchangeable.

Quantification of MBF can be obtained routinely by several imaging modalities including dynamic computed tomography perfusion (CTP) imaging (3-5). The direct comparison between FFR and hyperemic MBF using any measurement technique is often discordant because these 2 entities account for different aspects of coronary physiology. FFR reflects the hyperemic pressure gradient across a specific epicardial stenosis, whereas MBF represents the entire vascular bed supplied by a specific coronary artery, and therefore, it is influenced by both coronary stenosis and microvascular resistance (6). Consequently, differences between these 2 measurements do not imply the failure of 1 of the 2 methods but rather the complex and heterogeneous mechanism of ischemic heart disease.

If the goal of dynamic CTP is to predict invasive FFR, relative flow reserve (RFR) has been shown to be a better alternative to absolute MBF (7). As such, the article by Yang et al. (8) in this issue of *iJACC* revisits the known relationship between FFR and RFR, previously evaluated by positron emission tomography studies. The authors compared the diagnostic performance of computed tomography (CT)-derived hyperemic MBF and stress myocardial blood flow ratio (RFR) for the detection of hemodynamically significant coronary lesions in 82 symptomatic patients with 1 or 2 coronary stenoses >30% (8). RFR was determined to be the ratio of regional hyperemic MBF subtended by a stenotic artery to hyperemic MBF of a reference vascular territory supplied by a nonstenotic coronary artery. This study produced several insights that are worth noting.

RATIONALE FOR THE COMPARISON BETWEEN RFR AND FFR

If the assumptions about uniform myocardial vascular resistance and absence of stenosis in the reference vessel are fulfilled (8), FFR can also be expressed as the ratio of hyperemic flow in a stenotic vessel divided by hyperemic flow in a normal vessel (9), making RFR and FFR comparable. As such, previous work (7-10) showed that RFR and FFR have a close relationship approaching linearity. The current study confirmed these data, demonstrating a strong correlation between flow-based RFR and pressure-derived FFR ($r = 0.66$) with a mean difference between the absolute values of 0.02. The deviation from linearity and the imperfect agreement between the 2 parameters can be partially explained by the definition of the reference vessel, namely a vessel with stenotic diameter of <30%. In fact, the presence of diffuse coronary atherosclerosis, although not obstructive, may be associated with a continuous FFR decline along the length of the vessel. Similarly, a slight decrease of MBF in the reference myocardial area due to diffuse atherosclerosis may lead to an overestimation of RFR compared to FFR.

DIAGNOSTIC ACCURACY

The overall accuracy and C-statistic of RFR are higher, although not statistically significant, than that of

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hyperemic MBF, using FFR <0.80 as a reference value for the identification of hemodynamically significant lesions (80% and 0.88% vs. 72% and 0.79%, respectively). Importantly, the combination of hyperemic MBF and RFR has been shown to provide the best performance compared to FFR, as it integrates information from focal epicardial stenosis, diffuse atherosclerosis, and microvascular vasodilatory capacity (7).

CUTOFF VALUES

Despite growing evidence for the diagnostic accuracy of CTP, a robust cutoff value for hyperemic MBF that allows identification of hemodynamically relevant stenosis is lacking. In this study, the optimal cut-point for hyperemic MBF is 113 ml/100 mg per min. Previous work has reported an optimal threshold of hyperemic MBF in the range of 75 to 156 min/100 l/min (11). Several reasons can explain these disparities. First, different study populations were evaluated. Second, there is inconsistency in image acquisition due to different CT technologies and site-specific scanning protocols. Third, there is no consensus on the best approach for image analysis. More importantly, many reference standards have been used to validate this new technology, leading to discordant data. In several studies, angiographic lesion severity was used as a surrogate to identify myocardial ischemia (12). It is well known that the correlation between stenotic severity and myocardial ischemia is poor and that this discrepancy may be present in coronary stenosis beyond the intermediate range. In particular, the RIPCORD study showed that 13% of coronary stenoses with <30% reduction in diameter were associated with an FFR of <0.80 (13). In addition, hyperemic MBF derived from CT data is systematically lower than the known physiological range estimated by positron emission tomography, due mainly to different contrast kinetics and limited temporal sampling of CT (11). On the other hand, the optimal RFR cut point identified in this study was 0.75, which also corresponds to the invasive FFR value associated with the highest prognostic value (14).

INTEGRATION OF ANATOMY AND PHYSIOLOGY

Because a normal reference vessel is required for the calculation of RFR, the use of this parameter is limited only to patients with 1- or 2-vessel disease. In this regard, CT can offer a unique approach providing both the coronary anatomy and the coronary physiology in a "one-stop shopping" modality (15,16). Accordingly, in the current study the combination of RFR and coronary stenosis >50% has the highest diagnostic accuracy. A more comprehensive picture can be obtained adding details of plaque features and plaque burden, which have been shown to be related to myocardial ischemia through vascular inflammation, endothelial dysfunction. and altered shear stress (17,18).

We congratulate Yang et al. (8) because their work has further emphasized the potential of dynamic CTP imaging. Although several issues remain to be addressed, the comprehensive use of a CT-based protocol helps clarify the complex mechanisms underlying the pathophysiology of ischemic heart disease in an appropriate selection of patients who will benefit most from coronary revascularization.

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