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EDITORIAL

Imaging of coronary flow capacity: is there a role for dynamic CT perfusion imaging?

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The assessment of myocardial ischaemia in patients with coronary artery disease (CAD) being considered for myocardial revascularization procedures is of paramount importance. The detection of a large area of myocardial ischaemia by functional imaging is associated with impaired prognosis of patients and identifies patients who should undergo revascularization [1]. Non-invasive functional evaluation of myocardial ischaemia should be the first approach and can be achieved with a variety of techniques.

Nevertheless, invasive coronary pressure-derived fractional flow reserve (FFR) is the current standard of care for the functional assessment of angiographically intermediate-grade stenosis (typically around 40–90% stenosis) without evidence of ischaemia in non-invasive testing, or in those with multivessel disease.

In the FAME 2 trial, percutaneous coronary intervention (PCI), as compared to medical therapy, was associated with lower incidence of the primary composite endpoint of death, myocardial infarction, and urgent revascularization in patients with stable CAD and at least one stenosis with FFR ≤0.80 [2]. Recently, two large-scale randomized trials showed broadly comparable results between FFR-guided and the resting index instantaneous wave-free ratio (iwFR)-guided revascularization strategies in patients with intermediate-grade stenosis [3, 4].

Myocardial blood flow and coronary flow reserve (CFR, i.e. the ratio between hyperemic to rest flow) are the critical determinants of myocardial ischaemia. Invasive pressure-derived FFR, originally validated by comparison to stress positron emission tomography (PET), is the derivative approximation of the relative regional distribution of stress perfusion expressed as a fraction of maximum stress perfusion in ml/min/g [5].

Coronary flow capacity (CFC), originally developed using PET, integrates the simultaneous regional size severity of resting myocardial blood flow (MBF), hyperemic MBF, and CFR [6]. CFC maps provide specific patterns that are more accurate than CFR for distinguishing the effects of focal CAD, diffuse non-obstructive CAD and microvascular dysfunction by accounting for perfusion heterogeneity [7]. Severely reduced CFC, defined as the coexistence of stress MBF ≤0.91 ml/min/g and CFR ≤1.74, has been shown to predict a significant reduction in death or myocardial infarction after revascularization compared with medical treatment or less severe perfusion abnormalities [7].

In the current issue of the Journal, Bober et al. assessed the effects of coronary revascularization by percutaneous coronary intervention on stress MBF by PET [8]. Fifty patients, who underwent clinically indicated dipyridamole myocardial ^{82}Rb PET, were enrolled in the study after coronary revascularization. A follow-up dipyridamole myocardial ^{82}Rb PET was performed within 90 days from coronary revascularization. For image analysis the left ventricle was divided into four quadrants corresponding to the distribution of the coronary arteries: anterior, septal, lateral and inferior [9]. Each quadrant was visually inspected for the presence of baseline significant relative perfusion abnormality (PA) defined as ≥10% change in size and/or severity from the resting scan. In addition, rest and stress MBF, CFR and CFC were calculated for each quadrant. Four different

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patterns were reported according to the presence of PA and severe reduction in CFC: (1) normal (PA-/CFC-), (2) severely abnormal (PA+/CFC+), (3) flow capacity abnormal (PA-/CFC+), and (4) perfusion abnormal (PA+/CFC-).

The main findings of this study can be summarized as follows: (1) severely reduced CFC at baseline was found to be the only independent predictor of significant improvement of stress MBF after including baseline PA, stress MBF and CFR in the multivariable regression model. In particular, stress MBF improved by 59% when relative PA and reduced CFC were present at baseline and by 40% when baseline CFC only was reduced in the absence of a significant relative PA; (2) stress MBF did not change significantly after revascularization if baseline relative PA only was reduced and CFC was within normal limits, therefore underscoring the poor accuracy of relative PA as stand-alone perfusion metric for the identification of patients who may benefit from revascularization; (3) in a small subgroup of nine patients undergoing FFR-guided revascularization using an FFR threshold of <0.80, there was high discordance between FFR and CFC, as only one of the six quadrants with normal relative perfusion images and preserved CFC demonstrated improvement in stress MBF.

The authors should be congratulated on performing this elegant study which is the first to investigate the value of PET-derived CFC in predicting MBF response to coronary revascularization. Nevertheless, the decision to proceed to PCI was mainly based on angiographic evaluation of the severity of a coronary stenosis, and the study lacks clinical outcome data. Yet, the study findings support future prospective randomized clinical trials comparing PET-derived CFC-guided revascularization vs FFR or iw-FR guided revascularization in terms of clinical outcomes among patients with stable CAD and angiographically intermediate-grade stenosis.

Although CFC was first validated using PET technology [6] and invasive coronary flow measurements by Doppler wire [10], the concept of CFC can be applied to all imaging modalities which allow the absolute quantification of myocardial perfusion. In this perspective, dynamic myocardial computed tomography perfusion (CTP) imaging is a non-invasive imaging modality which provides absolute quantification of MBF. For quantitative CTP imaging, serial sampling is performed to evaluate the iodine distribution into the myocardium and into a reference artery at different time points enabling the construction of time-attenuation curves (TACs). Applying specific mathematical models to the TACs, perfusion parameters, such as MBF, can be calculated. The feasibility of dynamic CTP was initially demonstrated in few animal studies [11–13]. Although in experimentally controlled settings CT-derived MBF showed an excellent correlation with microspheres [11], invasive fractional flow reserve [12] and coronary blood flow [12], first pass extraction of iodinated contrast material is generally low, especially for high flow rates, mainly due to the limited temporal sampling, with consequent underestimation of MBF [14, 15]. Despite this limitation, dynamic CTP succeeded in demonstrating the well-known transmural blood flow gradient through the myocardium, showing lower endocardial values of CT-derived MBF in the ischaemic territories compared to the corresponding epicardial measurements [16]. In addition, Ho et al. showed that CT-derived stress MBF and CFR were higher in a low-risk population compared to patients with documented coronary artery disease [17] with a 1.5 difference between stress and rest MBF in normal myocardium [18]. Promising results on the ability of dynamic CTP in detecting myocardial ischaemia have been also shown in selected groups of symptomatic patients with suspected or known CAD with a pooled sensitivity and specificity on a vessel-based analysis of 85% and 81%, respectively [19].

Quantitative imaging has introduced new diagnostic opportunities, first of which is evaluation of the status of the microcirculation. Specifically, a significant reduction of stress MBF associated with the absence of obstructive coronary artery disease is likely indicative of microvascular dysfunction. As such, a CT-based approach can offer both the anatomical information regarding the coronary tree and the functional information on myocardial perfusion as a "one-stop-shop" modality. In this context, recent studies have shown that the entire coronary tree can be extracted directly from the CTP dataset, preserving the imaging quality and the diagnostic accuracy in the detection of coronary plaques [20, 21].

When speaking about dynamic CTP one of the main concerns remains the higher radiation dose compared to nuclear medicine modalities [22, 23]. On average the mean effective dose reported for a single dynamic CTP scan was 9 mSv [22]. Nevertheless, implementations of radiation dose reduction techniques, such as the use of low-tube-voltage settings [24] or the reduced number of scan acquisition for TACs construction [21], were able to reduce the radiation dose up to 40%.

The manuscript by Bober et al. has further emphasized the need for a functional assessment of patients with stable coronary artery disease before coronary revascularization. In this context, despite the fact that dynamic CTP is still in its infancy and efforts have to be made to standardize scan acquisition and image analysis, it has the potential to enter into the clinical arena next to the well established functional imaging modalities.

Compliance with ethical standards Dr. A. Rossi and Dr. G. Ferrante declare they have no conflicts of interest.

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