Editorial

Myocardial CT perfusion for the prediction of obstructive coronary artery disease, valuable or not?

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Abstract: Adenosine stress myocardial computed tomography perfusion (CTP) is a relatively new myocardial perfusion imaging technique. Together with coronary CT angiography (CTA) it provides anatomic and functional information of coronary artery disease (CAD). In previous studies, the combination of these techniques demonstrated to be valuable for identifying hemodynamically significant stenoses. George *et al*., performed a secondary analysis on the CORE320 study and compared the diagnostic performance of CTP to single positron emission computed tomography (SPECT) myocardial perfusion imaging (MPI) to diagnose obstructive CAD (defined as ≥50% luminal stenosis). In this editorial the results and limitations of the study are discussed, as well as opportunities that this new perfusion technique brings with it.

Keywords: Coronary artery disease; myocardial CT perfusion; imaging; ischemia

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This editorial refers to "Myocardial CT Perfusion Imaging and SPECT for the Diagnosis of Coronary Artery Disease: A Head-to-Head Comparison from the CORE320 Multicenter Diagnostic Performance Study" by George *et al*. published in *Radiology* (1).

The diagnosis and assessment of coronary artery disease (CAD) consists of clinical evaluation, identifying risk factors for CAD and the use of specific cardiac investigations as myocardial stress testing or imaging of the coronary arteries. Non-invasive cardiac investigations can provide diagnostic and prognostic information in patients with suspicion of CAD. To select the optimal test, the pre-test probability of CAD should be assessed for each patient, as determined in the guidelines (2). Coronary computed tomography angiography (CTA) is a valuable diagnostic tool to rule out CAD in patients with low-intermediate probability. Due to its relatively low diagnostic accuracy to identify hemodynamically significant CAD, coronary CTA is not indicated in patients with intermediate to high probability of CAD (3). In these patients, the documentation of myocardial ischemia by using non-invasive stress testing is recommended before performing invasive coronary angiography (ICA) eventually followed by percutaneous revascularization (2).

A relatively new myocardial perfusion imaging (MPI) technique is adenosine stress myocardial CT perfusion (CTP). Together with coronary CTA, anatomical and functional information of CAD is provided. Since 2005, several clinical studies have established the value of myocardial CT perfusion compared to reference standards as single photon emission computed tomography myocardial perfusion imaging (SPECT) MPI, ICA [with or without Fractional Flow Reserve (FFR)] and magnetic resonance (MR) (4-7). CTP demonstrated a higher diagnostic accuracy for myocardial ischemia than coronary CTA (7). Furthermore, the combination of myocardial ischemia on CTP in addition to obstructive CAD on coronary CTA (≥50% luminal stenosis) appears of great value for the prediction of myocardial ischemia (6,7).

Recently, this was confirmed by a large multicenter trial: the CORE320 study (8). Sixteen centers enrolled 381 patients with suspected or known CAD. All patients underwent SPECT MPI, coronary CTA and CTP prior

to ICA. The aim of the study was to determine the diagnostic accuracy of coronary CTA combined with CTP to predict hemodynamically significant CAD. Patients were classified as having hemodynamically significant CAD if ≥50% luminal stenosis by ICA and an accompanying perfusion defect by SPECT MPI was noticed. Patients with either <50% stenosis on ICA or normal SPECT MPI were classified as normal. Analysis was based on the area under the receiver operating characteristics curve (Az). The Az for combined coronary CTA and CTP to predict hemodynamically significant CAD was 0.87 [95% confidence interval (CI): 0.84-0.91]. Coronary CTA alone (without CTP) predicted hemodynamically significant CAD with an Az of 0.84 (95% CI: 0.79-0.88). Until present, the CORE320 study is the largest study demonstrating the additional value of CTP on coronary CTA in predicting the presence of hemodynamically significant CAD.

George *et al*. performed a secondary analysis on the CORE320 study (1). The primary aim of this sub-study was to compare the diagnostic performance of CTP to SPECT MPI to diagnose obstructive CAD. In this study, obstructive CAD was defined by quantitative ICA (QCA) as ≥50% luminal stenosis which correlates to ≥70% stenosis on visual assessment (9). CTP was classified as positive based on a summed stress score (SSS) >2 for CTP and ≥1 for SPECT MPI on a 13-segment myocardial model. In total, 229 of the 381 (60%) patients had obstructive CAD on QCA. In the patient-based analysis the Az for CTP to diagnose obstructive CAD by ICA was 0.78 (95% CI: 0.74-0.82). The Az of SPECT MPI was 0.69 (95% CI: 0.64-0.74), which was significantly less compared with CTP (P=0.001). Of the 229 patients with obstructive CAD, CTP identified 202 patients [sensitivity: 88% (95% CI: 83-92)] and SPECT MPI 143 patients [sensitivity: 62% (95% CI: 56-69)], which is significantly better (P<0.001). However, the specificity of CTP [55% (95% CI: 46-63)] was significantly lower compared with SPECT MPI [67% (95% CI: 59-75)] (P=0.02). In a vessel-based analysis, the prevalence of left main disease was 3.1%, three-vessel disease 17.3%, two-vessel disease 19.7% and single-vessel disease 19.9%. In all categories, the sensitivity for CTP was significantly higher. It is generally known that, especially for patients with three-vessel and left main disease the diagnostic accuracy of SPECT MPI is limited (10,11).

In this comparison, George *et al*. demonstrate the higher diagnostic accuracy of CTP compared with SPECT MPI in predicting obstructive CAD on QCA. However, this endpoint has a strong limitation. The authors directly link the presence of ≥50% stenosis on QCA to presence of myocardial ischemia. This assumption is based on two trials determining myocardial blood flow with positron emission tomography (PET) scans in relation to stenosis severity (12,13). In these studies, myocardial blood flow was assessed at rest and during hyperemia and stenosis severity was assessed by QCA. Uren *et al*. demonstrated a progressively decrease of myocardial blood flow during hyperemia in stenoses >40% and no change in basal flow regarding the severity of stenosis (12). However, they report a poor correlation of stenosis severity to coronary flow reserve and subsequently myocardial blood flow. Specifically, they underscore a widely variation in coronary flow reserve in relation to severity of the coronary diameter reduction alone. For instance, 38% of patients with stenosis >50% had only a slight decrease or even normal estimated coronary flow reserve. They suggest this poor correlation to be due to the use of normal arterial segment as a reference. For example, diffuse CAD underestimates the true normal lumen diameter and therefore a valid calculation of percentage stenosis will not be possible. More recently, this poor correlation has been reassessed in a sub-study of the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) trial (14). The study analyzed the relationship between angiographic stenosis severity and hemodynamic significance as measured by FFR in 1,005 patients with multi-vessel CAD. Patients were randomly assigned to angiography-guided PCI or FFR-guided PCI. In the angiography-guided group, all lesions with a diameter stenosis of ≥50% were stented. In the FFR-guided PCI group, patients only underwent PCI in case of FFR ≤0.8. In stenoses categorized as 50-70% by visual assessment, the FFR was >0.8 in 65% of the cases. In stenoses of 71-90%, the FFR was >0.8 in 20% of the cases. In stenoses of 91-99% the FFR was >0.8 in only 4% of the cases.

With regards to the above, the clinical relevance of the diagnostic accuracy of CTP for predicting ≥50% stenosis on QCA, is uncertain. The use of obstructive CAD as reference standard could result in overestimation of hemodynamically significant lesions. Furthermore, patients with a normal CTP and obstructive CAD on QCA are classified as false negative in this study. However, it is possible that these patients had no myocardial ischemia despite obstructive CAD on QCA. Performing FFR would have clarified the discrepancy. This is overcome in the CORE320 trial by performing SPECT MPI as a mean to confirm myocardial ischemia alongside ≥50% stenosis on QCA. In the sub-study by George *et al*. SPECT MPI is used in the comparison and not as an endpoint.

Visual assessment of CTP images is the most common approach of assessment of myocardial perfusion. Myocardial

areas with reduced perfusion appear hypo-enhanced compared with normal myocardium and imply ischemia or infarction. However, the contrast resolution of myocardium in CTP is poor (15). The maximum difference between normal and hypo-enhanced myocardium is approximately 50 Hounsfield Units (HU) and occurs in the upslope of arterial contrast bolus peak. The difference in myocardial enhancement quickly disappears in the downslope of the contrast bolus (16). Therefore, optimal contrast timing is required. The short time interval of maximum attenuation difference between normal and ischemic myocardium, and patient-related contrast timing deviations make the protocol prone to myocardial contrast enhancement artefacts. Furthermore, artefacts caused by motion, beam hardening or cone beam can deteriorate the interpretability. Due to these factors the interpretation of CTP requires much experience and is often difficult. For many years SPECT MPI is an established standard for the detection of myocardial ischemia. High inter-observer and intra-observer variability in single testing and high reproducibility in sequential testing have been demonstrated (17,18). To the best of our knowledge this reliability has not been determined yet in CTP.

Another confounder in relation to myocardial ischemia and significant CAD is microvascular disease. The principle of SPECT MPI and CTP is based on myocardial blood flow and myocardial ischemia is detected by relative myocardial perfusion defects. However, perfusion defects do not necessarily need to be caused by hemodynamically significant CAD, as is the case in microvascular disease. As mentioned by George *et al.*, another factor is coronary collateral circulation that will give extra myocardial perfusion downstream the area of a significant stenosis. This will also result in a false negative MPI by SPECT or CTP.

A limitation of all studies that determine the diagnostic accuracy of CTP (with or without coronary CTA) compared to their reference standards is the high prevalence of CAD in the study populations. It is well known that the positive (PPV) and the negative predicting value (NPV) strongly depend on disease prevalence. Sensitivity and specificity are often regarded as constant benchmarks of test performance which assumes comparing with alternative tests, or the same test in different populations, to be possible. However, test validity measurements (sensitivity, specificity and likelihood ratio) are exclusively independent of disease prevalence in truly binary diagnosis parameters, which is extremely rare for a diagnosis (19). For instance, the diagnosis of myocardial ischemia in the CORE 320 trial consists of a continuum of SSS for SPECT MPI and CTP and therefore cannot be seen as a true dichotomous outcome parameter. The patient population included for the CORE320 was already clinically referred for ICA. This population had a very high cardiovascular burden; 30% previous PCI, 34% diabetes and a mean coronary calcium score of 423 HU. Subsequently 60% met the reference standard (≥50% stenosis). As mentioned before, CTP had a high sensitivity (88%) and a relatively low specificity (55%). A high prevalence of disease is in favor of positive predicting value (20). Despite this specificity, the PPV of CTP is preserved, possibly due to the high disease prevalence. Hence, likely with a lower prevalence of CAD, the PPV of CTP would be worse.

In conclusion, CTP is a promising technique that has already proven additional value alongside coronary CTA. The two techniques provide anatomic and functional information in one session. Although CTP can be performed without or before coronary CTA, the prevailing regime is first to perform coronary CTA and only CTP in case of potentially obstructive CAD. This protocol takes advantage of the high sensitivity and NPV of coronary CTA and avoids additional radiation in normal or mildly abnormal coronary CTA. Currently, the diagnostic accuracy of coronary CTA and CTP has, to our knowledge, only been determined in populations with high cardiovascular burden (5-8,21,22). All patients included in these studies had known CAD, intermediate to high pre-test probability or were already referred for ICA. That subsequently resulted in analyses in populations where at least 35% was classified as positive according to the defined criteria. As mentioned earlier, the diagnostic accuracy of a test is strongly dependent of prevalence of the disease and therefore future studies must determine the value of the combination of coronary CTA and CTP in patients with low to intermediate probability of CAD.

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