Seminars in NUCLEAR MEDICINE

Noninvasive Imaging in Coronary Artery Disease

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Noninvasive cardiac imaging is widely used to evaluate the presence of coronary artery disease. Recently, with improvements in imaging technology, noninvasive imaging has also been used for evaluation of the presence, severity, and prognosis of coronary artery disease. Coronary CT angiography and MRI of coronary arteries provide an anatomical assessment of coronary stenosis, whereas the hemodynamic significance of a coronary artery stenosis can be assessed by stress myocardial perfusion imaging, such as SPECT/PET and stress MRI. For appropriate use of multiple imaging modalities, the strengths and limitations of each modality are discussed in this review.
Semin Nucl Med 44:398-409

Introduction

Coronary artery disease (CAD) is one of the leading causes of death, and the prevalence has increased worldwide.[1-3] To diagnose and define the severity of CAD, various imaging modalities have been introduced. For choosing the appropriate test, we review the strengths and limitations of each modality. Available modalities include the following: coronary CT angiography (CCTA), CT perfusion (CTP), computed fractional flow reserve (FFR) derived from CT (FFR_{CT}), nuclear myocardial perfusion imaging (MPI) (SPECT/PET), and cardiac MRI (CMR).

Coronary CT Angiography

As coronary revascularization is the main approach to treat CAD, CAD imaging has often been driven by the evaluation of anatomical stenosis severity. For this anatomical approach toward CAD, CCTA has gained its value with a rich evidence base that supports its clinical utility. In 3 prospective multicenter studies, the diagnostic performance of a 64-slice CCTA was reported in various populations.[4-6] The assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography (ACCURACY) trial was a 16–U.S. center study in patients without known CAD. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CCTA to detect ≥70% stenosis were 94%, 83%, 48%, and 99%, respectively.[4] The coronary artery evaluation using a 64-row multidetector CT angiography (CORE64) study followed the ACCURACY trial as another multicenter study that was conducted in 291 patients both with and without known CAD who had baseline coronary artery calcium score less than 600 Agatston units. In this study, the per-patient sensitivity, specificity, PPV, and NPV for detecting ≥50% stenosis were 85%, 90%, 91%, and 83%, respectively. Furthermore, evaluation of stenosis using CCTA demonstrated that an area under the curve (AUC) was 0.91 for high-grade anatomical stenosis for invasive coronary angiography (ICA)–confirmed CAD, and it was similar to that demonstrated by ICA for the prediction of subsequent coronary artery revascularization.[5] In a third multicenter trial with 360 patients without known CAD presenting with both acute and stable chest pain, the CAD prevalence (≥50% stenosis) was high (68%), and diagnostic performance of CCTA was maintained, demonstrating a per-patient sensitivity, specificity, PPV, and NPV of 99%, 64%, 86%, and 97%, respectively.[6] The NPV for CCTA has generally been high (eg, 95%-100% in the 2 multicenter studies that constrained enrollment to those individuals without known CAD).[4,6,7] Based on these results, CCTA is now generally considered as a valuable tool for the exclusion of significant CAD.[8,9]

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This study was funded by grants from the National Institutes of Health, USA (R01HL115150 and R01HL118019), as well as generous gifts from the Dalio Foundation and the Michael J. Wolk Foundation.
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 http://dx.doi.org/10.1053/j.semnuclmed.2014.05.004
0001-2998/

In addition to coronary stenosis severity, CCTA enables the study of other important atherosclerotic plaque characteristics with generally high accuracy. As an example, CCTA offers the diagnostic ability to assess measures of arterial remodeling, plaque composition, presence of intraplaque calcification, and aggregate plaque volume. Of these, positive arterial remodeling, low attenuation plaque, and spotty intraplaque calcification have shown a relation to both presently occurring and future acute coronary syndrome.[10-14] Plaque volume on CCTA determined by manual methods demonstrates a high correlation and a modest agreement with that determined by intravascular ultrasound.[12,15,16]

CCTA findings of CAD also inform measures of risk stratification in both asymptomatic and symptomatic individuals. In a meta-analysis evaluating 9592 patients, CCTA demonstrated a graded increase in adverse events following CCTA performance for no CAD, nonobstructive CAD, and obstructive CAD (any vessel with greater than 50% luminal stenosis).[17] Particularly for individuals without known CAD, the pooled annualized event rate was low compared with that of obstructive CAD (0.17% vs 8.8%).[17] CCTA also demonstrated a good prognostic value in various groups, such as young patients with a family history of CAD[18] and ethnic groups.[19] Combining CAD data with measures of left ventricular (LV) function provides incremental prognostic utility, with LV ejection fractions less than 50%, conferring a worsened prognosis. Perhaps most importantly, a normal finding on CCTA was associated with a very low annual mortality rate of 0.13%.[20]

Current-generation CCTA is nevertheless not without limitations. Although anatomical assessment by CCTA is diagnostically sound with a robust ability to predict prognosis,[11,14,20,21] CCTA measurements of stenoses do not accurately predict their functional significance.[22] Furthermore, usage of iodinated contrast material and exposure to radiation are also important considerations. Pertaining to the latter, numerous radiation dose–reduction methods have been introduced and now enable CCTA performance at levels similar to that of background radiation exposure from radon.

The near-term future of CCTA holds promise for better detection of coronary artery lesions. One such effort to overcome certain limitations of current-generation CCTA is in dual-energy CT, which exhibits improved image quality by a reduction in noise without additional radiation dose than that with single-energy CT.[23] When compared with ICA images, dual-energy CT showed 90% sensitivity, 94% specificity, and 93% accuracy for the detection of greater than 50% luminal stenosis.[24] Certain CT acquisition systems also demonstrate increased temporal resolution than single-energy CT does,[25] an attribute that obviates the need for heart rate control in all individuals and may improve the ability of CT to evaluate the severity of lesion stenosis, particularly in patients who do not achieve adequate heart rate control during the examination.

Cardiac CTP

Recent advances in technology allow for assessment of myocardial perfusion by CT. Multidetector CT systems can image in a dynamic mode, in which sequential images are obtained over a period to record the kinetics of iodinated contrast in the arterial blood pool and the myocardium.[26] George et al,[26] using a 64-detector CT in a canine ischemia model, performed CTP during adenosine infusion. They found strong correlations between the ratio of myocardial to LV upslope and microsphere-derived myocardial blood flow (MBF). The authors replicated the study in humans with adenosine stress 64- and 256-row detector CCTA and CTP (Fig. 1). In the human study, they calculated transmural perfusion ratio (subendocardial attenuation-subepicardial attenuation), which had a significant inverse linear correlation ($r = -0.63$, $P = 0.001$) with percentage diameter stenosis on quantitative ICA. Furthermore, the combination of CTP and CCTA was 86% sensitive and 92% specific for identifying patients with atherosclerosis causing perfusion abnormalities when compared with that of the combination of ICA and SPECT-MPI as the gold standard.[27] In a prospective multicenter international trial, the combined coronary atherosclerosis and myocardial perfusion evaluation using 320-detector row CT (CORE320) trial evaluated CT for the identification of CAD ($\geq$50% luminal stenosis) and corresponding myocardial perfusion defect in patients with suspected CAD. This method demonstrated a utility of CTP in patients with chest pain, as CCTA with concomitant CTP was as effective as sequential SPECT-MPI and invasive angiography for identifying flow-limiting atherosclerotic lesions.[28] In 381 patients from 16 centers, the patient-based diagnostic accuracy defined by AUC of integrated CTA-CTP for detecting or excluding flow-limiting CAD was 0.87 (95% CI: 0.84-0.91). It showed better accuracy in patients without prior myocardial infarction (MI) (AUC = 0.90) and without prior CAD (AUC = 0.93).[29]

Given the nascent stage for CTP, data regarding the prognostic utility of CTP deficits remain unknown and require evaluation in prospective multicenter efforts. Furthermore, the cost and the clinical effectiveness need to be examined, with a particular focus on safety because of additional ionizing radiation exposure. Continuing development of CT technology may ameliorate some of these concerns, with new acquisition protocols such as using prospective electrocardiogram-gated scans.[30]

Fractional Flow Reserve Derived From CT (FFR_{CT})

At present, the "gold"-standard assessment of the hemodynamic significance of coronary stenosis is FFR.[31] Recent advances in computational fluid dynamics now enable the calculation of coronary flow and pressure fields from anatomical image data (Fig. 2).[32] Applied to CT, these technologies enable calculation of FFR, which is defined as the ratio of maximal MBF through a diseased artery to the blood flow in the hypothetical case in which the artery was normal. Several studies have demonstrated an incremental value of FFR_{CT} for the diagnosis of hemodynamically significant CAD. In the diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve (DISCOVER-FLOW) trial, when