Perspectives of new imaging techniques for patients with known or suspected coronary artery disease

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Abstract

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality in western society. Over recent decades, major advances have been made in non invasive imaging techniques, resulting in an enormous growth in their role in the clinical assessment of patients with known and suspected CAD. Indeed, although invasive coronary angiography remains the current gold standard in the diagnosis of CAD, first-line non invasive assessment with functional techniques has become essential, particularly in patients at intermediate risk for CAD, to select those patients needing further invasive evaluation and intervention. For this purpose, nuclear imaging has since long been available, while more recently functional imaging can also be performed with stress-echocardiography (with contrast) and magnetic resonance imaging (MRI). Importantly, these techniques visualize the consequences of obstructive CAD, namely ischemia, rather than the coronary arteries directly, and the presence of atherosclerosis that is not flow limiting cannot be evaluated. For the latter purpose, non invasive coronary angiography with MRI and computed tomography techniques is under extensive investigation. The purpose of this review is to provide an overview of the non invasive imaging techniques currently available in the evaluation of CAD.
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Functional imaging

The rationale underlying functional imaging is the detection of perfusion or wall motion abnormalities that occur under stress-induced conditions in patients who have physiologically relevant coronary artery lesions. Stress can be achieved using physical exercise or pharmacological stress.

Nuclear imaging: gated-single photon emission computed tomography

Myocardial perfusion imaging with single photon emission computed tomography (SPECT) (*Figure 1*) is the most commonly used and well documented technique in the assessment of patients with suspected or known coronary artery disease (CAD). The average sensitivity and specificity to detect significant CAD based on a pooled analysis of 79 studies in 8964 patients were found to be 86% and 74%, respectively [1]. Since the introduction of this technique in the early 1970s, the quality and accuracy of its images have improved substantially as a result of technical developments. In addition, the more recently introduced technetium tracers have enabled acquisition gated to the electrocardiogram, which has allowed simultaneous evaluation of ventricular function.

Direct comparisons between gated SPECT and magnetic resonance imaging (MRI) have shown excellent correlations for the evaluation of both global and

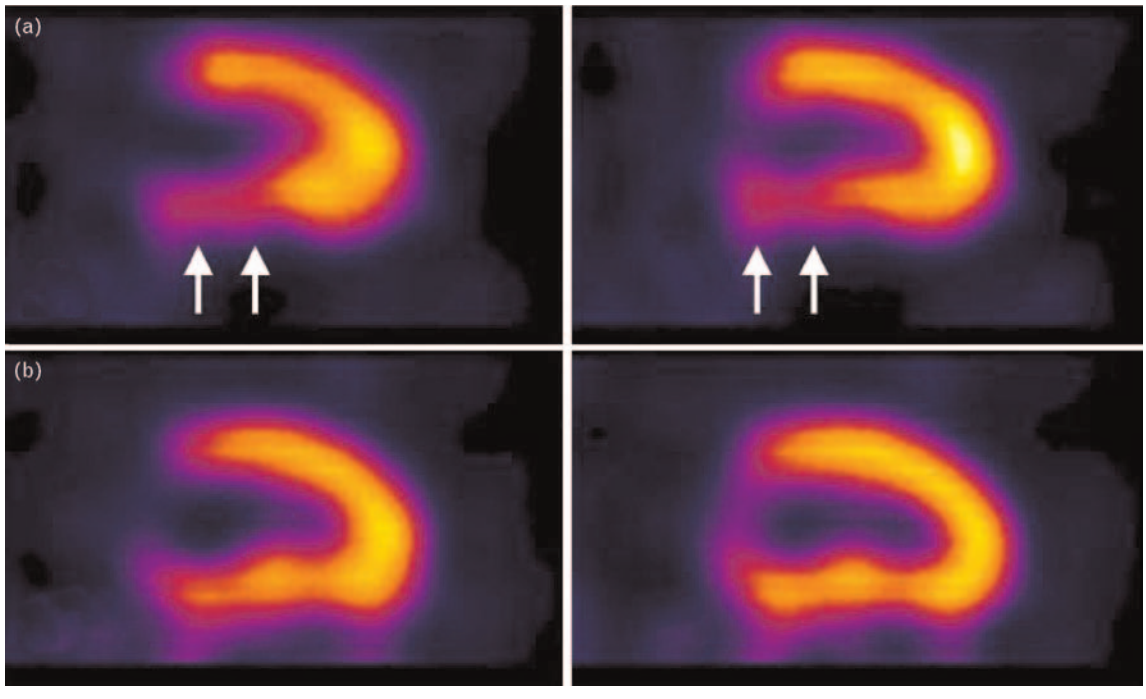

Figure 1. Example of functional imaging by means of gated single photon emission computed tomography. Vertical long-axis reconstructions during (a) adenosine stress and (b) rest. A reversible defect (white arrows) can be observed in the basal inferior wall, indicating the presence of ischemia.

regional left ventricular function [2,3]. Also, through identification of normal wall motion in segments with attenuation artifacts, a substantial reduction in the number of false-positive test results can be obtained, as demonstrated by Smanio and colleagues [4]. Limitations of SPECT include the relatively long imaging procedures, and the fact that it measures relative perfusion, as a result of which high-risk patients with balanced reduced perfusion can be missed. In addition, no information regarding early atherosclerotic disease can be obtained.

Echocardiography

In addition to SPECT, echocardiography is widely used to assess patients with suspected or known CAD, as it provides a comprehensive assessment of cardiac structure and function, while being completely non invasive and associated with little patient discomfort.

To date, studies comparing this technique and invasive coronary angiography have shown average weighted sensitivities and specificities, respectively, of 84% and 82% for exercise echocardiography (15 studies, $n = 1849$ patients) and 80% and 84% for dobutamine (28 studies, $n = 2246$ patients) [5].

Known disadvantages of echocardiography include the limited value in detecting single-vessel disease and, in contrast to SPECT, a lack of quantitative reporting algorithms. In addition, the technique is highly dependent on the expertise of both the operator and the interpreting cardiologist. Finally, difficulties are encountered in patients who are obese or have chronic obstructive pulmonary disease, because of the lack of an acoustic window.

With the aim of improving border delineation, ultrasound contrast agents are currently under investigation. In addition to improved image quality, administration of contrast offers another advantage, namely assessment of perfusion in addition to ventricular wall contractility [6]. Pooled analyses of the available preliminary studies suggest improved sensitivity (on average 89%) at the cost of reduced specificity (63%) [7]. To some extent, however, this reduced specificity may be attributable to the fact that experience is still limited, in addition to a current lack of image standardization.

Magnetic resonance imaging

Myocardial perfusion can also be evaluated with MRI. For this purpose, short-axis slices are acquired during the first pass of contrast agent in both resting and stress conditions. Relative perfusion defects are subsequently recognized as regions with little or reduced contrast agent. A pooled analysis of 17 studies of perfusion MRI, including 502 patients, revealed a weighted mean sensitivity of 84% and a specificity of 85% to detect obstructive CAD [7]. A particular advantage of the technique is the high spatial resolution, which allows distinction between subendocardial and transmural perfusion defects. In addition, wall motion can be assessed accurately; MRI is even

considered as the gold standard for the evaluation of left ventricular volumes and ejection fraction.

Using inducible wall motion abnormalities during dobutamine infusion as the hallmark for obstructive CAD, MRI was found to have average weighted sensitivity and specificity of 89% and 84%, respectively, on the basis of 10 studies obtained in 654 patients [7]. The excellent contrast and resolution are particularly beneficial for patients with poor echocardiographic windows. Unfortunately, although the technique provides safe and reliable evaluation of CAD, it is still time-consuming, and limited to highly specialized centers.

Anatomical imaging

Functional imaging provides safe and accurate assessment of the presence of clinically relevant CAD, but atherosclerosis in the absence of flow-limiting lesions can not be evaluated. Accordingly, extensive research is being undertaken with the aim of developing non invasive methods of visualization of atherosclerosis. Initially, only assessment of coronary calcifications, which can serve as a marker for the presence and extent of the atherosclerotic burden, was possible. However, it is important to realize that no direct relationship exists between the extent of calcium and the severity of stenosis, and extensive coronary calcifications can be observed in the absence of obstructive CAD [8]. As a result, the technique, although sensitive, lacks specificity and appears to be more suited for risk stratification than for detection of obstructive CAD [9].

More recently, direct non invasive coronary angiography has become possible by means of MRI, electron beam computed tomography and multislice computed tomography (MSCT). Of these techniques, MSCT appears at present to be the most robust for non invasive coronary angiography.

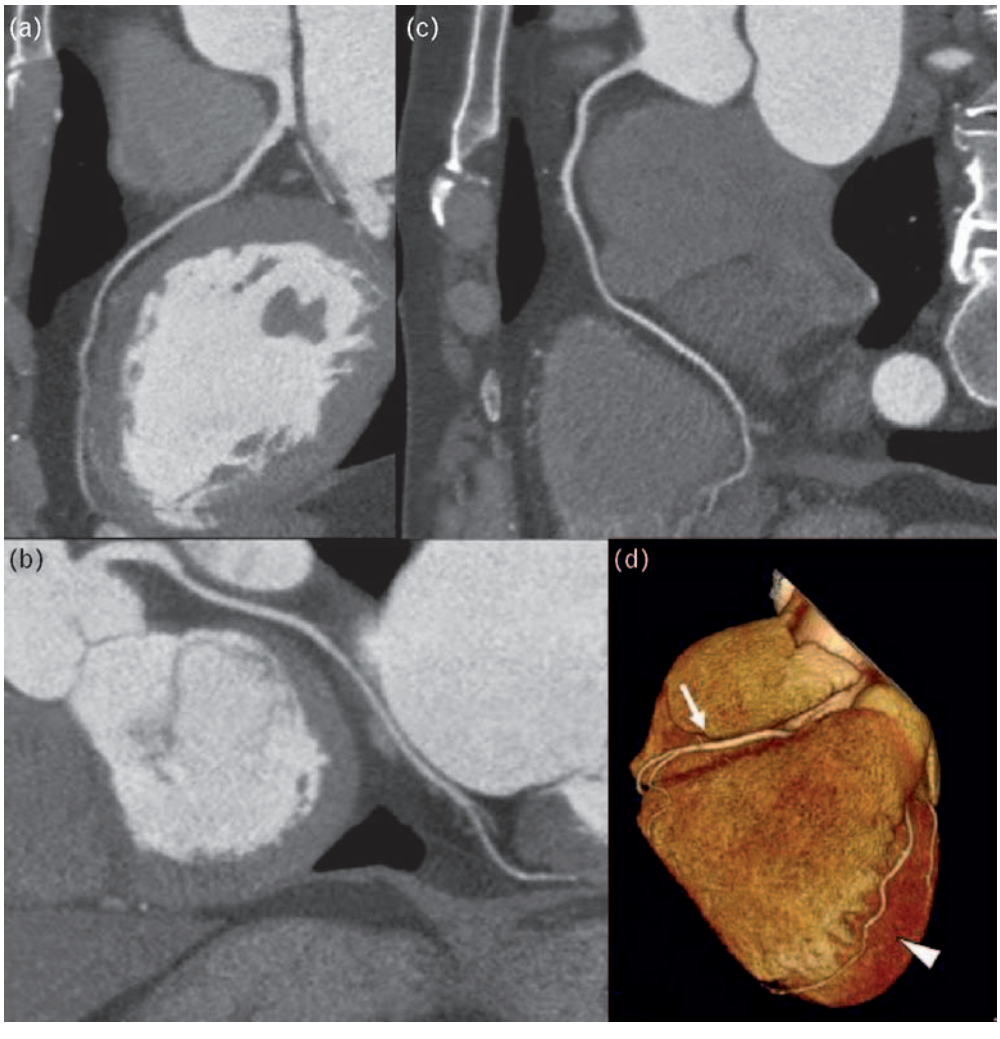

Figure 2. Example of non invasive coronary angiography using 64-slice multislice computed tomography. Curved multiplanar reconstructions of (a) the left anterior descending coronary artery, (b) the right coronary artery, and (c) the left circumflex coronary artery. (d) 3-Dimensional volume-rendered reconstruction showing patency of the right coronary artery (white arrow) and left anterior descending coronary artery (white arrowhead). No significant lesions were demonstrated.

Multislice computed tomography

Since the introduction, in 1998, of multislice scanning using four detector rows, the technique has undergone an extremely rapid development. Currently, 64-slice scanners are commercially available, allowing the acquisition of a 4-dimensional data set in a breath-hold of less than 10 s duration. To date, 11 studies of 64-slice MSCT, in 663 patients, have been published, revealing average weighted sensitivity and specificity of 91% and 96%, respectively [10–12]. Importantly, the negative predictive value was consistently high, ranging from 92% to 100%, indicating that a normal MSCT is associated with an extremely low likelihood of CAD. Accordingly, the technique may be most valuable to rule out CAD. An example of a normal MSCT coronary angiogram is provided in *Figure 2*.

Another advantage of MSCT is the fact that, in contrast to functional imaging, it is unlikely to miss severe, high-risk CAD, such as left main disease or three-vessel disease. However, borderline stenoses pose significant problems, as the precise degree of coronary stenosis can currently not be reliably determined with MSCT. Management of these lesions is further hampered by the fact that no information on ischemia can be obtained [13]. Other limitations include the dose of radiation, the need for iodinated contrast, and a limited value in patients with irregular heart rates.

Integration of functional and anatomical imaging

During recent decades, the role of non invasive imaging has increased enormously. Initially, first-line evaluation of CAD was performed by means of functional imaging techniques, and the presence or absence of ischemia served as gatekeeper for invasive coronary angiography. Whereas the initial functional techniques relied on either inducible perfusion or wall motion abnormalities, continuous development of the technology has enabled more comprehensive evaluation. Both nuclear imaging and echocardiography currently allow simultaneous assessment of both perfusion and function, thus enhancing their diagnostic accuracy. Similarly, MRI allows integrated assessment of both function and perfusion in a single examination.

The recent introduction of non invasive atherosclerosis imaging techniques has generated considerable interest in visualization of preclinical atherosclerosis, which could be used for more individualized identification of patients who may benefit from further testing and treatment. Although these techniques allow accurate exclusion of CAD, the precise meaning of a positive examination is currently unclear, as the presence of ischemia cannot be determined. Indeed, preliminary studies suggest a large discrepancy between stenotic lesions on MSCT and

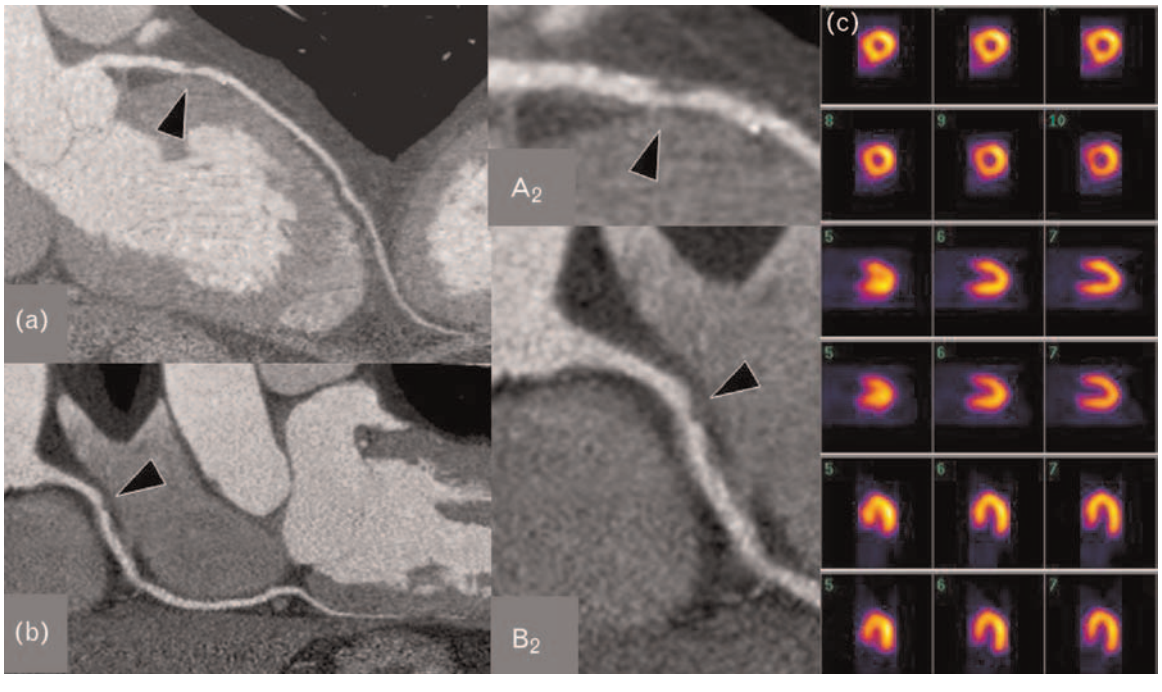

Figure 3. Non invasive imaging in a 55-year-old man with suspected coronary artery disease. Multislice computed tomography coronary angiography showed borderline stenoses in both (a) the left anterior descending coronary artery and (b) the right coronary artery. (c, d) Enlargements of the lesions indicated by the black arrowheads in (a) and (b), respectively. The patient was referred for functional imaging to determine the hemodynamic relevance of the detected lesions. (e) Results of gated single photon emission computed tomography perfusion imaging, indicating normal myocardial perfusion.

perfusion abnormalities on SPECT, with only 50% of lesions actually resulting in ischemia [13,14].

The current expectation is thus that integrated use of both anatomical and functional modalities may be most beneficial in the evaluation of CAD, and for this purpose hybrid or dual modality imaging techniques are currently being investigated. In addition, advanced software programs that allow retrospective fusing of images from different modalities are under development. However, from a practical point of view, sequential imaging may be preferred and cost-effective. A potential strategy in these patients may be first to evaluate the presence of atherosclerosis by means of coronary calcium scoring or non invasive coronary angiography. If no coronary atherosclerosis is demonstrated, the patient may be discharged from further investigation; in contrast, if atherosclerosis is observed, additional functional evaluation is needed to assess the presence and extent of myocardial ischemia (*Figure 3*). Subsequently, the decision between invasive angiography (and possibly intervention) and medical therapy in combination with aggressive risk-profile modification may be based on the further evaluations. Accordingly, the combination of both anatomical and functional information may allow superior evaluation of CAD, resulting in more individualized management and potentially improved outcome. However, it is important to realize that data supporting such algorithms are currently lacking, and large studies addressing the accuracy, safety, and cost-effectiveness of integrated imaging strategies are required. ■

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