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Review Article

Non-invasive imaging modalities for the diagnosis of coronary artery disease: The present and the future

Wen-Chun Lan [a,b], Yu-Hung Chen [c,*], Shu-Hsin Liu [c,d]

[a] Department of Pharmacy, Mennonite Christian Hospital, Hualien, Taiwan
[b] Department of Nuclear Medicine, Mennonite Christian Hospital, Hualien, Taiwan
[c] Department of Nuclear Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[d] School of Medicine, Tzu Chi University, Hualien, Taiwan

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ABSTRACT

The prevalence and economic burden of coronary artery disease are high. New noninvasive diagnostic imaging methods have evolved in recent decades, including coronary computed tomography angiography and cardiac magnetic resonance angiography. Investigations into functional ischemic parameters have also been added to anatomical imaging to improve diagnostic performance, including the fractional flow reserve calculated from contrast computed tomography, perfusion computed tomography, perfusion cardiac magnetic resonance imaging, a combination of coronary computed tomography angiography with myocardial perfusion scintigraphy and the myocardial flow reserve calculated from perfusion positron emission tomography. In this article, we will discuss progress in noninvasive imaging modalities for the diagnosis of coronary artery disease and trends for the future.

1. Introduction

Despite advances in diagnosis, prevention and treatment, coronary artery disease (CAD) is still a prevalent disease worldwide. Data from the National Health and Nutrition Examination Survey 2007–2010 showed that an estimated 15.4 million Americans ≥20 years of age have CAD [1]. CAD causes a large economic burden, which is growing with its increasing prevalence.

The traditional noninvasive imaging modality for CAD is myocardial perfusion scintigraphy (MPS), which can assess physiological evidence of significant coronary artery stenosis. Emerging noninvasive modalities include coronary computed tomography angiography (CCTA) and cardiac magnetic resonance imaging (CMRI) angiography, which provide anatomical evidence of CAD. However, the anatomical information lacks hemodynamic information for CAD and the literature has demonstrated that anatomical lesions do not correlate with the ischemic indicator, the fractional flow reserve (FFR) [2]. During the past few years, the trend has changed to incorporate anatomical images with functional parameters to make up for the disadvantages of anatomical imaging modalities. In this review, we discuss the recent evolution of noninvasive imaging modalities for the diagnosis of CAD, and also the recent usage of positron emission tomography (PET) in CAD.

The traditional noninvasive imaging approach to detecting CAD is radionuclide myocardial perfusion imaging (Fig. 1). This tool provides pathophysiological evidence of CAD. However, sometimes there are nondiagnostic or conflicting situations that require coronary angiography (CA) for anatomical assessment. Unfortunately, CA is invasive and expensive, and may result in severe complications such as coronary artery dissection. Thus, noninvasive anatomical imaging modalities were developed. CMRI angiography was first described by Manning et al in 1993 and CCTA was first described by Moshage et al in 1995 [3,4].

2. Diagnostic performance of CCTA and CMRI angiography

CCTA demonstrates excellent coronary artery anatomy (Fig. 2) and many single-center trials have investigated its diagnostic performance. In a systemic review of 23 studies with a total of 2045 patients with suspected or known CAD, Stein et al compared 64-slice CCTA with invasive CA in the diagnosis of CAD [5]. The sensitivity for detecting significant stenosis (≥50%) in patient-

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* Corresponding author. Department of Nuclear Medicine, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 8561825x2024; fax: +886 3 8564629.

E-mail address: jedimasterchen@hotmail.com (Y.-H. Chen).

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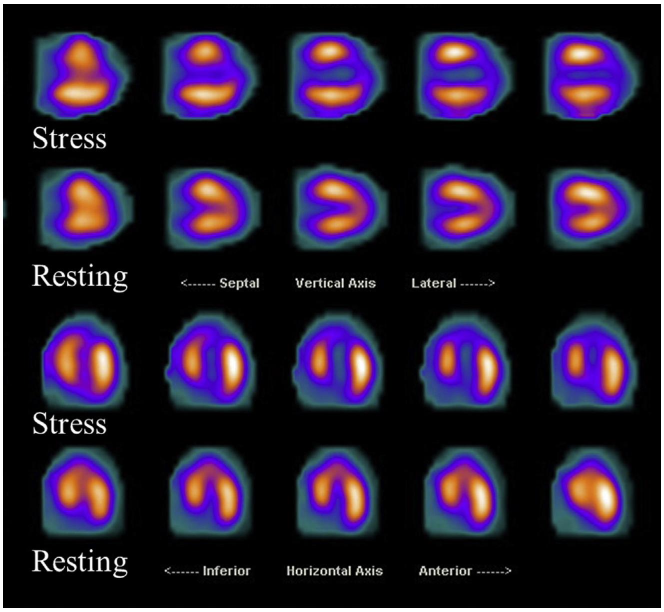

Fig. 1. Myocardial perfusion scintigraphy shows myocardial ischemia at the apical segment of the left ventricle.

based evaluations was not less than 90% and the specificity in patient-based evaluations was 88%. The positive predictive value (PPV) for patient-based evaluations varied widely according to vascular site (69–93%), and the negative predictive value (NPV) was 96–100%. Another meta-analysis investigating 28 studies including 1286 patients yielded similar results [6]. The per-patient pooled sensitivity, specificity, PPV and NPV were 99%, 89%, 93% and 100%, respectively. The high NPV has prompted the use of CCTA to rule out CAD.

Multicenter studies, however, have had more variable results. Four multicenter studies investigating the use of CCTA in diagnosing CAD, the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY), The Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CORE 64), Meijboom et al and Ontario Multi-detector Computed Tomographic Coronary Angiography Study (OMCAS) studies, showed widely varying diagnostic performance with sensitivities of 81.3% (OMCAS) to 99% (Meijboom et al) and specificities of 64% (Meijboom et al) to 93.3% (OMCAS). The PPV also varied widely from 64% (ACCURACY) to 91.6% (OMCAS) and the NPV from 83% (CORE 64) to 99% (ACCURACY) [7–10]. The varied results might be related to different prevalences of CAD among the patient groups in the different trials. With a lower CAD prevalence (ACCURACY trial), the diagnostic performance was more similar to those in single-center trials. However, the higher CAD prevalence in other multicenter trials resulted in a more variable diagnostic performance. This may also indicate that more multicenter trials are needed for better documentation of the diagnostic performance of CCTA [11]. Nevertheless, to sum up the results from single-center and multicenter studies, the NPV of CCTA is still valuable for low-risk patients to rule out CAD.

Two multicenter studies of CMRI are available. In the earlier study, which included 109 patients with comparison to invasive CA, CMRI had an overall sensitivity and specificity of 93% and 42% respectively for detecting $\geq$50% coronary artery stenosis [12]. The more recent multicenter study of 138 patients yielded a patient-based sensitivity, specificity, PPV and NPV of 88%, 72%, 71% and 88%, respectively [13]. The diagnostic performance of CMRI angiography was inferior to that of CCTA.

3. Downstream results comparison with MPS

The downstream results including patients' health outcomes, subsequent procedures and cost-effectiveness of CCTA compared with MPS, have been less investigated. Min et al demonstrated that patients without known CAD initially evaluated by CCTA had lower subsequent costs (around 30%) compared with patients initially evaluated by MPS. Although healthcare expenditures were lower, the health outcomes were similar, including CAD-related hospitalization, myocardial infarction, onset of angina, and CAD outpatient visits [14]. A more recent prospective study of 180 patients presenting with chest pain and suspected CAD who were followed-up for 55 days showed similar results [15]. In contrast, Shreibati et al's retrospective study which included 282,830 patients showed that total spending and CAD-related spending were significantly higher in the CCTA group than the MPS group. There was more noninvasive and invasive cardiac testing and more revascularization in the CCTA group [16]. This can be explained by a higher prevalence of CAD in

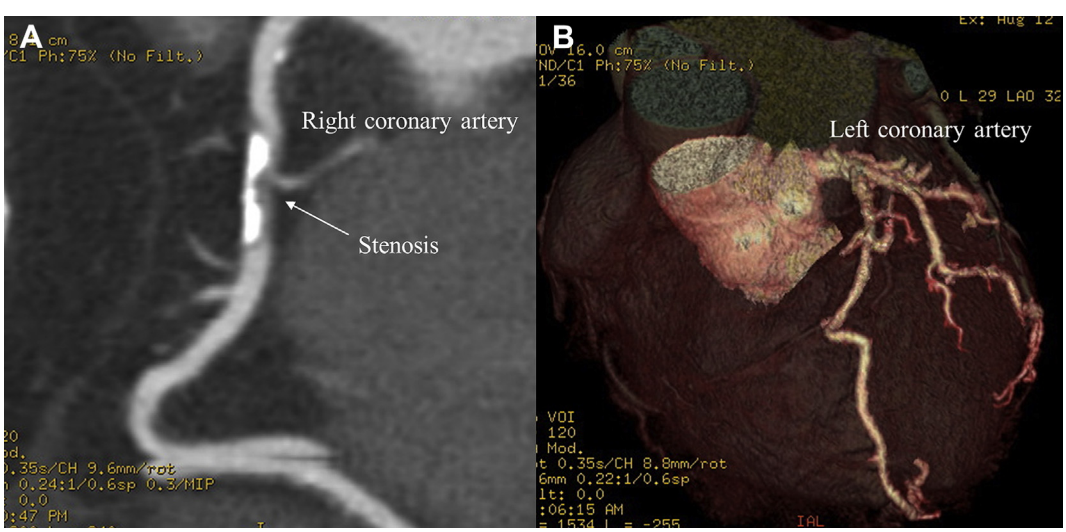

Fig. 2. (A) A coronary computed tomography angiography reformatted image reveals stenosis in the right coronary artery (arrow). (B) Coronary computed tomography angiography in another patient shows absence of the right coronary artery, indicating complete occlusion of the right coronary artery.

the Shreibati et al study and the fact that CCTA is not cost-effective in populations with a high pretest likelihood of CAD [11]. In this group, patients with anatomical stenosis on CCTA without significant ischemia may undergo unnecessary revascularization.

4. Limitations of CCTA and CMRI angiography

Although the NPV of CCTA is high, this modality has several limitations. A rapid heart rate, irregular rhythm and severe coronary calcification interfere with image quality [17,18]. This was demonstrated in the ACCURACY trial, where the specificity fell from 83% to 53% in patients with an Agatston score greater than 400 units [7]. In addition, narrow coronary arteries (diameter <1.5 mm) cannot be analyzed and have been excluded from most trials of CCTA. Small-artery CAD is often undiagnosed.

Intracoronary metal stents, which produce metal artifact in CCTA and image distortion in CMRI angiography, mask nearby coronary lesions. Also, many implants such as cardiac pacemakers and defibrillators are contraindicated in CMRI examinations [19].

Recent studies have demonstrated that stenosis on angiography does not correlate with the FFR. Meijboom et al used the FFR in invasive coronary angiography as the reference standard to calculate the correlation between ischemic indicators and anatomical lesions. The correlation coefficient of quantitative CCTA and the FFR was −0.32; and that of quantitative invasive coronary angiography and the FFR was −0.30 [2]. These results indicate that coronary stenosis on angiography does not necessarily represent ischemia. Patients may therefore be over-treated if only angiographic results are considered. The limitations of anatomical imaging have prompted the emergence of new functional imaging.

Recent imaging strategies have included a combination of anatomical images with functional parameters. Examples include a combination of CCTA with MPS (CCTA/MPS), CCTA with perfusion computed tomography (CCTA/CTP), CCTA with FFR_{CT} (FFR calculated by CCTA), and CMRI perfusion images and cardiac perfusion PET.

5. Combination of CCTA and MPS

Rispler et al evaluated the diagnostic performance of CCTA/MPS in 56 patients, and the sensitivity, specificity, PPV and NPV of CCTA alone for the detection of greater than 50% coronary stenosis were 96%, 63%, 31% and 99%, respectively, with a positive likelihood ratio of 2.6 [20]. The same measures for CCTA/MPS were 96%, 95%, 77% and 99%, respectively, with a positive likelihood ratio of 19.2. This suggests that with a combination of MPS, specificity can be improved. However, the specificity of CCTA alone in this study was much lower than that in previously published data [5,6]. A possible explanation for this is that CCTA was performed by 16-slice computed tomography, which may provide poor quality images compared with 64-slice computed tomography. More recently, Sato et al used 64-slice computed tomography and the diagnostic performance was better [21].

6. CCTA/CTP

CCTA is limited to anatomical evaluation and cardiac perfusion computed tomography has been investigated to provide functional information. A recent systemic review and meta-analysis evaluated the diagnostic performance of vasodilator stress cardiac computed tomography perfusion imaging in CAD [22]. If only vasodilator stress perfusion imaging was used, the specificity was only 59% when invasive coronary angiography was used as a reference. The results were unfavorable compared with MPS (which has a specificity of 76% based on a recent systemic review and meta-analysis) [23]. However, CCTA/CTP showed excellent diagnostic performance when combined with invasive coronary angiography using MPS as a reference; the sensitivity, specificity, PPV and NPV were 86%, 92%, 92% and 85%, respectively. A similar diagnostic performance was obtained for CCTA/CTP when invasive coronary angiography with the FFR was used as a reference; the pooled sensitivity, specificity, PPV and NPV in the two studies were 81%, 93%, 87% and 88%, respectively [22]. Although the results of CCTA/CTP seemed promising, the sample sizes in the studies were relatively small, with only 26 patients in the study comparing CCTA/CTP to a combination of invasive coronary angiography with MPS, and a total of 75 patients in the comparison of CCTA/CTP to invasive coronary angiography with the FFR. Thus, more trials are needed for further validation of the usage of CCTA/CTP in diagnosing CAD.

7. CCTA with FFR_{CT}

Recently, evidence has shown that CCTA/FFR_{CT} has good performance in diagnosing CAD. The Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve

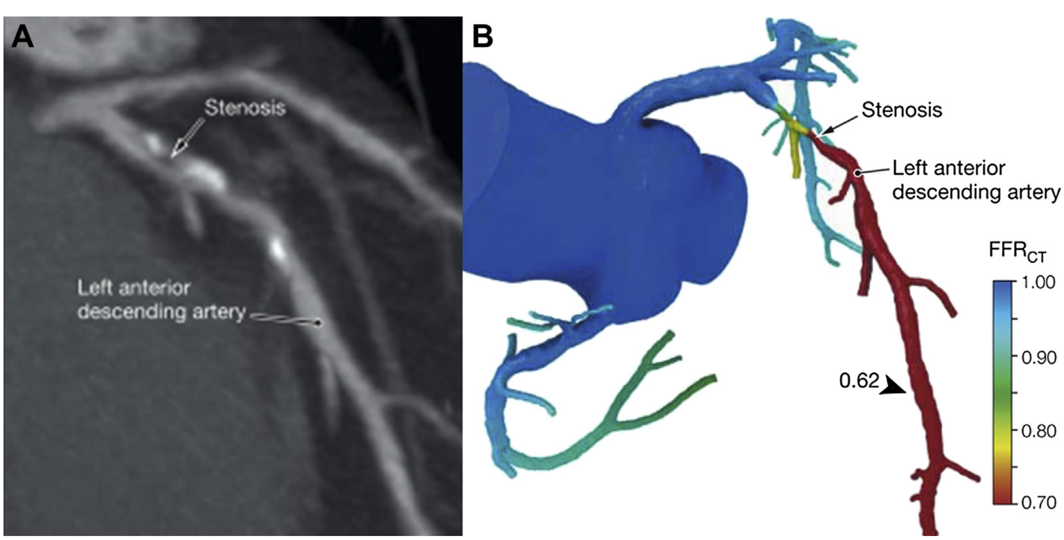

Fig. 3. (A) Left anterior descending artery stenosis on coronary computed tomography angiography in the study by Min et al. (B) The FFR calculated by coronary computed tomography angiography is <0.80 (arrowhead) [26].

Table 1
Comparison of diagnostic performance between cardiac magnetic resonance imaging (CMRI) and myocardial perfusion scintigraphy (MPS).

Reference	Patients	Prevalence of CAD	Comparison	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
MR-IMPACT II [33,34]	515 (60 ± 10 y, 73% male)	49%	CMRI vs. MPS	75 (68–82) vs. 59 (49–69)	59 (51–67) vs. 72 (58–86)	70 (65–75) vs. 73 (65–81)	65 (60–70) vs. 60 (57–53)	0.75 ± 0.02 vs. 0.65 ± 0.03
CE-MARC [35]	752 (60 ± 10 y, 63% male)	39%	CMRI vs. MPS	87 (82–90) vs. 67 (60–72)	83 (80–87) vs. 83 (79–86)	77 (72–82) vs. 71 (65–77)	91 (87–93) vs. 79 (75–83)	0.84 ± 0.03 vs. 0.69 ± 0.04

AUC = area under the curve; CAD = coronary artery disease; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

(DISCOVER-FLOW) study analyzed the diagnostic performance of CCTA/FFR_{CT} with the reference of invasive CA and the FFR in 103 patients. The per-segment based sensitivity, specificity, PPV, NPV and accuracy were 87.9%, 82.2%, 73.9%, 92.2% and 84.3%, respectively, with an area under the receiver-operator characteristics curve (AUC) of 0.90. The diagnostic performance greatly exceeded that of CCTA alone (same statistical measures 91.4%, 39.6%, 46.5%, 88.9% and 58.5%, respectively). The study also demonstrated a good correlation ($r = 0.717$) between the FFR_{CT} and FFR [24,25]. A more recent and larger trial by Min et al included 252 patients for per-patient based analysis using invasive CA and the FFR as a reference. The sensitivity, specificity, PPV, NPV and accuracy for CCTA/FFR_{CT} were 90%, 54%, 67%, 84% and 73%, respectively, with an AUC of 0.81; the results for CCTA only were 84%, 42%, 61%, 72% and 64%, with an AUC of 0.68 (Fig. 3) [26]. Although the diagnostic performance was not as impressive as in the DISCOVER-FLOW study, it consistently outperformed CCTA alone and it seems promising that the functional ischemic indicator, the FFR, can be measured noninvasively.

8. CMRI perfusion images

Two large trials have compared the diagnostic performance of CMRI and MPS in CAD: the Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial (MR IMPACT II) [27,28] and The Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease study (CE-MARC) (Table 1) [29].

In MR-IMPACT II, the sensitivity of CMRI was better than that of MPS (75% vs. 59%); however, the specificity of MPS (72%) was better than that of CMRI (59%). The calculated positive likelihood ratios of CMRI and MPS were 1.83 and 2.11, respectively. The MR-IMPACT II showed that the AUC of CMRI significantly outperformed that of both gated and non-gated MPS.

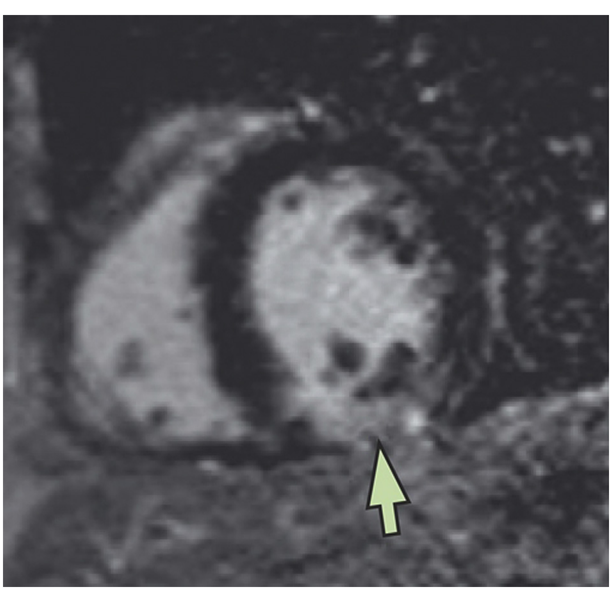

Fig. 4. In the CE-MARC trial, late gadolinium-enhanced cardiac magnetic resonance imaging shows a transmural inferior myocardial infarct (arrow) [29].

The CE-MARC study (Fig. 4) showed that the sensitivity [29], specificity, PPV, NPV and AUC were all better than MPS (Table 1), indicating that the diagnostic performance of CMRI is better than MPS.

The sensitivity of MPS in the two studies, however, was unexpectedly low and was inconsistent with previously reported results from multiple single-center and multicenter trials [23,30]. Flotats et al and Schaefer et al also demonstrated that the difference may be due to the technical limitations of single-photon emission computed tomography (SPECT) [31,32].

Another randomized controlled trial, the Cost-Effectiveness of Functional Cardiac Testing trial (CECaT trial), evaluated different functional cardiac tests in the diagnosis and management of CAD in comparison with angiography in 898 patients. The results showed that MPS was as useful as angiography in identifying patients who should undergo revascularization and the additional cost was not significant. On the contrary, CMRI had the largest number of test failures [33]. Therefore, as it is a new technique, CMRI still requires further work and more multicenter studies before adoption in routine clinical practice.

9. Cardiac perfusion PET

Although not used widely in clinical practice, cardiac PET perfusion imaging offers technical benefits over MPS with SPECT. A recent meta-analysis using invasive coronary angiography as a reference standard demonstrated that the sensitivities of cardiac perfusion PET and SPECT MPS were 92.6% (95% confidence interval: 88.3–95.5%) and 88.3% (95% confidence interval: 86.4–90.0%) with $p = 0.035$. No significant difference in specificity was noted between the two image modalities [34]. PET offers improved image

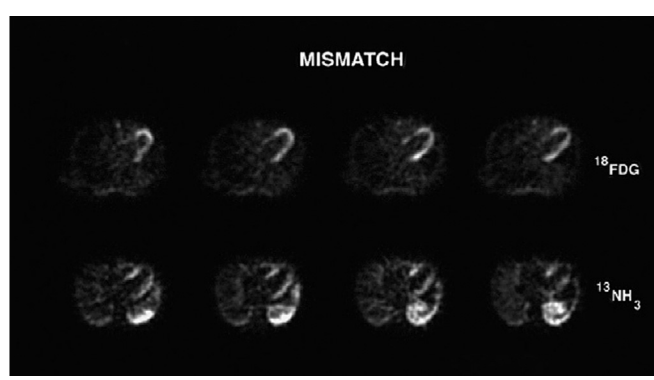

Fig. 5. An apical perfusion defect is demonstrated by perfusion radiotracer (^{13}N-ammonia) whereas ^{18}F-fluorodeoxyglucose positron emission tomography shows no decrease in glucose metabolism. This typical perfusion–metabolism mismatch indicates viable myocardium under ischemia [37].

Table 2
Limitations and advantages of existing noninvasive diagnostic modalities.

	Image tool	Limitation	Advantage
Angiography-based images	CCTA	Tachycardia, irregular rhythm, coronary calcification, diameter <1.5 mm, contrast nephropathy or allergy, lack functional parameter	The procedure is fast, good spatial resolution, high NPV in low risk patients
	CCTA/FFR_{CT}	Same as above except the functional parameter	The procedure is fast, good spatial resolution, provides a functional parameter to CCTA
Perfusion images	CCTA/MPS	Radiation hazards	Provides a functional parameter to CCTA
	CCTA/CTP	Similar to CCTA, except the limitation of vascular diameter and functional parameter	The procedure is fast, good spatial resolution, provides a functional parameter to CCTA
	CMRI	Metal implants, irregular rhythm or breath, technology insufficiency or operator inexperience, nephrogenic systemic fibrosis	No ionizing radiation, delayed enhanced image can assess viability
	PET (Perfusion/MFR and metabolism)	Expensive, less accessible, lack of anatomical information	Better diagnostic performance than SPECT, MFR improves the sensitivity for balanced ischemia, can assess viability, no contrast-related adverse effects, rhythm or breath is not a concern

CCTA = coronary computed tomography angiography; CMRI = cardiac magnetic resonance imaging; CTP = perfusion computed tomography; FFR_{CT} = fractional flow reserve measured by computed tomography; MFR = myocardial flow reserve; MPS = myocardial perfusion scintigraphy; NPV = negative predictive value; PET = positron emission tomography.

quality, more interpretive confidence and better inter-reader agreement compared with SPECT [35]. However, PET perfusion imaging has poor sensitivity in detecting balanced myocardial ischemia. This limitation may be overcome by the use of the myocardial flow reserve (MFR) [36]. Fiechter et al assessed the diagnostic performance of N-13 ammonia perfusion PET with MFR in 73 patients using invasive coronary angiography as a standard of reference. When the cutoff was less than 2.0 for the global MFR, the sensitivity, specificity, PPV, NPV and accuracy of perfusion PET/MFR were 96%, 80%, 93%, 89% and 92%, respectively. The same results for perfusion PET images were only 79%, 80%, 91%, 59%, and 79%, respectively. The sensitivity, NPV and accuracy were significantly improved ($p < 0.05$) when the MFR was used [36]. This finding indicates that adding MFR can compensate for limitations in diagnosing balanced myocardial ischemia.

Another merit of PET in evaluating CAD is the use of F-18 fluorodeoxyglucose PET in evaluating myocardial viability (Fig. 5) [37]. Although there are other noninvasive modalities capable of assessing myocardial viability, such as delayed contrast-enhanced MRI and stress echocardiography [38], diagnosis of a hibernating myocardium by flow-metabolism mismatch cannot currently be replaced by other examinations. Information on myocardial hibernation is very important in the management of CAD because revascularization can allow resumption of myocardial function, while an infarcted or scarred myocardium does not benefit from this procedure.

10. The future of CAD diagnosis

Data from currently available studies show promising results in the diagnosis of CAD with emerging noninvasive imaging modalities. However, the evidence is insufficient for each technique to be used routinely in clinical practice. New technologies are being invented, including dual-energy computed tomographic techniques to evaluate the myocardial blood pool as well as newer PET myocardial perfusion tracer flurpiridaz F 18 imaging [39,40].

The current trend is to add more functional parameters to traditional anatomical imaging to improve the accuracy and

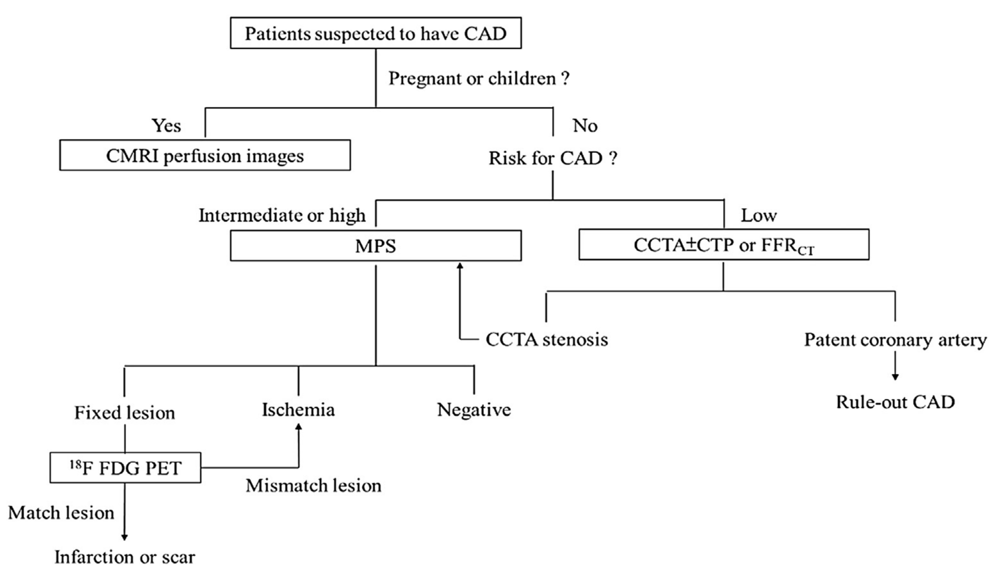

Fig. 6. Diagnostic algorithm for non-invasive imaging modalities. Note that for low-risk patients, CCTA alone is enough according to the evidence. However, CTP and FFR_{CT} can be performed simultaneously. (CAD = coronary artery disease; CMRI = cardiac magnetic resonance imaging; MPS = myocardial perfusion scintigraphy; CCTA = coronary computed tomography angiography; CTP = perfusion computed tomography; FFR_{CT} = fractional flow reserve measured by computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography.)

overcome existing limitations (Table 2). For angiography-based images, although FFR_{CT} adds functional information to CCTA, it still cannot assess vessels narrower than 1.5 mm; perfusion images, however, are not limited by vascular caliber. Clinicians need to be cautious about the potential insufficiency of using invasive coronary angiography or the FFR as a reference standard for assessing the diagnostic performance of emerging image tools. Small vascular stenosis may not be detected by invasive coronary angiography or the FFR, but it can appear as a perfusion defect on perfusion images. This then can be erroneously registered as a false-positive finding [29]. For this reason, investigators may have to consider which tool (or tools) should be used as a reference standard for assessing the diagnostic performance of imaging modalities in CAD.

11. Conclusion

In recent decades several new noninvasive imaging modalities have emerged, and most studies have shown promising results. Each of the tools has limitations and advantages over the others (Table 2). In diagnostic performance, the high NPV for CCTA suggests its use in ruling out CAD. The downstream results of CCTA in comparison with MPS, however, have been conflicting. This suggests that CCTA might be better than MPS only in low-risk groups. For the other tools, data are insufficient to make conclusions about their use in comparison with MPS, the most commonly used noninvasive diagnostic modality today. The algorithm in Fig. 6 may help in understanding the roles of various modalities in diagnosing CAD. With advancements in technology, the references used in assessing diagnostic performance might become unsuitable. Analogously, the diagnosis of CAD might not be sufficient with invasive angiography only, since small vascular stenosis cannot be detected.

Finally, new noninvasive image modalities are emerging and the race between different tools for CAD diagnosis continues. Newer technologies seek better diagnostic accuracy, lower radiation dosages, more functional parameters and more delicate images. However, all efforts should eventually be examined against health outcomes and cost-effectiveness to ascertain the benefits to patients.

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