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Updates on Stress Imaging Testing and Myocardial Viability With Advanced Imaging Modalities

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Introduction

The goal of identifying myocardial perfusion deficits has a twofold purpose, to identify functionally significant coronary artery disease (CAD) and to assign appropriate risk stratification. The ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease provides a rating for each of the imaging modalities in serving this twofold purpose in setting of common clinical scenarios [1]. The perfusion deficits due to ischemia are more apparent on stress in comparison with rest. Myocardial stress perfusion can be assessed either by physiologic or pharmacologic vasodilator stress agents. The selection of appropriate stress test depends on the multiple factors including the clinical profile of patients and availability of expertise [2]. Viability assessment in setting of either acute or chronic ischemia can guide clinical decision-making in terms of revascularization or optimization of medical therapy [3]. With the advent of newer guidelines and improvised technology, more scientific data is becoming available in regard to each of the non-invasive

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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stress imaging modalities and its ability to provide an objective assessment of myocardial perfusion. The aim of the following review is to provide a consolidated overview of recent advances in computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) myocardial perfusion stress and viability imaging.

Computed tomography

Resting coronary computed tomography angiography (cCTA) has proven to be a useful screening tool in excluding significant coronary artery disease when there are no lesions resulting in moderate ($>50\%$) or severe ($>70\%$) coronary artery luminal narrowing. When such lesions are present, however, the accuracy of predicting the “functional significance” of the lesion (i.e., whether it causes ischemia) can vary widely. This is an important shortcoming of cCTA as well as invasive coronary angiography (ICA), as multicenter randomized trials (i.e., FAME: Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease) have shown that when the decision to revascularize patients is made using a functional evaluation (fractional flow reserve, FFR) during ICA, patients have better outcomes than when the gold standard for anatomic evaluation, ICA stenosis grading, is used. A stress CT perfusion (CTP) protocol was thus developed, aiming to become a single, noninvasive test that could provide reliable anatomic and functional images to assess the presence of lesions causing myocardial ischemia (Fig. 1a–d). Several articles have recently been published highlighting the strides CTP has made towards becoming widely adopted clinically, while acknowledging the questions that remain on the methodology and utility of CTP.

Multiple recent studies have compared the accuracy of CTP versus CT-derived fractional flow reserve (CT-FFR). CT-FFR uses a software, which may be on site or off site, that generates a simulation of coronary blood flow using patient-specific dimensions and physical laws of fluid dynamics; although only one vendor (at the time of this writing) has an approved method for clinical use, several vendors have proposed differing softwares, all of which aim to use computational fluid dynamics to predict functional ischemia using only anatomic features of the coronary tree and, in some cases, the myocardial thickness being perfused, using only resting, static cCTA images. Yang et al. [4] published results demonstrating similar accuracies for CTP and CT-FFR in identifying hemodynamically significant stenosis defined by the invasive FFR. While CT-FFR was more sensitive, it was not as specific as CTP. Moreover, in patients with elevated calcium scores, the specificity and positive predictive value for CT-FFR were significantly lower than in CTP, underscoring the importance of acquiring artifact-free resting coronary CTA images at baseline from which to produce the models necessary for CTFFR. Of note, neither CT-FFR nor CTP was significantly more accurate than resting cCTA. Another publication by Pontone et al. [5] laid out the design of a prospective study of 300 subjects that will compare CT-FFR and CTP. In the study, half of the subjects will undergo dynamic CTP (sequential scans during adenosine infusion) while the other half will undergo static CTP (single scan during adenosine infusion) to illustrate any differences in accuracy between those two methods of CTP.

Utilizing a prospective CTP registry of 262 patients, Yang et al. [6] performed a study analyzing the accuracy of CTP for the 75 patients who underwent ICA, using invasive FFR

as the reference standard. In the study, licensed software was used to evaluate for quantitative perfusion deficits on stress imaging; however, the software was less accurate than the radiologists who performed a qualitative assessment. Interestingly, the only group of patients for which the CTP images added any incremental benefit in accuracy compared to resting cCTA, was patients with calcium scores >400 .

Another recent study evaluating the incremental benefit of CTP in addition to resting cCTA was performed by Magalhaes et al. [7] in the CORE320 study. Using $>50\%$ stenosis on ICA with a matched perfusion deficit on single photon emission CT (SPECT) as a reference, 381 patients were analyzed. Using each alone, resting cCTA showed much greater sensitivity and specificity compared to CTP when used alone. The addition of CTP led to marginally higher accuracy compared to resting cCTA alone (75 compared to 69%), but the difference was not statistically significant.

The design of the DECIDE-Gold trial was recently published by Truong et al. [8], which is a prospective study that will evaluate the accuracy of CTP using a dual energy scanner, with FFR on ICA as the gold standard. The study will also compare dual energy CTP to other stress imaging modalities such as MRI, PET, and SPECT.

There continues to be disagreement as to whether a CTP protocol should have the rest portion of the exam prior to the stress, or vice versa, as both techniques were used in the referenced publications. By obtaining the rest exam first, a quick (but accurate) interpretation might determine if the stress part of the exam is necessary at all, as multiple studies have shown that CTP may only add incremental value if there is at least a moderate ($>50\%$ narrowing) lesion or if the calcium score is high (i.e., >400 or >1000 , depending on equipment). A recent publication by Ladeiras-Lopes et al. [9] specifically showed how utilizing CTP only on patients with a calcium score >400 can optimize diagnostic accuracy. If the CTP portion of the exam is carried out, it is still not known whether dynamic or static CTP is a more accurate method, highlighting the ongoing dilemma between radiation dose optimization and quality (and quantity) of images, as well as the proper methodology of analysis. Hopefully, the referenced articles on the design of ongoing trials will help elucidate the answers to such questions.

There have been no recent publications investigating the accuracy of CT in evaluating for myocardial viability. Prior studies however have shown that myocardial viability can be accurately assessed using delayed enhancement on CT, particularly when used in a comprehensive protocol that includes cine imaging to evaluate for regional wall motion abnormalities and resting perfusion deficits [10].

Positron emission tomography

Cardiac PET is a method of imaging that provides a means of performing perfusion and metabolic imaging with radionuclide tracers. Standard protocols require the acquisition of CT images for attenuation correction and emission images of radionuclide decay [11]. Two radionuclides are commonly used clinically as perfusion tracers for stress testing, 82-rubidium (^{82}Rb) and N-13 ammonia ($^{13}\text{NH}_3$). These agents are primarily distinguished

by their half-lives, 1.25 and 10 min, respectively, and available forms [12]. Commercially available ^{82}Rb generators are available that allow for elution of radiotracer at the time of need, whereas $^{13}\text{NH}_3$ requires the availability of a cyclotron for the production of each dose of radionuclide [12]. A dose of 10–20 mCi and an acquisition time of approximately 3–6 min is required for both rest and stress perfusion imaging with ^{82}Rb [11, 12], and a dose of 10–20 mCi and an acquisition time of 10–15 min is required for both rest and stress imaging for $^{13}\text{NH}_3$ [12]. While dobutamine or exercise stress testing can be performed with $^{13}\text{NH}_3$, the preferred method of stress is pharmacologic with a vasodilator (i.e., regadenoson, adenosine, or dipyridamole) given the need to optimize the timing of tracer injection and minimize patient motion [11–13]. The data is typically recorded in list mode with electrocardiographic gating, which allows reconstruction of static, dynamic, and functional gated images [11]. The images are then evaluated visually (Fig. 1e–g), semi-quantitatively, and quantitatively to identify the presence of abnormal perfusion at rest and/or stress [12, 13]. Cardiac PET stress dynamic imaging and mathematical modeling allow for the assessment of myocardial blood flow (MBF) and coronary flow reserve (CFR), a ratio of absolute myocardial blood flow at peak hyperemia compared to absolute myocardial blood flow at rest [14, 15], which has been shown to have a number of clinical applications, including excluding high-risk coronary artery disease when normal [16] and correlating with cardiovascular death and adverse cardiac events independent of epicardial coronary artery disease [17, 18]. Myocardial perfusion imaging with PET has a significantly improved sensitivity and similar specificity for obstructive coronary artery disease when compared to single photon emission computed tomography [19]. The low-dose CT scan used for attenuation correction should be evaluated not only for incidental findings but also for atherosclerotic calcification as well as alternative causes of symptoms. A formal calcium score can be performed for patients without known coronary artery disease [11].

Metabolic imaging of the myocardium can be performed using 18-fluorodeoxyglucose (18-FDG) to evaluate for viable or hibernating myocardium, which is defined as metabolically active tissue in the presence of a coincident resting perfusion defect [12]. Normal myocardium preferentially uses free fatty acids for metabolism, but hibernating myocardium shifts towards utilizing glucose preferentially in conditions of reduced oxygen [12]. Patients are typically prepared for imaging with the administration of a glucose load and subsequent doses of insulin prior to 5–15 mCi intravenous 18-FDG [11, 12]. Imaging is typically performed 45–90 min after radiotracer administration and is completed in approximately 15–30 min. As above, a low-dose CT scan is required for attenuation correction [11]. A combination of perfusion and metabolic PET imaging has a sensitivity of 88% and a specificity of 74% for myocardial viability [20].

Cardiac PET perfusion and metabolic imaging is most limited by image reconstruction artifacts, patient motion, count density, and errors in attenuation correction [12]. The typical radiation doses from a rest-stress protocol with ^{82}Rb or $^{13}\text{NH}_3$ is 2–4 mSv, while a typical injection of 18-FDG delivers a radiation dose of 7 mSv [12, 21, 22].

Recent advances in cardiac PET stress testing have largely involved increasing knowledge about the implications of coronary flow reserve, applications of hybrid imaging, and improvements in image acquisition and processing.

Coronary flow measurements have been implicated in the risk for adverse cardiovascular events in a number of conditions and have recently been shown to provide incremental information about the risk of cardiovascular and all-cause mortality in patients with end-stage renal disease [23]. Flow measurements were shown to improve with improved left ventricular synchrony under stress conditions [24] following a 12-week program of cardiac rehabilitation program in patients with non-ischemic cardiomyopathy [25] and to assist in clarifying the underlying pathophysiology in Takatsubo cardiomyopathy by demonstrating basal hyperemia [26]. Patients with HIV on stable anti-retroviral therapy were shown to have reduced peak MBF under stress conditions with preserved CFR [27]. A study by Valenta et al. demonstrated a close correlation between the longitudinal MBF and invasively measured fractional flow reserve under conditions of hyperemia for the assessment of a coronary stenosis [28]. In the future, it will be important to pursue more studies to attempt to use CFR as both a tool to assist with clinical decision-making and a marker of cardiac health and correlate improvement in CFR with a reduction in primary cardiovascular outcomes.

A complete characterization of disease processes will become possible by combining PET imaging with CT angiography (CT-A), coronary artery calcium scoring (CAC), or MRI. By combining imaging modalities, we will learn more about underlying diseases and the information available from each separate imaging modality. For example, in one recent study, a cohort of patients underwent cCTA and 13-NH3 PET perfusion imaging, demonstrating that the burden of non-calcified plaque better predicted abnormal MBF than the degree of stenosis. Likewise, those with abnormal MBF were shown to have significantly more non-calcified arterial plaque, low-density non-calcified plaque, and total plaque [29]. Assante et al. redemonstrated the finding that CAC correlates inversely with stress MBF and CFR and serves as an independent risk factor for reduction in CFR [30]. A recent hybrid 18-FDG PET and MRI study explored the characteristics of myocardium at risk following reperfusion after ST-elevation myocardial infarction at 5 days and 12 months follow-up. On the early images, there was a region of reduced 18-FDG uptake that matched a region identified by T2 mapping. The defect on 18-FDG images often improved at follow-up and correlated with late gadolinium enhancement on the follow-up scan [31]. These studies are only several of many examples of using hybrid imaging to evaluate an array of cardiac pathologies.

A third group of recent projects has sought to improve image acquisition and processing. Suda et al. demonstrated that time-of-flight PET provides improved image quality, recovery coefficients, and contrast over background as compared to conventional PET without changes in the quantification of myocardial blood flow [32]. Given the limitations of attenuation correction, several recent studies describe novel automated algorithms for image reconstruction and the optimization of data quality [33, 34]. While it has been shown that patient motion may affect MBF measurements by up to 500% [35], other studies have pursued methods to minimize this effect [36, 37].

Perfusion and metabolic imaging with cardiac PET has a growing list of applications in the non-invasive assessment of cardiovascular diseases beyond the assessment of epicardial coronary artery disease. The clinical role of MBF and CFR will continue to be refined through further research and follow-up. Novel hybrid imaging techniques and methods of

data acquisition and processing will continue to improve the diagnostic and prognostic utility of PET imaging as the technology becomes increasingly available for cardiovascular care.

Cardiac magnetic resonance imaging

Stress perfusion cardiac magnetic resonance imaging (CMR) offers a comprehensive assessment of ventricular function, status of myocardial perfusion, wall motion, and viability assessment in one setting without ionizing radiation exposure. In a recent large multicenter trial of nearly 12,000 patients, CMR showed a favorable safety profile with extremely low incidence of serious immediate complications [38]. Technological advances in CMR and automated image acquisition techniques are facilitating reduced scan time and increased utilization. While the detailed discussion on indications for stress CMR is beyond the scope of this review, the 2013 multimodality appropriate use criteria for detection and risk assessment of stable ischemic heart disease deemed use of stress CMR as appropriate in following categories: (A) diagnosis of CAD in symptomatic patients, (B) newly diagnosed heart failure and arrhythmias, (C) sequential testing in patients with prior abnormal exercise or imaging studies, and (D) follow-up testing with new or worsening symptoms [1] (Fig. 1h–k). The CE-MARC trial established superior sensitivity of CMR over SPECT (86.5 vs. 66.5%, $p < 0.001$) of CMR and myocardial stress MR perfusion [39]. A recent review and meta-analysis showed a significant decrease in consequential invasive testing for ischemia evaluation while maintaining comparable diagnostic accuracy in comparison with dobutamine stress echo and SPECT [40]. An evolving indication for CMR stress perfusion is risk stratification in individuals with high risk of developing coronary artery disease like diabetes. In one of the first studies evaluating stress CMR in diabetic patients, Heydari et.al. demonstrated that inducible ischemia was the strongest predictor non-fatal myocardial infarction and death from a cardiac cause [41].

The superiority of late gadolinium enhancement (LGE) in assessing myocardial viability in the setting of acute or chronic myocardial infarction has been well established with sensitivity as high as 99 or 94%, respectively [42, 43]. The extent of LGE <50% of the transmural thickness of the wall to predict functional recovery post revascularization is widely validated and has become a standard clinical practice [44, 45]. LGE images can also identify thrombi in the left ventricle, which can cause catastrophic outcomes as a result of systemic embolization. LGE imaging can also identify microvascular obstruction seen as a persistent hypointense (dark) area, surrounded by abnormal late gadolinium on delayed images, in comparison with unaffected healthy myocardium in setting of acute myocardial infarction indicates adverse prognosis [46–48].

CMR stress perfusion can be performed after the myocardium is put under stress either by exercise or pharmacologic stressor agents as mentioned earlier. T1-weighted breath-held first-pass perfusion images are acquired at peak stress after administration of intravenous gadolinium-based contrast agent. Typically 3 short axis slices are acquired at the base, mid, and apex, and one four-chamber view of the heart are acquired during each phase of perfusion. The image acquisition typically spans across 60–80 heartbeats, with phases acquired every 1–2 s. Image interpretation relies on differences in T1 time shortening of the

ischemic area versus the healthy, normally perfused myocardium [49]. Availability of in-line motion correction techniques further can improvise the image quality in patients with limited breath-holding capabilities [50]. Images are reviewed qualitatively for the presence or absence of perfusion deficits in each myocardial segment per the 17-segment AHA model [51]. Viability is assessed by the presence of abnormal LGE on the backdrop of well nulled healthy myocardium on either 2D or 3D T1-weighted gradient echo images with an inversion pulse for myocardial nulling, obtained 10–15 min following administration of intravenous gadolinium-based contrast agents [52]. The 2D T1-weighted images offer high resolution but typically require patients to hold their breath. The 3D technique allows free breathing navigated image acquisition, or shortened, volumetric acquisitions, at the cost of prolonged image acquisition time, and/or compromised signal to noise ratios, while the continuous interplay of contrast washout and scar enhancement evolves. Eventually, this interplay results in suboptimal suppression of healthy myocardial signal [53], in the later stages of enhancement.

Recent studies on stress CMR have largely addressed two key areas: technical developments in image acquisition and assessment of clinical effectiveness. Semi-quantitative or quantitative analysis of perfusion by measuring signal intensity changes in the myocardium can increase the sensitivity of CMR in detection of ischemia, especially in qualitatively negative cases. In a recent study by Yun et al., in 58 patients, the sensitivity and specificity in detection of flow limiting stenoses were 77 and 80%, respectively, but when supplemented by quantitative assessment, the sensitivity increased to 83%. The quantitative assessment had the greatest impact on lesions in the circumflex territory wherein the sensitivity increased from 63 to 83% [54]. Quantitative evaluation allows measurement of significant indices, for example, signal up-slope, myocardial perfusion reserve, transmural perfusion reserve, and coronary flow reserve [55] as mentioned in the section on PET perfusion imaging.

Artifacts can limit stress perfusion MRI image quality, most importantly image quality degradation in patients with limited breath-holding capacity and arrhythmias. Dark rim artifact due to Gibb's ringing can affect the image interpretation given its subendocardial presence and ability to mimic real perfusion deficit. Sharif et al. showed optimized image quality by using radial sampling in healthy volunteers [56]. Another strategy to reduce this artifact is systolic image acquisition using a real-time image-based navigator which resulted in high contrast to noise ratio in a preliminary investigation by Sharif et al. [57]. Recently, Zhou et al. demonstrated free breathing acquisition with Cartesian sampling, which reduced the width and number of dark rim artifacts [58]. Another quality improvement step described by Manisty et al. recently is the "splenic switch-off sign" (absence of decreased splenic attenuation on stress), a simplistic tool to identify likely false-negative stress exam as a result of submaximal stress. The sign is however limited to adenosine stress MRI and cannot be used for other stressor agents like dobutamine and regadenoson [59]. One of the drawbacks of routine 2D myocardial perfusion scanning is undersampling of the myocardium. Newer parallel acquisition techniques enable 3D acquisition of the entire left ventricular myocardium without compromising spatial and temporal resolution, in a matter not unlike CTP [60]. These advances are, however, preliminary and yet to become a clinical standard. The exercise stress using MRI compatible treadmill testing is another newer development in the field of stress CMR. The EXACT trial showed excellent diagnostic value

and agreement with invasive coronary angiography [61]. The setup, however, poses many technical challenges and is currently limited to a few research centers.

Integrated PET/MR system offers a perfect union of two modalities evaluating myocardial metabolism and scar assessment in a single imaging study. Recent studies show good agreement between PET and MRI. A combined viability assessment with PET and MRI may improve diagnostic accuracy and correct for overestimation of the scar by LGE imaging alone [62, 63]. Although very promising, this technique is largely restricted to clinical and animal model research and access to the necessary equipment is not widely available in routine clinical practice.

Conclusion

Recent advances in myocardial stress perfusion and viability assessment either by CT, PET, and MRI are progressing towards offering a comprehensive assessment of ischemia in a single imaging test. Technical advances are facilitating improved image quality and focusing on artifact reduction as well as radiation dose reduction for CT and PET and decreased scan time for MRI. Many prospective studies are currently underway in all the three modalities. These studies will eventually improve our understanding of myocardial ischemia and viability and influence clinical decisions in the near future.

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Opinion statement

Non-invasive stress testing plays a key role in diagnosis and risk stratification in patients with coronary artery disease. Technical advances in CT, MRI, and PET have lead to increased utility of these modalities in myocardial perfusion imaging. The aim of the review is to provide a succinct update on CT, PET, and MRI for myocardial stress perfusion imaging.

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Fig. 1.

CT perfusion images at stress (**a**) and at rest (**b**) demonstrate a focal perfusion defect (*arrows*) in the basal inferior wall more apparent on stress imaging. Maximum intensity projection reformat from the rest scan of the right coronary artery (**c**) shows a subtotal occlusion of the proximal right coronary artery secondary to non-calcified plaque. On subsequent invasive coronary angiography (**d**) 4 days later, there was a corresponding subtotal occlusion of the proximal right coronary artery. Myocardial stress positron emission tomography correlated with invasive coronary angiography. **e** Myocardial stress positron emission tomography with N-13 ammonia demonstrates a small region of non-transmural scar with a medium-sized region of moderate stress-induced ischemia in the distribution of the proximal left circumflex and posterior descending arteries (*yellow arrows*) and a small area of moderate diagonal artery ischemia (*white arrow*). Invasive coronary angiography images show (**f**) an occluded proximal left circumflex (*yellow arrow*) and severely stenosed diagonal artery (*black arrow*) and (**g**) an occluded proximal right coronary artery. Stress and rest myocardial perfusion cardiac MRI (**h**, **i**) in a 75-year-old man with prior history of revascularization by coronary artery bypass graft (CABG) presetting with stable angina showing a stress perfusion deficit in the basal inferior and inferoseptal segments (**h**). The rest perfusion was unremarkable (**i**). Patient underwent invasive coronary angiography which

showed severe stenosis in the proximal RCA and moderate stenosis in the mid RCA (**j**) both successfully treated by drug-eluting stents (**k**).

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