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Advances in stress cardiac MRI and computed tomography

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Abstract

Stress cardiac MRI and stress computed tomography (CT) perfusion are relatively new, noninvasive cardiovascular stress-testing modalities. Both of these tests have undergone rapid technical improvements. Data from randomized controlled trials in stress cardiac MRI are becoming gradually incorporated into cardiovascular clinical practice, not only to assess physiological significance of coronary artery disease, but also to provide prognostic information. As CT perfusion protocols become more uniform with adequate handling of artifacts and decreasing radiation exposure with combined CT coronary angiography/CT perfusion imaging, it has the potential to become a comprehensive diagnostic test.

Keywords

cardiac computed tomography; cardiac MRI; coronary angiography; fractional flow reserve; perfusion; quantitative; stress

Invasive coronary angiography (ICA) has traditionally been used to confirm the presence of epicardial coronary artery disease (CAD), leading to intervention on 'significant' coronary stenoses. An ongoing need exists for improved accuracy of noninvasive tests for the identification of CAD.

Although much of the focus has been on anatomic imaging, an accurate assessment of the physiological significance of coronary lesions may be even more critical [1,2]. Fractional flow reserve (FFR) is often used in the cardiac catheterization laboratory for this purpose. Current guidelines recommend the performance of noninvasive stress testing in patients presenting with stable angina pectoris to assist in the decision-making process [3]. Treadmill exercise stress testing is commonly used, either alone or in combination with nuclear stress testing or echocardiography. In patients who cannot exercise, nuclear imaging or echocardiography with pharmacologic techniques (i.e., dobutamine or vasodilators) is typically performed.

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In addition to these more commonly utilized methods, several new modalities are now becoming more frequently used; PET myocardial perfusion imaging, stress cardiac MRI (CMR) and stress cardiac computed tomography (CT), the latter only in research studies at present. More data are accruing as to their clinical effectiveness in patients with suspected CAD.

In this review, our goal is to examine recent advances in stress CMR and CT.

Recent advances in stress CMR

CMR is most commonly performed using a vasodilator stress agent: adenosine or regadenosone. Dobutamine is used less frequently for stress functional studies. MRI-compatible treadmills are currently under development for exercise stress in the CMR environment [4]. For research, stationary recumbent bicycles and isometric exercise have also been used as physiologic stress agents.

Stress CMR for detection of CAD

Comprehensive stress CMR includes assessment of biventricular size and function, resting myocardial perfusion, wall motion analysis at rest and stress, stress-induced myocardial perfusion and late gadolinium enhancement for scar and viability. Stress CMR can be performed by using dobutamine as the stress agent to detect regional wall motion abnormalities [5,6] and/or by using a vasodilator agent to detect perfusion abnormalities during first-pass contrast enhancement of the myocardium (Figure 1).

Review of data over the past several years reveals the following additions to our current knowledge.

Dobutamine stress CMR

A meta-analysis was published in 2007 on 14 dobutamine stress CMR studies, which included 754 patients [7]. The prevalence of CAD in this population was 70.5%. Final analysis was performed on 13 studies with 735 patients, using ICA significant coronary stenosis (varying from 50 to >75% in different studies) as the gold standard. On a per-patient-based analysis, dobutamine stress CMR-induced wall motion abnormalities were found to have a sensitivity of 83% (95% CI: 79–88), specificity of 86% (95% CI: 81–91), positive likelihood ratio of 5.24 (95% CI: 3.28–7.21) and negative likelihood ratio of 0.19 (95% CI: 0.15–0.24).

With the development of innovative pulse sequences, it is possible to perform rapid acquisition of first-pass perfusion images at the higher heart rates seen during dobutamine infusion. Studies have thus looked at combining perfusion imaging with wall motion analysis on dobutamine stress CMR. In 455 patients, Gebker *et al.* demonstrated that by combining the two, sensitivity can be increased from 85 to 91% ($p = 0.001$) [8]. However, the specificity decreased from 82 to 70% ($p = 0.001$) without affecting overall accuracy (84% in both scenarios). Falcão *et al.* addressed the same question in 42 patients [9]. In this group, the sensitivity of CMR combining perfusion with wall motion analysis increased from 80 to 92%, with no difference in specificity (82%). The accuracy of stress CMR was 88% in the combined wall motion and perfusion analysis.

Vasodilator stress CMR

Recent clinical studies—The meta-analysis by Nandalur *et al.* examined 24 vasodilator stress CMR studies performed on 1516 patients [7]. After exclusion of 50 patients with unsuccessful CMR, 14 datasets on 11,183 patients were used for final analysis. The

prevalence of CAD in this population was 57.4%. Using ICA significant coronary stenosis (varying from 50 to >75% in different studies) as the reference standard, the sensitivity and specificity of stress CMR was 91% (95% CI: 88–94%) and 81% (95% CI: 77–85%), respectively, while the positive likelihood ratio and negative likelihood ratio were 5.10 (95% CI: 3.92–6.28) and 0.11 (95% CI: 0.07–0.15), respectively.

Since the publication of this meta-analysis, multicenter randomized controlled trials using vasodilator stress CMR have been published. The MR-IMPACT trial of 241 patients from 18 centers compared single-photon emission CT (SPECT) and adenosine stress CMR at 1.5 T using ICA (>50% stenosis) as the gold standard [10]. Patients with decompensated heart failure, prior coronary artery bypass surgery and significant arrhythmias were excluded from the analysis. A 16-segment model (excluding the apical cap) was used for CMR perfusion analysis. The area under the receiver operator characteristics curve for CMR was greater than with SPECT (CMR vs SPECT: 0.86 ± 0.06 vs 0.67 ± 0.5 ; $p = 0.013$). However, gated SPECT data was not available in half of the patients. The area under the curve (AUC) for stress CMR versus gated SPECT was not statistically different (CMR vs gated SPECT: 0.86 ± 0.06 vs 0.75 ± 0.08 ; $p = 0.18$). When multivessel CAD patients were analyzed separately, CMR outperformed SPECT with AUCs of 0.89 ± 0.06 versus 0.70 ± 0.5 ; $p = 0.006$.

A landmark prospective study (the CE-MARC trial) was published in 2012 [11]. This study included 752 patients with suspected angina and at least one cardiovascular risk factor, and excluded patients with prior bypass surgery. The prevalence of significant CAD was 39%. Adenosine stress CMR was compared with gated SPECT in all patients and ICA (>70% stenosis or left main disease) was used as the gold standard. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CMR versus SPECT was 86.5 versus 66.5%; 83 versus 83%; 77 versus 71% and 90.5 versus 79%, respectively. The sensitivity and NPV of CMR was higher compared with SPECT ($p < 0.001$), while specificity and PPV were similar ($p > 0.05$). This study revealed superior diagnostic accuracy of stress CMR over SPECT. This study has been criticized due to its single-center nature and lower accuracy of SPECT compared with prior publications.

The MR-IMPACT II study was recently published, with a similar comparison in 533 patients from 33 centers with a 49% prevalence of CAD [12]. This study revealed higher sensitivity of CMR versus SPECT; that is, 67 versus 59%. However, a lower specificity of CMR versus SPECT was noted; that is, 61 versus 72%. This study has confirmed noninferior performance of stress CMR in a realistic clinical environment.

It has been increasingly recognized that using ICA as the gold standard has its limitations. Hence, the physiologic standard, FFR, is now increasingly utilized as the gold standard for invasive and noninvasive studies. Bettencourt *et al.* performed adenosine stress CMR and ICA, along with assessment of FFR, on 103 consecutive symptomatic patients with suspected CAD [13]. These patients were at intermediate or high risk of CAD. The FFR cut-off for significant CAD was <0.80 . The sensitivity, specificity, PPV, NPV and accuracy of CMR on per-patient analysis was 89, 88, 85, 91 and 88%, respectively. The MR-INFORM study, aimed at comparing medical treatment versus coronary intervention in patients with stable CAD, is currently in progress [14]. In this study, adenosine stress CMR-based coronary intervention will be performed compared with FFR-based coronary intervention, and major adverse cardiac events (MACEs) over 1 year will be analyzed as the final end point.

Recent technical advances—Adenosine stress CMR perfusion imaging at 1.5 T is well established. However, the potential superiority of imaging at 3 T has recently been tested. Manka *et al.* studied 146 patients with known or suspected CAD with adenosine stress CMR

[15]. In comparison with ICA coronary stenosis (50%), the sensitivity, specificity and accuracy of 3T CMR perfusion was 92, 74 and 83%, respectively.

To build on the above results, Walcher *et al.* [16] performed adenosine stress CMR on both 1.5 T and 3 T scanners on 52 patients and compared the results with ICA. The sensitivity of 3 versus 1.5 T was 90 versus 84%, with a similar specificity of 75 for 50% stenosis. When using >70% stenosis as the reference standard, the sensitivity and specificity of a 3 versus 1.5 T scanner was 88 and 96% versus 80 and 89%, respectively (Figure 2). The authors concluded that 3 T might become the preferred CMR field strength for adenosine stress CMR in clinical practice.

Whole-heart coverage with 3D CMR is another recent technical advance. Jogiya *et al.* examined the agreement of 3D whole-heart CMR at 3 T with FFR in 53 patients with 64% prevalence of CAD [17]. A total of 45% of the vessels had 50% stenosis on cardiac catheterization. Amongst them, 61% had FFR <0.75. The mean FFR in vessels reported positive versus negative for ischemia by CMR was 0.61 versus 0.82, respectively (Figure 3). When whole-heart perfusion was used, per-vessel sensitivity, specificity, accuracy and AUC of stress CMR with FFR as the gold standard was 78, 92, 88 and 0.88%, respectively. The same values for traditional three-slice CMR perfusion were 74, 88, 84 and 0.81%, respectively, which was not statistically different from the whole-heart analysis. Technical development continues and new methods may offer reduced artifacts and increased spatial coverage, but specific techniques are too numerous to list here.

Quantitative perfusion analysis—Myocardial flow reserve (MFR) or perfusion reserve (PR), which is indicative of increased myocardial flow at stress compared with rest, has been well studied using cardiac PET scan (¹³N-ammonia [18] as well as ⁸²Rb [19] isotopes). Abnormal global MFR in patients with suspected CAD has been shown to be independently associated with higher rates of MACEs and cardiac death over 3 years [19]. It is also a predictor of multivessel CAD and provides incremental information on the qualitative perfusion data [20], and in diabetics without CAD [21], is a predictor of cardiac death.

Similarly, quantitative CMR perfusion has been developed over recent years. Patel *et al.* showed that, in 30 patients, PR decreased in a stepwise manner, with an increase in coronary artery stenosis from <50 to 50–70% and >70% [22]. They also showed that patients with triple-vessel CAD had a higher burden of ischemia detected by a decrease in MFR rather than visual analysis, whereas visual analysis was performed equally in patients with single-vessel disease (Figure 4). Morton *et al.* compared CMR (adenosine stress) with PET (¹³N-ammonia) with regard to assessment of MFR in 41 patients [23]. The absolute MFR values correlated significantly but weakly between the two modalities both at rest ($r = 0.32$; $p = 0.002$) and under stress ($r = 0.37$; $p < 0.0001$). When ICA was used as the gold standard, both PET and CMR had similar AUCs (0.83) and sensitivity (82%), while the specificity for PET versus CMR was 87 versus 81%, respectively. It was concluded that further refinements in CMR quantitative perfusion are required due to differences in voxel size, acquisition methods, postprocessing methods, misregistration artifacts and partial volume effects.

In a recent study, Bhawe *et al.* performed regadenoson-induced stress–rest vasodilator stress CMR to assess MFR. MFR was underestimated due to longer half life of regadenoson and the resting images represented partially reversed vasodilatory effect instead of true resting myocardial perfusion [24].

Fast and nearly automatic techniques are in development to quantify myocardial perfusion both at rest and under stress. Tarroni *et al.* used a technique that required <1 min to analyze

each image sequence along with generation of high-quality contrast-enhancement curves [25]. At rest and stress, the mean signal:noise ratio was 17 ± 7 and 22 ± 8 , respectively, and very high correlation ($r =$ up to 0.94) of automated perfusion indices with manual analysis (AUC: 0.72 vs 0.73, respectively) was reported (Figures).

Prognostic utility—In low-to-intermediate-risk patients suspected of CAD, stress testing can be used as a tool to assist with diagnosis of CAD, as well as to provide prognostic data. The prognostic value of nuclear myocardial perfusion imaging is well established, with an annual MACE rate of approximately 1% with a negative scan [26]. Similar prognostic information is also noted with dobutamine stress echocardiography [27] and coronary CT angiographic anatomic assessment of CAD [28].

The prognostic information of a negative-stress CMR has also been studied [29]. Janhke *et al.* examined the prognostic value of a negative dobutamine test, as well as vasodilator stress CMR, in 513 patients [30]. Three-year event-free survival was 99.2% in the presence of a negative CMR stress examination. Buckert *et al.* followed 1229 patients with stable angina, who had adenosine stress CMR performed at 1.5 T [31]. The mean follow-up period was 4.2 ± 2.1 years. A significantly increased risk of cardiac death ($p < 0.0001$) and nonfatal myocardial infarction ($p = 0.001$) was seen in patients with reversible perfusion defects. In the absence of reversible perfusion defects, the 5-year survival of the patients was 95.6%. In another study performed by Bertaso *et al.* in 362 patients followed-up for approximately 2 years (inclusive of patients with known CAD), the rate of composite MACEs was 24% in the presence of ischemia versus 2.7% in the absence of ischemia [32]. NPV of a normal CMR from MACEs was 97.3%. Similar information was obtained using dipyridamole as the stress agent in 1722 patients by Bodi *et al.*, who noted an event rate of 2% over median follow-up of 308 days in the presence of a normal scan [33]. Our group has performed a meta-analysis on the prognostic value of stress CMR on 19 studies inclusive of 11,636 patients, demonstrating that a positive-stress CMR is associated with a significantly greater risk of cardiovascular death, myocardial infarction and the combined outcome compared with patients with no evidence of ischemia [34].

Recent advances in cardiac CT

Noncontrast cardiac CT for the assessment of coronary artery calcium has established itself as a powerful tool for risk-stratifying patients for CAD, as well as for predicting prognosis [35]. CT coronary angiography (CTA) is often used to evaluate for anatomic epicardial CAD in symptomatic patients at intermediate risk (American College of Cardiology/American Heart Association appropriateness criteria [36]), particularly those presenting to the emergency department [37,38]. CTA, in multicenter randomized controlled trials [39,40], is shown to have a very high sensitivity (77–100%) and a NPV (98–100%). Cardiac CT scanners are constantly being technically improved. The number of detector rows has geometrically increased over recent years to 320, and dual-source cardiac CT is now available for clinical use.

However, CTA is limited by low specificity (54–83%) and PPV (64–87%) [40,41]. Calcium in atherosclerotic coronary arteries causes blooming artifacts and partial volume effects [41,42], leading to the overestimation of the degree of stenosis. This, in turn, leads to further downstream invasive or noninvasive testing, which may lead to increased cost and radiation exposure to the patient. Over the past few years, efforts have been invested in performing rest and stress perfusion imaging at the time of CTA, thus gathering information with regard to both coronary anatomy and physiology in a single examination.

CT stress perfusion imaging is presently in its developmental and initial application stages. The protocols are not yet uniform, as different CT scanners differ in their performance. Myocardial contrast enhancement variation is often seen with 'step and shoot' CT protocols. Cardiac CT perfusion analysis is also prone to intra- and inter-observer differences, as it is dependent on reader expertise. The reference modalities to assess for accuracy of CT stress perfusion have varied in different clinical trials. Data regarding its cost-effectiveness, effects of long-term radiation and follow-up clinical outcomes remain lacking. Additionally, β -blockers and nitroglycerin used in exercise and dobutamine stress tests have been shown to mask perfusion defects [43]. However, they are commonly used during CTA to prevent motion artifacts with heart rates >65 bpm. The effect of β -blockers on vasodilator perfusion imaging is being tested, but the results are so far inconclusive [44]. Most CT perfusion studies have been performed using adenosine; however, a multicenter study testing the accuracy of regadenoson in CT perfusion is underway [101].

Diagnostic performance of stress perfusion CT

Tashakkor *et al.* published a systematic review on 13 studies of stress CT, published through November 2011 [45]. The CT scanners used for perfusion analysis consisted of 16–320 detector rows. Using invasive angiography (definition of significant stenosis varying from 50 to 75%) [46–48] as the gold standard: the total calculated sensitivity, specificity, PPV and NPV of CT perfusion was 94, 59, 81 and 84%, respectively (per-patient analysis), and 84, 73, 69, and 86%, respectively (per-vessel analysis). Amongst various studies that had looked at both CT and SPECT perfusion against ICA, the authors compared CT perfusion (without incorporating CTA results) with SPECT perfusion [49–51]. The total calculated sensitivity, specificity, PPV and NPV of CT perfusion was 87, 69, 72 and 83%, respectively (per-vessel analysis), and 87, 82, 76 and 89%, respectively (per-segment analysis).

The results of studies comparing CT perfusion with CMR perfusion are presented in Table 1 [52–54]. However, with regard to quality of image comparison [54], relatively more CTA images were classified as poor or moderate in quality compared with CMR. Only one study with CT perfusion was of excellent image quality versus 22 with CMR.

There are only a few studies that have used combined CTA/CT perfusion as the noninvasive test and compared it against a gold standard. George *et al.* used CTA (>50% stenosis) combined with SPECT perfusion as the reference standard and found the per-patient sensitivity, specificity, PPV and NPV of combined CTA and CT perfusion to be 86, 92, 92 and 85%, respectively (per-patient analysis) and 79, 91, 75 and 93%, respectively (per-vessel analysis) [55]. Rocha-Filho *et al.* used ICA coronary stenosis (>50%) as the reference standard and did not find improved sensitivity of combined CTA and CT perfusion study [56]. However, a significantly improved specificity, PPV and PVV of the combined test was evident on per-vessel analysis (Figure 6).

Studies are increasingly using a combination of ICA stenosis and FFR as a gold standard (Table 2 & Figure 7) [57–59]. These studies indicate that the presence of perfusion defects in the myocardium subtended by a coronary artery with >50% stenosis on CTA, have significantly increased specificity for the detection of hemodynamically significant stenosis on ICA.

Results with latest-generation CT scanners

CT cardiac perfusion has been performed using 64-detector [56,57,60], 128-detector [53,61] and 256-detector row scanners [62]. In <320-detector row scanners, imaging of the heart is accomplished by acquiring images over several heart beats. This can lead to misregistration artifacts with a potential overestimation of degree of stenosis. Also, imaging different

sections of the heart at different times makes it difficult to draw perfusion curves for quantitative analysis. However, qualitative assessment of perfusion can be performed. A 320-detector row scanner allows complete cranio-caudal coverage in a single heartbeat and also allows temporal contrast uniformity during the first pass of contrast medium, with lower radiation exposure to the patient. However, 320-detector row scanners are limited by lower temporal resolution.

Ko *et al.* published the first study on 320-detector row scanners in high-risk patients, comparing combined CTA/CT perfusion against ICA with FFR [54]. The AUC for accuracy was 0.67. The total radiation dose was 11.3 mSv. Gervaise *et al.* compared 320-CT perfusion with SPECT and found the AUC for accuracy to be 0.92 [63]. The total radiation dose was 13.8 mSv. Recently, Nasis *et al.* compared CT perfusion in 20 patients with SPECT and ICA, and found that combining CTA with CT perfusion significantly increased the PPV of the test [64]. The sensitivity, specificity, PPV, NPV and AUC for combining CT coronary angiography with CT perfusion was 94, 98, 94, 98 and 0.96% ($p < 0.001$), respectively, on a per-vessel/territory basis versus 100, 84, 71, 100 and 0.92%, respectively, for CTA alone. Mean radiation dose from the combined CT scan was 9.2 ± 7.4 mSv (separately for CTA: 4.4 ± 3.5 and CT perfusion 4.8 ± 3.9), compared with 13.2 ± 2.2 mSv for SPECT ($p < 0.001$). The results of the CORE-320 study, a large multi-center study of 320-detector row scanners, are eagerly awaited [65,66].

Dual-source CT (DSCT) scanners have a better temporal resolution (~83 ms), but reduced z-axis coverage [67]. DSCT can be performed in a dynamic mode as well as in a high-pitched spiral mode. Bamberg *et al.* performed a feasibility study in 33 patients with dynamic stress perfusion acquired over 30 s using a second-generation DSCT scanner, compared with invasive angiography and FFR < 0.75 [68]. They found an increased PPV of CTA combined with CT perfusion versus CTA alone from 49 to 78%. The main limitations included a relatively high radiation exposure; that is, 12–13 mSv, despite skipping the rest perfusion scan to minimize radiation exposure, and in a third of their patients, only partial coverage of the heart was obtained [68]. Feuchtnner *et al.* performed DSCT in a spiral mode at high pitch or using prospective gating. These techniques decreased the radiation exposure to 2.5 mSv in combined CTA, CT perfusion imaging. The accuracy (for detection of $> 70\%$ stenosis on ICA) of combined CTA, CT perfusion was 95% as compared with 84% in the CTA only imaging [53]. Using stress CMR as the gold standard, the AUC for CT perfusion was 0.82 on per-segment and 0.93 on per-vessel analysis.

For optimal analysis of rest and stress CT perfusion images, studies have suggested use of thick slices (3–8 mm) with minimum intensity projection settings. The window and level setting have been suggested to be optimized for myocardial assessment; that is, using a narrow window width of approximately 100–200 HU, centered at a window level of approximately 100 HU [69].

Radiation exposure with stress CT perfusion

Radiation exposure during stress CT imaging has ranged from 2.5–22 mSv. Stress cardiac CT can be performed using either retrospective or prospective ECG triggering. The benefit of retrospective gating is the ability to assess myocardial perfusion through different phases of the cardiac cycle, perform quantitative perfusion analysis and assess wall motion abnormalities and ejection fraction; however, at the cost of higher radiation exposure. Kim *et al.* performed a study on 330 patients, comparing the radiation dose and image quality of three different stress–rest CT protocols on a 128-detector row DSCT scanner [70]. In the first protocol, retrospective ECG gating with a tube current modulation (TCM) was performed with the total duration of scan of 30 s. In the second, a 30-s scan with retrospective ECG gating but ‘on’ automatic TCM was performed. In the third, a 14-s scan

with 'on' automatic TCM was implemented. Diagnostic image quality was obtained with all three protocols. However, the mean radiation doses associated with protocols I, II and III were 12.1 ± 1.6 mSv, 7.7 ± 2.5 mSv and 3.8 ± 1.3 mSv, respectively ($p < 0.01$). In the prospective ECG scans, 'padding' (i.e., widening the window to incorporate 3–4 phases of cardiac cycle) can be performed to get more information, but still minimizing radiation exposure to the patient [70]. Blankstein *et al.* used a DSCT scanner for perfusion analysis using retrospective ECG gating, with a radiation dose of 21.6 mSv [71].

Variations in stress CT protocols

In stress CT perfusion imaging, either the stress or rest scan can be performed first. Usually, a 20–30-min waiting period is used between the two scans to prevent contamination with residual iodine contrast in the myocardium. If stress imaging is performed first and found to be abnormal, residual contrast on resting images can lead to underestimation of ischemia. Vice versa, if resting imaging performed first is normal, residual contrast in the stress images can lead to overestimation of ischemia. If the resting scan is abnormal, residual contrast in the stress images can lead to underestimation of ischemia. In addition, if the resting study is performed first and β -blockers and nitrates are used for the CTA portion of the test, interference with the accuracy of myocardial perfusion may occur [72]. It has been postulated that if the stress portion of CT is performed first in patients with high risk of CAD, for example, in patients with known CAD or higher calcium scores, the presence of normal stress scan can preclude the necessity of performance of a resting scan. An optional delayed scan (10 min after the second acquisition) can also be performed on stress CT, similar to stress CMR, to assess for late contrast enhancement, which indicates acute infarction or chronic scar/fibrosis, although its contrast:noise ratio is limited [73].

Dual-energy CT scanners

A great deal of research is currently being performed on dual-energy CT scans (DE CT). In a conventional CT scan, x-ray signal is generated over a wide-energy spectrum. In DE CT, images corresponding to individual x-ray photons emitting from various regions of the heart can be generated [74], allowing better tissue characterization and more accurate measurement of contrast, leading to more meticulous assessment of perfusion abnormalities [75]. Thus, DE CT has significant utility in myocardial perfusion analysis, both at stress and rest [76]. Beam-hardening artifacts that arise from the polyenergetic x-ray photons can also be reduced with DE CT [77].

DE CT can be performed on a dual-source scanner (Definition Flash; Siemens Healthcare, Erlangen, Germany) [78] on a single x-ray tube capable of rapidly switching between the low (80 kV) and high (140 kV) tube potentials (Discovery CT750 HD scanner; GE Healthcare, WI, USA) [79] on a single x-ray tube with dual layer (Philips prototype) [80], or in a single x-ray tube, switching the tube potential between gantry rotations so that the images are performed at different levels during different gantry rotations (Aquilion ONE; Toshiba America Medical Systems, CA, USA).

Ko *et al.* performed DE CT on a DSCT scanner in which one tube of the DSCT was operated with 82 mAs/rotation at 140 kV, and the second tube with 164 mAs/rotation at 80 kV [81]. In the 50 patients studied, Stress DE CT had 89% sensitivity, 78% specificity and 82% accuracy for detecting segments with reversible perfusion defects seen on stress CMR. Compared with CTA, stress DE CT had 89% sensitivity, 76% specificity and 83% accuracy for the detection of reversible perfusion defects in segments with significant CAD [52]. The same group looked at the incremental value of combining DE CT perfusion with CTA to detect anatomic CAD on invasive angiography (> 50% stenosis) [81]. They found that the sensitivity, specificity, PPV and NPV of CTA after combining DE CT increased from 92,

68, 74 and 87%, respectively to 93, 85, 88 and 91%, respectively. The AUC significantly increased from 0.79 to 0.89.

In ten patients in whom DE CT stress perfusion was performed, Nagao *et al.* calculated the coronary enhancement ratio by dividing the mean attenuation in the coronary artery by attenuation in the aortic root and found that use of coronary enhancement ratio on the iodine map separated myocardial segments with and without >50% stenosis on coronary CTA, with a sensitivity and specificity of 86 and 75%, respectively [82]. Weininger *et al.* studied 20 consecutive patients who presented with chest pain and noted that using CMR as the gold standard, DE CT perfusion (vs SPECT) had 93% (94%) sensitivity, 99% (98%) specificity, 92% (88%) PPV and 96% (94%) NPV for detecting hypoperfused myocardial segments [83].

Quantitative perfusion by CT

When stress CT is performed using retrospective ECG gating, quantitative analysis of perfusion in the left ventricular myocardium is possible. Tissue attenuation curves can be constructed in different myocardial segments relative to those in the aorta to measure blood flow/g of myocardium. Iodine in the contrast agent is an intravascular agent, which rapidly redistributes from the vascular to myocardial interstitial space. This distribution is a flow-limited process and leads to contrast enhancement of the myocardium during CT perfusion imaging, which, in turn, leads to absorption of x-rays based on the amount of iodine [84]. CT stress myocardial perfusion can be performed quantitatively and semi-quantitatively based on how the images are acquired [85].

Quantitative myocardial perfusion analysis has been reported using DSCT scanners. Ho *et al.* reported myocardial blood flow (ml/100 ml/min) of the normal myocardium at stress and rest to be 121 ± 31 and 82 ± 22 , respectively [50]. In fixed defects, myocardial blood flow was 57 ± 22 and 54 ± 23 at stress and rest, respectively [50]. According to Bamberg *et al.*, myocardial blood flow was 73.2 ± 26 and 104.8 ± 34 in segments with and without significant coronary artery stenosis on stress imaging, respectively [57]. Nakauchi *et al.* reported infarcted myocardial blood flows to be 52 ± 19 ml/100 ml/min [86]. Kim *et al.* studied 26 patients with at least one >50% stenosis on CTA. The blood flow (ml/100 ml/min) in normal versus abnormal myocardium in protocols I and II were 121.5 ± 25.9 versus 49.7 ± 13.4 , respectively, and 126.1 ± 16.4 versus 46.3 ± 6.2 ml/100 ml/min, respectively [70].

Conclusion & future perspective

Current decision-making about the significance of a coronary artery lesion that is based solely on anatomic imaging in the cardiac catheterization laboratory has been recently challenged [87]. Therefore, the accurate noninvasive assessment of the physiological significance of coronary artery stenosis is increasingly important. While traditional pharmacologic stress testing with echocardiography and SPECT is still common, rapid development in newer stress testing modalities with much higher spatial resolution, such as CMR and CT, are looked upon as methods to more accurately assess the significance of CAD outside the cardiac catheterization laboratory.

Multicentered randomized controlled trials, have established stress CMR to be noninferior and even more accurate than SPECT for CAD assessment. Additionally, it is now also utilized for assessing prognosis and risk of future MACEs in intermediate-to-high-risk patients. Ongoing studies are assessing the superiority of 3 T CMR scanners in perfusion assessment, as well as the effectiveness of quantitative myocardial PR assessment. The

future appears to be very promising with regard to technological innovation in CMR, resulting in reduced image acquisition time, automated analysis and decreased artifacts.

Stress CT perfusion is also under rapid development as it relates to accurate assessment of perfusion abnormalities, the use of detectors with wide coverage, single heart beat imaging and dual-energy CT. As the accuracy of perfusion CT imaging improves with regard to the uniformity of protocols and less inter- and intra-reader variability, and the required radiation dose decreases, it has the potential to become the primary method for the assessment of both coronary anatomy and physiology.

The results of two large studies: MR-INFORM study (using stress CMR) [88] and CORE-320 study (using CT and CT stress perfusion) [64,65] are eagerly awaited to understand where these modalities fit into everyday clinical cardiovascular care.

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Executive summary

Stress cardiac MRI

- Stress cardiac MRI (CMR) for the detection of coronary artery disease
 - Stress CMR imaging has emerged as a useful tool in functional cardiac imaging as well as in the assessment of physiologic significance of coronary artery disease in symptomatic intermediate-to-high risk patients.
- Methods of performing stress CMR
 - Stress CMR can be performed using dobutamine to assess for wall motion abnormalities and by using vasodilator agents to assess for myocardial perfusion abnormalities.
- Prognostic utility of stress CMR
 - Stress CMR can be used to obtain prognostic information. A normal stress CMR scan can provide reassurance to the patients in regards to future cardiovascular events.
- Stress CMR quantitative perfusion analysis
 - CMR is increasingly been used to assess quantitative myocardial flow and to calculate myocardial flow reserve. Myocardial flow reserve provides added information about the severity of coronary artery disease, microvascular dysfunction and helps predict major adverse cardiac events.

Stress cardiac computed tomography

- Diagnostic performance of stress perfusion computed tomography (CT)
 - The potential of cardiac CT to perform stress perfusion along with anatomical coronary artery imaging is very attractive. However, CT coronary angiography-stress/rest perfusion protocols need further improvements to address its limitations including:
 - Artifacts such as beam hardening, partial volume effects, misregistration and motion artifacts;
 - Protocol non-uniformity;
 - Radiation exposure.
- Potential of latest generation CT scanners
 - Latest generation scanners include multiple detector row scanners which allow complete cardiac coverage in one heartbeat, and scanners with dual source and dual energy CT capabilities. These scanners offer the potential to decrease radiation exposure and enhance image quality by improving temporal and spatial resolution.
- Radiation exposure with stress CT perfusion
 - Radiation exposure is a major limitation of performing rest/stress CT along with CT coronary angiography. This exposure is

however progressively decreasing with the latest scanners and with altering imaging techniques.

- Dual-energy CT scanners
 - Dual-energy CT has the potential for accurate myocardial tissue assessment. This technology needs further development.
- Quantitative perfusion by CT
 - Quantitative perfusion analysis on CT can be used to assess myocardial flow reserve. Research in this area remains preliminary.

Figure 1. Qualitative interpretation of cardiac magnetic resonance perfusion imaging
(A) Top row shows adenosine stress images, while the (B) bottom row shows rest images (left column: basal left ventricle; middle column: mid left ventricle; right column: apical left ventricle). The white arrows point to a large perfusion defect in the anterolateral, inferolateral, inferior and inferoseptal wall, extending from the basal to the apical slice. Adapted with permission from [22].

Figure 2. Comparison of stress cardiac magnetic resonance perfusion analysis with 1.5 versus 3 T scanners, with invasive coronary angiogram as gold standard

(A) Threshold of 50% stenosis. **(B)** Threshold of 70% stenosis. LGE: Late gadolinium enhancement.

Adapted with permission from [16].

Figure 3. Relationship between 3D whole-heart stress cardiac magnetic resonance with fractional flow reserve

Dotted line represents mean fractional flow reserve: 0.82 (normal CMR) versus 0.61 (abnormal CMR).

CMR: Cardiac MRI.

Adapted with permission from [17].

Figure 4. Quantitative perfusion analysis on stress cardiac magnetic resonance
(A) Relationship between perfusion reserve and percentage stenosis on cardiac catheterization. **(B)** Comparison of qualitative perfusion analysis with perfusion reserve to assess degree of ischemia in single and multivessel coronary artery disease. 1V: Single vessel; 3V: Three vessel; CAD: Coronary artery disease; LV: Left ventricle. Adapted with permission from [22].

Figure 5. Comparison of automatically generated contrast enhancement curves with manual tracing

Stress-induced perfusion abnormality is noted in the inferior and lateral walls. Manual tracing resulted in virtually identical curves both (A) at rest (top row) and (B) stress (bottom row).

Adapted with permission from [25].

Figure 6. Dynamic computed tomography perfusion in a patient with a history of coronary artery bypass graft
(A) Nearly transmural perfusion defect in the inferior wall. **(B)** Time attenuation curves demonstrate attenuation in the inferior walls to be lower compared with other segments. Adapted with permission from [70].

Figure 7. Comparison of cardiovascular computed tomography angiography/computed tomography perfusion with conventional coronary angiography/fractional flow reserve as gold standard (n per vessel)

CCA: Conventional coronary angiography; CCTA: Cardiovascular computed tomography angiography; CTP: Computed tomography perfusion; FFR: Fractional flow reserve.

Adapted with permission from [45].

Studies comparing computed tomography perfusion with cardiac magnetic resonance perfusion (per-vessel analysis)

Table 1

Study (year)	Type of study	Patients (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Ref.
<i>Using stress CMR as gold standard</i>							
Ko <i>et al.</i> (2011)	CT perfusion	55	91	72	82	88	[54]
Feuchtnet <i>et al.</i> (2011)	CT perfusion	39	96	88	93	94	[53]
<i>Using ICA stenosis or FFR as gold standard</i>							
Bettencourt <i>et al.</i> (2013)	CTA 50% + CT perfusion	101	71	90	68	93	[59]
	Stress CMR		79	93	79	85	

CMR: Cardiac MRI; CT: Computed tomography; CTA: Computed tomography angiography; FFR: Fractional flow reserve; ICA: Invasive coronary angiography; PPV: Positive predictive value; NPV: Negative predictive value.

Table 2

Studies using invasive coronary angiogram stenosis plus fractional flow reserve as gold standard (per-vessel analysis).

Study (year)	Type of study	Patients (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Ref.
Bamberg <i>et al.</i> (2011)	CTA 50%	33	100	51	47	100	[57]
	CTA 50% + CT perfusion		93	87	75	97	
Ko <i>et al.</i> (2012)	CTA 50%	42	93	60	68	90	[58]
	CTA 50% + CT perfusion		68	98	97	77	
Bettencourt <i>et al.</i> (2013)	CTA 50%	101	95	67	48	97	[59]
	CTA 50% + CT perfusion		71	90	68	91	

CTA: Computed tomography angiography; CT: Computed tomography; PPV: Positive predictive value; NPV: Negative predictive value.