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Pharmacological Stress Cardiovascular Magnetic Resonance

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Abstract

Over the past decade, cardiovascular magnetic resonance (CMR) has evolved into a cardiac stress testing modality that can be used to diagnose myocardial ischemia using intravenous dobutamine or vasodilator perfusion agents such as adenosine or dipyridamole. Because CMR produces high-resolution tomographic images of the human heart in multiple imaging planes, it has become a highly attractive noninvasive testing modality for those suspected of having myocardial ischemia. The purpose of this article is to review the clinical, diagnostic, and prognostic utility of stress CMR testing for patients with (or suspected of having) coronary artery disease.

Keywords

stress CMR; dobutamine; adenosine; myocardial ischemia

Introduction

Noninvasive imaging modalities are used to evaluate patients with (or suspected of having) cardiovascular (CV) disease. Cardiovascular magnetic resonance (CMR) is a relatively unique imaging modality in that it can be used to depict left ventricular (LV) wall motion and myocardial perfusion with high spatial resolution in virtually any imaging plane without exposure to ionizing radiation.^{1–5} Stress CMR tests may incorporate assessments of either LV wall motion and/or myocardial perfusion.^{6–9} In this article, we review the utility of dobutamine and vasodilator stress CMR for detecting myocardial ischemia and forecasting prognosis. This includes reviewing the utility of stress CMR in women, patients with prior revascularization, and those undergoing preoperative or emergency department evaluations. Finally, we review ongoing research and future developments in the field of stress CMR.

Stress CMR Agents

Pharmacological stress CMR can be performed using either inotropic or vasodilator stimuli. Inotropic stimuli, such as with dobutamine,^{10,11} promote myocardial ischemia by raising myocardial oxygen consumption (demand) in areas of reduced stress-induced perfusion (supply). Alternatively, adenosine^{12,13} or dipyridamole¹⁴ promote systemic arterial vasodilation. In myocardium subserved by coronary arterial segments without luminal

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Conflict of Interest Statement

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narrowing, flow increases after these vasodilators. However, blood flow does not increase in arteries with > 50% to 70% luminal stenoses because the arteriolar beds distal to the stenoses are already maximally dilated. In this way, hypoperfused regions of LV myocardium distal to 50% coronary arterial luminal narrowing become apparent after vasodilator stress.¹⁵ A variety of imaging techniques are used during stress CMR to identify abnormalities of wall motion or perfusion. Disorders of cardiac muscle function or LV wall motion are observed using one of several cine white blood imaging techniques.¹⁶⁻²⁰ In general, perfusion abnormalities are recognized after the first-pass of gadolinium contrast on T1-weighted images.^{21,22}

Identification of Myocardial Ischemia

Dobutamine CMR

In the early 1990s, Pennell et al²³ performed the first dobutamine CMR (DCMR) study in 25 patients with exertional chest pain. The sensitivity of DCMR-induced LV wall motion abnormalities (WMAs) was 91%, and there was 90% agreement between single-photon emission computed tomography (SPECT) and DCMR for identifying myocardial ischemia. Nagel et al²⁴ were the first to use high-dose dobutamine (up to 40 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and atropine during CMR without prior knowledge of the underlying coronary artery anatomy in 208 subjects. They compared DCMR results with those obtained from dobutamine stress echocardiography (DSE) by using contrast coronary angiography assessments of luminal narrowing as a gold standard. Dobutamine stress echocardiography demonstrated superior sensitivity (86% vs 74%), specificity (86% vs 70%), and diagnostic accuracy (86% vs 70%) in comparison with DSE ($P < 0.05$ for all) for identifying > 50% coronary arterial luminal narrowings. In another study, Hundley et al¹ studied 153 patients with a nondiagnostic DSE despite the use of second harmonic imaging. When compared with contrast coronary angiography, the sensitivity and specificity of DCMR were both 83% for detecting coronary arterial luminal narrowings of 50% by contrast coronary angiography. In a recent meta-analysis by Nandalur et al,²⁵ the sensitivity and specificity of high-dose DCMR WMAs for identifying > 50% coronary arterial luminal narrowings in patients with a relatively high burden of coronary artery disease (CAD) (disease prevalence, 70.5%) were 83% (95% confidence interval [CI], 0.79–0.88) and 86% (95% CI, 0.81–0.91), respectively.

One unique feature of DCMR is the ability to combine myocardial perfusion assessments with wall motion assessments during the same stress test (Figure 1). Lubbers et al²⁶ and Gebker et al²⁷ were the first to demonstrate the additional value of first-pass myocardial perfusion imaging to wall motion assessments during peak-dose DCMR to improve sensitivity for the diagnosis of significant coronary artery disease. The combined use of perfusion and WMAs were particularly useful in patients with concentric LV remodeling or hypertrophy.²⁸ It is important to recognize that the high heart rate associated with dobutamine stress increases artifacts and makes the acquisition of > 2 perfusion imaging slices per R-R interval difficult.

Vasodilator Stress CMR Perfusion

While several studies have reported on the utility of CMR using dobutamine stress, the majority of stress CMR studies worldwide are performed using vasodilating agents such as adenosine, dipyridamole, or regadenoson (Figure 2). In single-center studies involving 50 to 230 participants,²⁹⁻³⁴ the overall sensitivities (88%–96%) and specificities (83%–85%) have been high for identifying > 50% coronary luminal narrowings. In a recent meta-analysis involving 2456 patients with a 71% prevalence of CAD, Hamon et al³⁵ observed that the overall sensitivity and specificity of vasodilator stress CMR for the identification of 70% coronary arterial luminal narrowings were 89% (95% CI, 88%–91%) and 80% (95% CI,

78%–83%), respectively. Moreover, CMR perfusion stress with adenosine had a better sensitivity than that with dipyridamole (88%–92% vs 80–90%; $P=0.022$) and a tendency toward a higher specificity (78%–84% vs 71%–82%; $P=0.065$). Recently, stress CMR has also been performed at 3 T,^{36–38} with single-center results suggesting that high-field CMR has an improved signal-to-noise ratio and T1-contrast compared with 1.5 T.

Cardiac Prognosis

DCMR

In addition to diagnosing ischemia, DCMR results can be used to forecast cardiac prognoses. Hundley et al³⁹ addressed the utility of DCMR for evaluating cardiac prognoses in 279 patients referred for CMR stress because of poor LV endocardial visualization with echocardiography. After an average of 20 months, the participants with inducible ischemia (hazard ratio, 3.3; CI, 1.1–9.7) experienced an increased incidence of myocardial infarction (MI) and cardiac death relative to those without ischemia. Jahnke et al⁴⁰ demonstrated similar results in 513 study participants followed for an average of 2.3 years; in this study, the 3-year event-free survival was 99.2% in DCMR without inducible WMAs.

Vasodilator Stress CMR Perfusion

Like DCMR stress LV wall motion imaging, the results of vasodilator perfusion stress testing have been used to forecast adverse cardiac prognosis. In 601 patients with severe ischemia who exhibited a dipyridamole stress-induced perfusion deficit or a WMA, Bodi et al⁴¹ reported that the incidence of major adverse cardiac events (MACE) (defined as cardiac deaths, nonfatal MIs, and admissions for unstable angina with documented abnormal angiography) was 20% in those with versus 4% and in those without a perfusion or WMA after a median follow-up of 553 days. Interestingly, in those with a perfusion and WMAs, the MACE rate was 39%.⁴¹

Other studies have confirmed the prognostic importance of stress CMR-induced perfusion defects. Doesch et al⁴² demonstrated that patients with CMR perfusion defects and stenoses of intermediate severity on contrast coronary angiography are at higher risk for MACE within 18 months following the procedure. The utility of complementary prognostic associations with stress CMR myocardial perfusion and late gadolinium enhancement (LGE) imaging were also demonstrated in 254 patients with symptoms of myocardial ischemia by Steel et al.⁴³ They found that patients with neither a CMR perfusion defect nor LGE exhibited a 98.1% negative annual event rate for cardiac death and MI in 17 months of post-procedure surveillance. In a multivariable analysis, a reversible CMR perfusion defect was the most important prognosticator of an adverse cardiac event (hazard ratio, 10.92; $P<0.0001$).

The absence of vasodilator-induced perfusion defects is associated with a favorable cardiac prognosis. In a recent study by Lo et al,⁴⁴ 203 participants underwent adenosine stress CMR with known or suspected CAD. After a mean follow-up of 3.2 ± 1.6 years, normal CMR perfusion was associated with a very low long-term event rate, excellent long-term prognosis, and a 4-year event-free survival of 96.2%. In addition, stress CMR perfusion provided important incremental prognostic information over clinical risk factors and regional LV WMAs. Jahnke et al⁴⁰ performed DCMR and CMR perfusion stress and found these tests were equally valuable in predicting cardiac outcome. The combination of both techniques did not offer additional benefit for the prediction of event-free survival compared with each stress CMR test alone (log-rank, $P=0.18$).

DCMR Prognosis in Individuals with LV Hypertrophy

Several studies indicate that increased LV wall thickness or left ventricular hypertrophy (LVH) confer an increased risk of cardiac events even when there is an absence of inducible LV WMAs indicative of ischemia. Walsh et al⁴⁵ determined that increased LV end-diastolic wall thickness in the base of the septum or lateral wall was associated with MI and cardiac death in individuals with a resting left ventricular ejection fraction (LVEF) > 55% and no inducible LV WMAs indicative of ischemia. Charoenpanichkit et al⁴⁶ also found that LVH, defined as an LV mass index > 96 g/m² in men and > 77 g/m² in women, was an independent prognostic marker above and beyond assessments of LV WMAs. In fact, in those with LVH but without dobutamine-induced WMAs, the future risk of MI and cardiac death was found to be similar to those with inducible LV WMAs indicative of ischemia and no LVH. These results suggest that LVH, and perhaps LV mass index, should be measured and reported in those referred for dobutamine wall motion testing.

DCMR Prognosis in Patients with a Low LVEF

Dall'Armellina et al⁴⁷ addressed the association between dobutamine-induced LV WMAs and resting LVEF in patients undergoing DCMR. In 200 participants followed for 5 years, the occurrence of MI or cardiac death was similar in those with an LVEF < 40% regardless of the presence of inducible ischemia (68% and 70%, respectively). In 2010, Korosoglou et al⁴⁸ reinforced these results by undertaking one of the largest reported dobutamine stress studies, involving 1493 patients with suspected or known CAD. They demonstrated that the presence or absence of myocardial ischemia did not add incremental information regarding CV prognosis in individuals with a severely reduced LVEF at rest. Thus, the results of these studies indicate that for individuals with a resting LVEF of < 35%, dobutamine stress testing will only be useful in identifying myocardial ischemia or viability when selecting individuals who may be candidates for coronary artery revascularization procedures to relieve symptoms.⁴⁹

Women

DCMR

Several studies have determined the utility of DCMR stress testing in women. In comparison with men, Gebker et al⁵⁰ found that the diagnostic values (sensitivity/specificity/accuracy) for identifying myocardial ischemia indicative of coronary arterial luminal narrowings of > 70% were similar for men (86%, 83%, 85%) and women (85%, 86%, 85%). Wallace et al⁵¹ addressed the utility of DCMR results for predicting cardiac prognosis in women. In 266 consecutively referred women for DCMR followed for an average of 6.2 years, DCMR results were found to be efficacious for identifying women at risk for MI and cardiac death after accounting for known risk factors for cardiac events or CAD. Importantly, the prognostic utility of DCMR results in women was similar to those historically reported in men.

Vasodilator Stress CMR Perfusion

To date, only a few studies have been performed to determine the utility of vasodilator perfusion stress testing in women.⁵²⁻⁵⁵ Doyle et al⁵² assessed 183 women with symptoms suspect for CAD but a low disease prevalence (14% exhibiting > 70% luminal narrowings on contrast coronary angiography) and found the diagnostic accuracy of dipyridamole CMR to be similar to gated SPECT. In 82 women with low-risk chest pain who presented to the emergency department, Lerakis et al⁵³ demonstrated a sensitivity, specificity, and negative predictive value of 100%, 94.9%, and 100%, respectively, for identifying myocardial ischemia indicative of coronary arterial luminal narrowings of > 50%. Klem et al⁵⁴ assessed combined adenosine perfusion stress and delayed-enhancement CMR in 147 women with

chest pain or other symptoms suggestive of CAD and found that the diagnostic values (sensitivity/specificity/accuracy) for identifying myocardial ischemia indicative of coronary arterial luminal narrowings of > 70% were 84%, 88%, and 87%, respectively. These specificities are somewhat higher for CMR than historically reported for stress echocardiography or radionuclide scintigraphy (64%–79%).

Prior Coronary Artery Revascularization

DCMR

In 160 patients who underwent coronary artery revascularization procedures (either with stent placement or bypass grafting), Wahl et al⁵⁶ demonstrated that DCMR provided a sensitivity, specificity, and diagnostic accuracy of 89%, 84%, and 89%, respectively, for the detection of coronary arterial luminal narrowings > 50%. Based on these results and others,^{57,58} DCMR is considered well suited for identifying ischemia in patients after prior coronary artery revascularization procedures.

Vasodilator Stress CMR Perfusion

Over the past several years, many investigators have determined the utility of CMR perfusion stress testing for identifying restenosis of coronary arterial segments in those sustaining prior percutaneous revascularization or surgical bypass grafting. Since myocardial blood flow is more complex in patients with coronary artery bypass graft (CABG) surgery, the first-pass kinetics^{59,60} of a contrast bolus may be altered due to differences in the distance the contrast must travel. These distances influence the timing (systole vs diastole) of the arrival of the bolus of contrast. Moreover, after CABG, patients may experience an MI, which may further complicate analysis, as perfusion defects may be related to prior infarcts. Bernhardt et al⁶¹ performed stress CMR perfusion in those receiving either prior percutaneous or surgical bypass revascularization. In patients who were previously treated by percutaneous revascularization, the sensitivity and specificity for the results of adenosine-induced, gadolinium-enhanced first-pass perfusion to detect to identify flow-limiting stenoses were 91% and 90%, respectively. However, in those sustaining prior CABG, the sensitivities and specificities were lower (79% and 77%, respectively). To date, the recently published literature suggests that the diagnostic accuracy of stress CMR perfusion for identifying a flow-limiting stenosis after CABG is reduced compared with identifying stenoses in native coronary arteries.

Noncardiac Preoperative Evaluation

DCMR

Dobutamine CMR has been used to provide cardiac risk stratification in patients scheduled for noncardiac surgery. Rerkpattanapipat et al⁶² performed DCMR in 107 patients with clinical predictors suggesting an intermediate risk for the development of a cardiac event during noncardiac surgery. They demonstrated that a positive DCMR test was an independent predictor of MI, cardiac death, or congestive heart failure during or after noncardiac surgery. To date, no vasodilator stress CMR perfusion studies have been performed to assess perioperative cardiac risk.

Emergency Department Assessments

Vasodilator Stress CMR Perfusion

Thus far, DCMR has not been implemented in the emergency department (ED) to identify myocardial ischemia or assess CV risk. Several recent studies have focused on the use of vasodilator stress CMR in patients presenting to the ED with low- or intermediate-risk chest

pain. In 103 patients presenting to the ED with low-risk chest pain, as indicated by negative serial electrocardiograms and cardiac biomarkers for myocardial injury, Lerakis et al⁶³ demonstrated that the results of adenosine CMR performed within 24 hours of arrival to the ED can be used to identify myocardial ischemia. In this study, the negative predictive value of adenosine CMR for identifying myocardial ischemia was 100%. In 277 days of longitudinal follow-up, there were no cardiac deaths, nonfatal acute MIs, rehospitalizations for chest pain, or coronary revascularization procedures. Patients with negative adenosine CMR exhibited an excellent short- and mid-term prognosis.

When individuals experience intermediate- to high-risk chest pain for an acute coronary syndrome (ACS), the results of stress CMR may be used to cost-effectively manage patients presenting to the ED. Miller et al⁶⁴ conducted a trial involving 110 intermediate-risk ACS patients and randomized them to stress CMR in an observation unit versus standard inpatient care. The observation unit CMR strategy was equivalent to a hospital admission for identifying those with ACS, yet was accomplished at an incident visit cost savings of \$588 per patient (95% CI, \$336–\$811). These results suggest that stress CMR may be beneficial in managing those presenting to the ED, and this form of management may reduce health care costs relative to hospital admission.

Evaluating patients presenting to the ED with suspected ACS, Vogel-Claussen et al⁶⁵ studied the prognostic importance of the size and duration of perfusion defects identified during perfusion stress. In ED patients with chest pain at an intermediate probability for coronary artery disease, Vogel-Claussen et al⁶⁵ demonstrated that diffuse subendocardial hypoperfusion defects (less than half of the myocardial wall thickness in at least 2 different coronary artery territories of 6 beats in duration) were associated with return to the ED with chest pain compared with patients who had no CMR perfusion defect ($P = 0.02$). Thus, while large perfusion defects may represent ischemia due to epicardial coronary arterial luminal narrowings, smaller defects may represent a microvascular process associated with recurrent chest pain.

Limitations

A primary concern for physicians and health care providers who administer pharmacological stress CMR is safety. To date, several studies involving thousands of patients have documented the protocols and recommendations for safely performing stress CMR tests.^{11,12,66-68} These studies are not performed in general radiology imaging suites. Instead, they are performed in centers with nurses, technologists, and physicians familiar with the procedures (Figure 3).⁶⁹⁻⁷⁰ Adverse and serious adverse event rates are similar to or lower than those reported with other imaging modalities.^{3,4,71} The Society for Cardiovascular Magnetic Resonance, an international society composed of radiologists, cardiologists, physicists, and biomedical engineers, has established criteria for performing and reporting results of stress CMR studies.^{72,73} When perfusion stress CMR is considered, the estimated glomerular filtration rate should exceed 30 cc/min so as to avoid gadolinium-associated nephrogenic systemic fibrosis. In this situation, the patient should only undergo stress CMR with gadolinium if the benefit from the scan outweighs the risk.⁷⁴⁻⁷⁷

Future Developments in the Field of Stress CMR

Exercise Stress CMR

Several centers have begun to investigate the utility of upright treadmill stress CMR. The physiologic information, such as exercise capacity, heart rate and rhythm, and exertional symptoms, yielded by observing a patient's response to standardized exercise stress, helps to forecast cardiac prognosis. In 20 healthy participants, Jekic et al⁷⁸ performed treadmill

exercise CMR protocol and found that all LV myocardial segments could be visualized immediately after stress treadmill testing using a maximal Bruce protocol. In another study, Rerkpattanapipat et al⁷⁹ demonstrated a 79% sensitivity of maximal exercise treadmill CMR results for identifying 50% coronary arterial luminal narrowings in patients with primarily single-vessel CAD.

In addition to detecting or excluding flow-limiting CAD, treadmill stress CMR may also forecast adverse cardiac prognosis. Raman et al⁸⁰ performed a treadmill stress CMR involving wall motion, perfusion, and scar imaging in 43 patients with known or suspected ischemic heart disease and found moderate agreement ($k = 0.58$) with technetium-99m SPECT. After follow-up at 6 months, no CV events occurred in patients with a negative treadmill stress CMR. The results of these early studies highlight the feasibility of exercise treadmill stress CMR. Further studies are needed to discuss the clinical utility of this new imaging technology.

CMR Methods to Assess Myocardial Oxygenation and Perfusion without Contrast

While stress CMR perfusion tests involve the administration of gadolinium in clinical practice, research is ongoing to develop stress testing methods that do not use contrast. Blood oxygen level-dependent CMR has the potential to noninvasively measure myocardial oxygenation without exogenous contrast administration.⁸¹⁻⁸³ Whether this strategy will be useful clinically remains to be determined.

Conclusion

Two pharmacologic stress options are present with CMR: LV wall motion evaluations (which do not require contrast) and stress perfusion protocols (which require gadolinium contrast). In appropriately equipped centers with adequately trained staff, stress CMR testing can be performed safely and reliably for the diagnosis of inducible ischemia. For different patient subgroups, some procedures may be superior to others (Table 1). As shown in Table 1, DCMR wall motion is well suited to detect myocardial ischemia in patients with prior revascularization either bypass graft or stent placement, whereas vasodilator perfusion stress may be preferable in the setting of resting LV WMAs and LVH. Recent studies involving hundreds to thousands of participants also indicate that perfusion and/or wall motion testing results forecast cardiac prognosis in individuals with chest pain. Stress CMR procedures are particularly useful in both men and women with a body habitus not suitable for other imaging modalities.

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Figure 1.

Images from a dobutamine stress CMR test in a patient with evidence of inducible ischemia. End-diastolic (top) and end-systolic (middle) frames from cine white blood short-axis views of the left ventricle during a dobutamine stress CMR examination. The arrows in the end-systole panel (top and middle right) demonstrate an inducible LV wall motion abnormality in the inferoseptal, inferior, and inferolateral wall of the left ventricle at peak stress. Resting mid-left ventricular short axis slice in the same patient at rest (bottom left image) and at peak dobutamine (bottom right image). The arrows in the bottom right perfusion panel demonstrate low signal intensity after gadolinium in the inferoseptal, inferior, and inferolateral wall of the left ventricle in the same segments in which the wall motion abnormality is demonstrated above.

Figure 2.

Adenosine stress CMR images from a patient with evidence of inducible ischemia. The top right panel of a short-axis image obtained during adenosine stress after a 4-minute infusion of adenosine and then on the top left panel is displayed the same short-axis slice 10 minutes later at rest. During stress there is a mild perfusion abnormality (large arrows) that is not present at rest. This abnormality indicates reduced flow and myocardial ischemia. In the same patient, a caudal view of the right anterior oblique projection during contrast coronary angiography is displayed. The small arrow in the left image highlights an 100% proximal left anterior descending and a 60% proximal circumflex luminal narrowing.

Figure 3. A photograph of a stress CMR testing suite. The individual (technologist) on the left performs the scans and the individual on the right (physician) reviews the stress image results in near real-time. Through the window, the patient is seen in the CMR scanner with hemodynamic monitoring occurring during stress.

Table 1

Utility of Stress CMR Testing in Patient Subgroups

	Identification of Myocardial Ischemia				Cardiac Prognoses			
	Dobutamine		Vasodilator		Dobutamine		Vasodilator	
	Wall motion	Perfusion	Perfusion	Perfusion	Wall motion	Perfusion	Perfusion	Perfusion
Chest pain with GFR > 30 cc/min:								
Normal left ventricular wall thickness and no resting wall motion abnormalities	1	3	1	1	1	3		1
Prior revascularization								
Prior stent placement	1	4	1	1	1	4		4
Prior bypass grafting	1	4	2	1	1	4		4
Left ventricular hypertrophy	2	1	1	2	2	1		4
Left ventricular ejection fraction < 35%	1	1	1	1	3 ^a	4		4
Resting wall motion abnormality	2	1	1	1	1	1		4
Pre-noncardiac surgery evaluation	1	4	4	4	1	4		4
In emergency department chest pain	4	4	1	1	4	4		1

1, advantageous; 2, equivocal; 3, unnecessary; 4, uncertain.

^aThese techniques may be useful to assess viability and revascularization.

Abbreviations: CMR, cardiac magnetic resonance; GFR, glomerular filtration rate.