

# Myocardial Stress Perfusion Imaging using CMR

Andrew E. Arai, M.D.

*National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, M.D., USA*

## Clinical role

Adult cardiology and medicine focuses tremendous emphasis on the evaluation of patients with known or suspected coronary artery disease since this is one of the leading causes of death in industrialized nations. There are three major clinical presentations of coronary artery disease: chest pain syndromes, acute coronary syndromes (including acute myocardial infarction) and sudden death. Since relatively few patients suffering from coronary artery disease can be resuscitated from sudden death, most efforts are aimed at detecting coronary artery disease at earlier stages of the disease and at preventing permanent myocardial damage. Stress testing is one of the most powerful diagnostic approaches to detecting coronary artery disease. In general terms, it is necessary to understand why it is necessary to perform stress testing to detect physiologically significant coronary artery disease when using technologies that do not directly image the coronary arteries.

Coronary artery disease causes symptoms of chest discomfort in two major presentations: acute coronary syndromes or in chronic stable angina. In acute coronary syndromes, a thrombus developed on an unstable coronary plaque resulting in intermittent or complete obstruction of a coronary artery. In the most extreme cases this will cause an ST elevation myocardial infarction. In patients with unstable angina, no permanent myocardial damage may have occurred and further testing with either coronary angiography or stress testing may be needed to determine whether coronary disease could explain the symptoms or needs intervention.

Outside of the setting of acute myocardial infarction or the most severe rest perfusion defects associated with hibernating myocardium, perfusion of the heart is generally normal at rest. Even

in the presence of a severe coronary stenosis, autoregulation of the heart's blood vessels maintains normal perfusion to the heart muscle. Thus, at rest, a patient can feel normal and have no chest pain. Likewise, images of rest perfusion can look quite normal and uniform in the heart. A stress test uncovers the coronary stenosis by challenging the adequacy of the heart's ability to regulate blood flow. As the patient exercises or vasodilator medicines are administered, blood flow increases in the heart muscle served by a normal coronary artery. However, blood flow cannot increase as much downstream from a significantly stenosed coronary artery. Thus, high levels of exercise may induce chest pain and ST segment abnormalities. During a stress perfusion study, a relative defect in blood flow to some regions of the heart may be imaged by nuclear methods (SPECT) or by CMR. Alternatively, imaging can be performed during stress to detect a new or worsening wall motion abnormality. Such testing can be performed by echocardiography (during exercise or dobutamine) or by CMR (during dobutamine).

Stress imaging tests are generally indicated when a patient has an equivocal stress ECG or uninterpretable ECG due, for example, to baseline ST segment abnormalities. Pharmacological stress testing is generally required in patients that cannot adequately exercise. For an exercise stress test to be diagnostic, peak heart rate must be at least 85% maximal predicted for age. Such high heart rates can be difficult to attain if a patient has problems such as arthritis.

Directly imaging the coronary arteries is an alternative approach to detecting coronary artery disease. However, the consensus of medical experts indicates that coronary interventions should primarily be performed in clinical situations where

Stress testing is one of the most powerful diagnostic approaches to detecting coronary artery disease.

Coronary interventions should primarily be performed when there is clinical evidence of myocardial ischemia associated with the coronary stenosis.

**Table 1: Non-CMR stress tests used for the detection of coronary artery disease**

	# of patients	Sensitivity	Specificity
Exercise ECG	2456	52	71
Exercise SPECT	4480	87	73
Stress Echocardiography	2637	85	77

Adapted from Fleischmann et al. and Klocke et al. [1, 2]

Among stress tests, exercise ECG has the lowest sensitivity and specificity for detecting coronary artery disease.

**Table 2: Sensitivity and specificity of stress perfusion CMR for detecting coronary artery disease**

Reference	N	Stress	Sensitivity (%)	Specificity (%)
Klem <i>et al.</i> [3]	92	adenosine	89	87
Ingkanisorn <i>et al.</i> [4]	135	adenosine	100	93
Okuda <i>et al.</i> [5]	33	dipyridamole	84	87
Sakuma <i>et al.</i> [6]	40	dipyridamole	81	68
Plein <i>et al.</i> [7]	92	adenosine	88	82
Takase <i>et al.</i> [8]	102	dipyridamole	93	85
Paetsch <i>et al.</i> [9]	49	adenosine	79	75
Paetsch <i>et al.</i> [10]	79	adenosine	91	62
Wolff <i>et al.</i> [11]	99	adenosine	93	75
Thiele <i>et al.</i> [12]	32	adenosine	75	97
			80	91
Plein <i>et al.</i> [13]	72	adenosine	88	83
Bunce <i>et al.</i> [14]	35	adenosine	74	71
Nagel <i>et al.</i> [15]	84	adenosine	88	90
Ishida <i>et al.</i> [16]	104	dipyridamole	84	82
Doyle <i>et al.</i> [17]	184	dipyridamole	57	78
			52	82
Kinoshita <i>et al.</i> [18]	27	dipyridamole	55	77
			77	81
Ibrahim <i>et al.</i> [19]	25	adenosine	69	89
Schwitzer <i>et al.</i> [20]	48	dipyridamole	87	85
			91	94
Panting <i>et al.</i> [21]	26	adenosine	79, 72, 60	83, 83, 43
			77	83
Al-Saadi <i>et al.</i> [22]	34	dipyridamole	90	83
<b>Totals</b>	<b>1392</b>		<b>~83%</b>	<b>~80%</b>

Taking all studies into account, the sensitivity and specificity of stress perfusion CMR is around 83% and 80% respectively.

there is clinical evidence of myocardial ischemia associated with the coronary stenosis. Thus, even in patients with known intermediate stenosis of a coronary artery, there is frequently a need for

stress testing to define whether the stenosis is physiologically significant in that individual. Now that non-invasive coronary CT angiography has progressed to a point where it can detect high-

**Table 3: Image acquisition parameters for different perfusion pulse sequences**

Method	SR-SSFP	SR-FLASH	SR-GRE-EPI (research WIP)
TE (ms)	1.1	1.3	1.1 (TE1)
TR (ms)	2.3	2.2	6.1
BW (Hz/pixel)	1400	780	1630
Echotrain length	1	1	4
Readout Flip Angle	50	12	25
Matrix	128 × 80	128 × 80	128 × 80
Parallel Imaging Factor	R = 2	R = 2	R = 2
TD (ms) (to 1st line)	39	41	54
TI (ms) (to center)	85	85	85
Tslice (ms) (total)	132	130	117
Slices per RR @ 60/90/120 bpm	7/5/3	7/5/3	8/5/4

grade coronary artery stenosis in asymptomatic patients, there will be increasing need to define the physiological significance of these abnormalities. There is also a need to define the physiological significance of possible stenosis associated with highly calcified coronary arteries or in smaller coronary stents that cannot be adequately resolved with current generation CT scanners.

Cardiac risk factors are widely used clinically to help guide preventive treatments and to delay the onset of clinically overt coronary artery disease. The common risk factors for coronary disease include age, male gender, family history of premature coronary disease, diabetes, hypertension, hyperlipidemia, smoking, obesity, and physical inactivity. In addition, coronary calcium as detected and quantified by a CT scan has independent and additive risk as well as prognostic significance. Of the coronary risk factors identified, diabetes, hypertension, hyperlipidemia, smoking, obesity, and activity can all be modified through medical or individual intervention.

However, risk factors have a relatively weak short-term predictive value for coronary artery disease. For example, the Framingham risk score is commonly used to assess the likelihood that a patient has coronary artery disease but reports risk in probability of disease occurring over a 10-year period. For example, a non-smoking 55-year-old male patient with a cholesterol of 240 mg/dL, an HDL of 40 mg/dL, hypertension with a systolic blood pressure of 130 mmHg has a 10% risk of developing coronary artery disease over the next 10

years. That level of risk warrants intervention if the LDL cholesterol is high enough (130 mg/dL) per the ATP III guidelines [National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, NIH Publication No. 01-3670, May 2001] but remains a low enough risk for direct detection of asymptomatic disease to be controversial.

In summary, stress testing and risk factor analysis or preventive cardiology perform complementary approaches to detecting and managing patients with coronary artery disease. At the current time, the primary role of stress testing is in detection of coronary disease or physiological assessment of coronary disease. Risk factor analysis focuses on optimizing management of medically modifiable risk factors either in the prevention of disease or in more aggressive management of patients with known disease.

### Diagnostic accuracy

There are many forms of stress tests and significant differences in the sensitivity, specificity, and accuracy of these tests. Table 1 summarizes the sensitivity and specificity of non-CMR stress tests used for the detection of coronary artery disease. Table 2 presents similar statistics for stress perfusion CMR. The diagnostic accuracy of stress perfusion CMR is clearly comparable to the other stress imaging modalities and all stress imaging modalities have clinically significant increased sensitivity relative to stress ECG.

The diagnostic accuracy of stress perfusion CMR is comparable to the other stress imaging modalities.

## Sequences and protocols

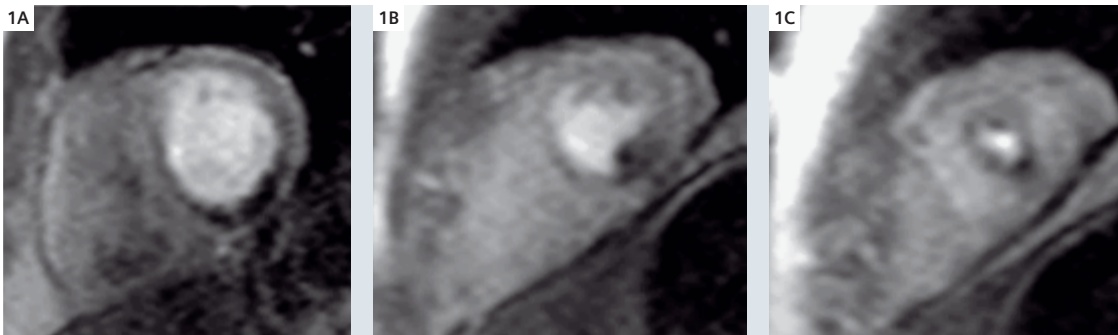
To perform first pass perfusion imaging, a series of T1 weighted images must be obtained every heartbeat or every other heart beat while a bolus of contrast passes through the heart and myocardium. As with many aspects of diagnostic testing, choices need to be made with regard to balance between anatomic coverage, spatial resolution within each imaging plane, temporal resolution, and image quality. We generally image 3 slices of the heart in a short axis orientation to assess at least 16 segments of the heart. In general, this allows acquiring all three slices every cardiac cycle. However, this choice was made since our group has focused much effort on developing fully quantitative analysis methods. It would be equally reasonable to image a total of 6 slices every other heartbeat to improve the anatomic coverage of the heart. Three main sequences have been used to acquire stress perfusion images: TurboFLASH (GRE), TrueFISP (SSFP), and hybrid echoplanar methods (GRE-EPI or hybrid EPI). Of these, TurboFLASH and TrueFISP are available as product level software and the hybrid echoplanar method is un-

der evaluation as a research “work-in-progress.” The main advantages of TurboFLASH are its simplicity and the minimal image artifacts. The main consideration for using the TrueFISP sequence is the higher signal-to-noise ratio and improved contrast-to-noise ratio. Either sequence produces high quality perfusion images. Examples of stress perfusion defects obtained with TurboFLASH, TrueFISP, and the hybrid echoplanar methods are shown in figures 1–4.

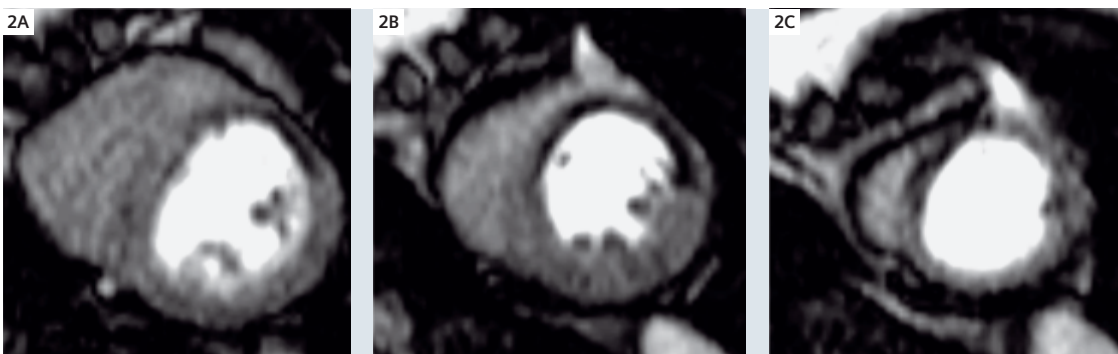
Table 3 summarizes recommended starting parameters for first pass perfusion studies. These are parameter sets that we have studied at the National Institutes of Health. Many groups push for higher spatial resolution but one must recognize that the time used to acquire more lines of k-space will lengthen the duration of the readout during the cardiac cycle opening the possibility of artifacts due to motion and will reduce the number of images per heartbeat (slices per RR). We have tried to aim for short imaging time during the cardiac cycle to minimize dark rim artifacts at the endocardial-blood interface. Parallel imaging factors (iPAT factors) are quite effective at im-

SR TrueFISP (SSFP) and SR TurboFLASH (GRE) sequences are available for CMR myocardial perfusion imaging.

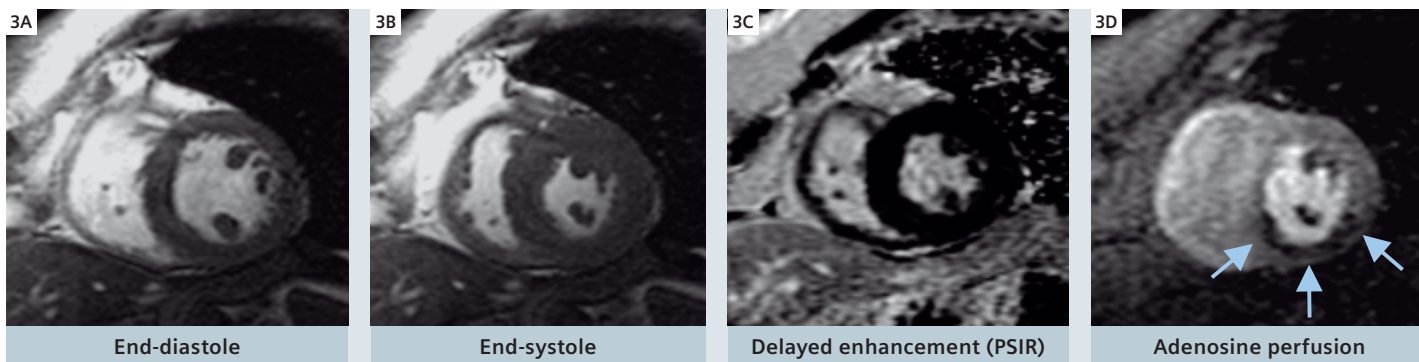
Up to 8 slices can be acquired in one or more orientations during the CMR first-pass perfusion imaging.



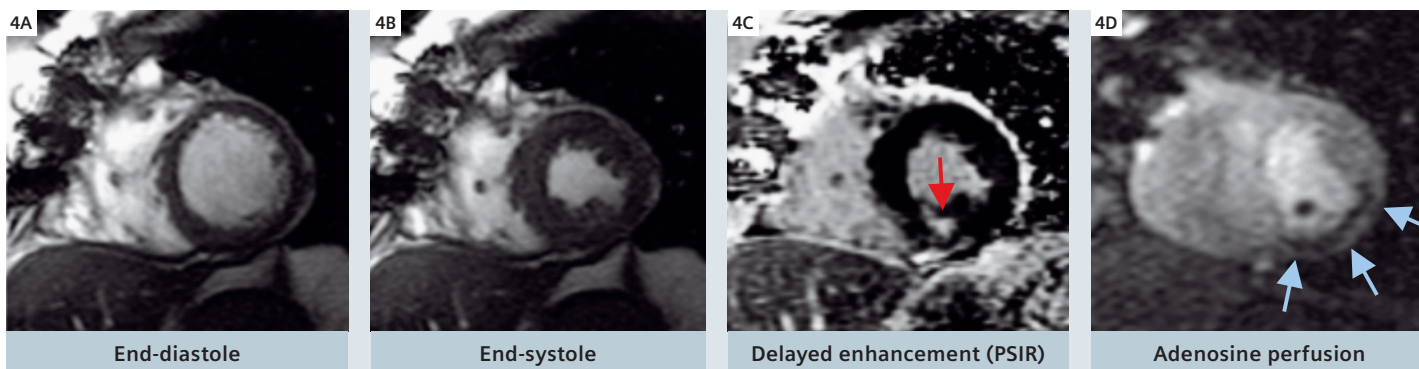
**1** Inferior perfusion defect during stress using the SR TurboFLASH perfusion sequence.



**2** Example of stress perfusion defect using SR TrueFISP.



3 Patient with stress induced perfusion defects but no myocardial scar.



4 Patient with prior bypass surgery, small inferior myocardial infarction, larger wall motion abnormality and perfusion defect. Findings consistent with stunned myocardium and inducible ischemia. PSIR is used as a fast technique for Delayed Enhancement MRI.

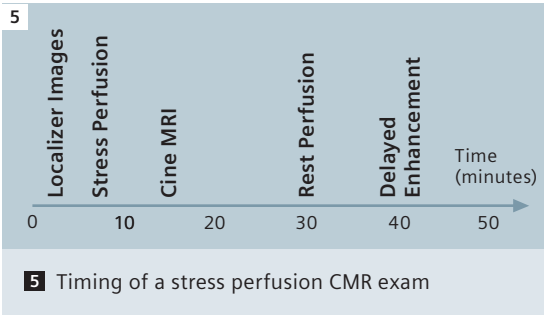
proving temporal resolution and well worth the tradeoff in signal-to-noise ratio. In our general experience, artifacts are a much larger issue than signal-to-noise ratio for perfusion images.

### Typical protocol for CMR stress perfusion imaging

Figure 5 shows the typical timing of a stress perfusion protocol. After localizer images, the vasodilator stress agent is started. In the case of adenosine, we recommend mixing enough adenosine to provide a 6 minute infusion at 140 micrograms/kg/min. By 3 minutes into the infusion, adequate vasodilation should be achieved to allow performing the stress perfusion imaging. Once the stress perfusion images are acquired, the adenosine infusion can be stopped. When using dipyridamole, we recommend a net dose of 0.56 mg/kg infused over 4 minutes. Peak vasodilation with dipyridamole may not be achieved until several minutes after completing the infusion. We usually do the stress perfusion imaging 4 minutes after finishing the dipyridamole unless severe symptoms require

us to image earlier. Aminophylline 100 mg IV is sometimes needed to reverse the effects of dipyridamole symptoms due to the significantly longer half-time. When carrying out a rest perfusion study after the stress perfusion, it is generally a good idea to reverse the dipyridamole since it may have lingering effects that alter the rest perfusion. After stabilizing the patient following the stress test, cine CMR can be performed to assess anatomy, ejection fraction, and regional wall motion. Some centers acquire rest cine images prior to the injection of adenosine and additionally during adenosine stress. A rest perfusion study is then performed using identical parameters to the stress test to facilitate comparisons. Finally, delayed enhancement imaging of myocardial infarction can be performed. If additional imaging is required one could do velocity encoded phase contrast before or after the rest perfusion study. Turbo spin echo (black blood imaging) should be completed prior to the stress perfusion imaging to avoid poor blood suppression related to having contrast in the circulation. A contrast-enhanced MRA could

Due to the very short half-life time (< 30 s), adenosine is mostly used as a vasodilator for stress tests.



be performed in place of the rest perfusion study if desired. Coronary MRA can generally be performed at any point along the time line since most of the sequences are not too severely affected by the presence of contrast. As regards the dosage of contrast, several factors have to be considered in the main decision. In general, for a given set of parameters, the signal-to-noise ratio will be better for higher doses of contrast but the linearity between gadolinium concentration and signal intensity may become an issue. The dual bolus and dual sequence methods were introduced by researchers attempting to benefit from higher doses of contrast for the myocardium but to preserve the linearity in the blood pool necessary to quantify perfusion [23, 24]. If one is not performing quantitative analysis, it is reasonable to use a dose of gadolinium contrast of 0.5 mmol/kg.

### Pitfalls with CMR first-pass perfusion imaging

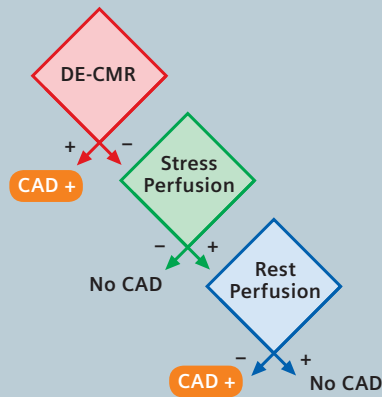
The pitfall in CMR first pass perfusion imaging is making a reasonable balance between sensitivity and specificity when interpreting images. There is no substitute for experience that includes correlation with invasive coronary angiography. Even as a center with experience in over 1000 stress perfusion cases, we found it extremely helpful to go back to correlation with cardiac catheterization when we switched imaging methods to the True-FISP perfusion sequence. You learn the most from cases with an unequivocal normal angiogram and also from true defects in patients with a significant stenosis in the absence of a myocardial infarction. When we project a perfusion study to a group of physicians, it is inevitable that one or more physicians will have a question about a gray rim near the endocardial border on one or more slices of a perfusion scan. There are many tricks that can be used to help determine the likelihood that these defects may or may not be real perfusion defects:

- Perfusion defects tend to follow the typical perfusion territories of the coronary artery.
- Perfusion defects tend to affect distal segments first depending on how distal or proximal the location of the stenosis is.
  - Exception: Patients with coronary artery bypass surgery.
  - Exception: Branch vessel disease such as diagonal or septal perforators.
- True perfusion defects tend to last several heartbeats beyond the initial rapid upslope of myocardial enhancement. Susceptibility artifacts tend to be worst during peak concentration of gadolinium during the intracavity RV and LV phases of enhancement and tend to disappear rapidly.
  - Corollary: If a dark rim disappears by the time most segments have reached about 90% maximal enhancement, then the rim is probably an artifact.
- Perfusion defects tend to be subendocardial except in the most severe cases. This allows using differences between endocardial and epicardial enhancement as another way to control for issues like surface-coil intensity drop off. It also makes it possible to detect balanced ischemia associated with multi-vessel disease.
- True perfusion defects usually have significantly lower enhancement than normal segments. If in doubt, place a small region of interest on the questionable dark rim artifact and a region of normal heart (close proximity to avoid surface coil intensity issues). Many of the things people list as possible defects are within 3–4% of the signal intensity of neighboring myocardium. A 15 or 20% difference in signal intensity is more likely to be a real defect.
- Use all information available to you when interpreting images. The delayed enhancement is a very specific tool for diagnosing coronary artery disease (see figure 6). The group at Duke University tested a simple interpretation algorithm that they find helps improve the specificity of reading perfusion scans [3]. Essentially, if the patient has a myocardial infarction on delayed enhancement imaging, it is very likely he has significant coronary disease. If an apparent perfusion defect is seen at rest and at stress in the absence of an MI on delayed enhancement imaging, it must be an artifact (only in the absence of wall motion abnormalities!). A defect

A typical stress MRI exam consists of function, perfusion and delayed enhancement imaging.

Low doses of Gadolinium are used for quantitative perfusion analysis, in order to preserve linearity between gadolinium concentration and signal intensity.

**6** Duke method for using delayed enhancement and rest perfusion to improve the accuracy of interpreting stress perfusion images (Adapted from Klem et al.).



- seen at stress but not at rest is most likely to represent a true defect.
- An unequivocal regional wall motion abnormality on cine CMR can also be very informative. However, do not put too much weight on marginal variations in wall motion.
  - Also look for artifacts associated with sternal wires, vascular clips, and coronary stents. These findings increase the pretest likelihood of disease considerably.
  - Time-intensity curves can also help distinguish true defects from false positive defects. It is not uncommon that one or more segments of the heart appears delayed by 1–2 heartbeats relative to the other segments. This can create a region of the heart being 25% or more darker than all other segments and appear like a severe perfusion defect. Time-intensity curves show such a region enhances at a similar rate to the other segments but is simply delayed in time relative to the other segments.

### Advantages and benefits of CMR stress perfusion imaging

The main advantages of CMR stress perfusion imaging relate to the completeness and quality of the information obtained during this single examination. Figure 4 shows the utility of a CMR stress perfusion exam in a patient with known coronary artery disease. Thus, the clinical question is not a simple binary presence or absence of coronary disease. This patient had prior bypass surgery and a prior myocardial infarction. She presented with chest pain that occurred at rest but remained troponin negative throughout her hospitalization. The clinically relevant question is whether there is myocardial ischemia beyond the infarct. Follow-

ing the principles listed in the section on “pitfalls,” there are many pieces of useful information. Starting with the delayed enhancement image, there is a small inferior myocardial infarction (red arrow). Interestingly, the wall motion abnormality is more extensive than the small infarct and includes the inferolateral segment. The cine CMR also shows the sternal wire artifacts in the chest wall. Finally, the stress perfusion defect is also more extensive than the infarct. This study thus shows a patient with known coronary disease with evidence of stunned myocardium (viable myocardium with a wall motion abnormality in the setting of recent clinical suspicion of ischemia) and a stress induced perfusion defect consistent with inducible ischemia.

There are also advantages of stress CMR in terms of diagnostic workflow. A high-quality exam can be accomplished within 45–60 minutes covering cine CMR, stress perfusion, rest perfusion, and delayed enhancement images. This exam allows assessment of ejection fraction, regional wall motion, the valves, evidence of inducible perfusion defects, and the extent of myocardial infarction. The fact that these imaging methods can be displayed side-by-side in the same imaging planes facilitates interpretation, particularly for subtle abnormalities. Thus, stress CMR studies can be performed with an efficiency that is significantly higher than most nuclear methods. The time of exams is comparable to echocardiographic stress tests but with significantly more diagnostic information about ischemia and viability. Thus, as a complete package, the rest-stress CMR study provides more information than either echocardiography or SPECT.

The image resolution of CMR perfusion studies is also unique and a distinct advantage. Compared with SPECT, the image resolution is at least 10 times higher on a volumetric basis. Considering the normal left ventricular wall is only about 10 mm thick, SPECT operates at an acquisition resolution incapable of resolving epicardial from endocardial perfusion. Typical resolution CMR perfusion scans operate at an acquisition resolution smaller than ~3 mm and thus routinely resolve endocardial from epicardial perfusion abnormalities. The greatest advantage of this comes in detecting multivessel disease, left main disease, or microvascular disease [16, 25]. Recent papers have documented that stress perfusion imaging has prog-

CMR and echo stress tests have comparable exam times, however, CMR comes with significantly more diagnostic information about ischemia and viability.

Compared to SPECT, CMR offers an at least 10 times higher volumetric image resolution.

nostic value. In a series of patients studied after presenting to the emergency department, adenosine stress CMR had excellent sensitivity and specificity for diagnosing coronary artery disease [4]. A negative adenosine stress CMR study had excellent prognosis. In another study, the prognosis of positive or negative stress tests was nearly identical if the stress agent was adenosine or dobutamine [26]. Last but not least, when compared to SPECT imaging, instead of 4-20 mSv, no ionizing radiation is needed to perform a CMR stress exam.

## Conclusions

In a center with the equipment and expertise to perform stress CMR, vasodilator stress tests are a very powerful tool for diagnosing and managing ischemic heart disease. The stress perfusion information is an important step beyond viability imaging since the presence or absence of inducible perfusion defects can alter the management of a patient. The combined evaluation of function, perfusion, and viability provides the information needed for managing complicated patients with coronary artery disease.

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## Contact

Andrew E. Arai, MD  
Senior Investigator  
National Heart,  
Lung and Blood Institute  
National Institutes  
of Health  
Bethesda, MD, 20892  
USA