Introduction

The lack of blood flow and oxygen delivery to myocardial tissue results in a progression of events. These events begin with subendocardial ischemia and, if oxygen delivery to the tissue does not improve, transmural ischemia will ensue. This is followed by diastolic dysfunction, systolic dysfunction, electrocardiographic changes, and finally angina. The early occurrence of abnormal perfusion in this cascade of events emphasizes the importance of perfusion imaging.

Multiple modalities have been employed to evaluate myocardial perfusion. These include fluoroscopic angiography, single photon emission computed tomography (SPECT), positron emission tomography (PET), contrast echocardiography, and cardiac magnetic resonance imaging (CMR). This article focuses on the myocardial perfusion techniques of CMR including contrast agents, pharmacologic stressors, sequences, imaging planes, image post processing, and future applications.

With the exception of contrast echocardiography, CMR is the only listed modality that does not require ionizing radiation, making it a useful tool for serial exams. CMR offers high spatial resolution which is ideal for evaluating the subendocardial layer. Rapid tracking of contrast agents utilizing CMR’s high temporal resolution provides detection of myocardial blood flow both under pharmacologic stress and rest. The perfusion characteristics can be combined with anatomic structure, function, and tissue characterization in the same exam. Additional imaging including blood flow characteristics of both right and left sided valves can also be completed. A myocardial perfusion study including cardiac structure, biventricular function, valvular assessment, stress and rest myocardial perfusion, and infarct imaging can be completed in 30 minutes. This makes stress CMR a well fitting modality in today’s complex multimodality imaging world.

Contrast Agents

Cardiac MR techniques are being explored for the possible perfusion assessment without IV contrast agents. However, until methods of blood oxygen level dependent (BOLD) imaging or arterial spin labeling (ASL) of the heart are perfected, IV contrast agents are required for perfusion assessment. MRI contrast agents function by affecting the relaxation rates of surrounding water protons. While there are other paramagnetic metal ions, gadolinium is accepted as the standard MRI contrast agent. The majority of the different brands of gadolinium contrast agents all have similar properties when it comes to myocardial perfusion, differing predominantly in their chelation preparation around the gadolinium. Gadolinium chelates are water-soluble and are able to diffuse rapidly into the extracellular space across the capillary membrane. They are not, however, able to enter through intact cardiac cell membranes.

Coronary perfusion is the primary factor affecting the concentration of the gadolinium compound in the myocardial tissue. Myocardial ischemia is detected by reduced or delayed early-enhanced signal intensity. The heterogeneity of the ischemic tissue does not last long as recirculation leads to equilibration between the vascular and extracellular compartments, usually within seconds. This emphasizes the importance of first-pass imaging of the contrast agent.

The gadolinium contrast agent is delivered as a bolus intravenous injection. Intact right ventricular and left ventricular function is necessary to keep delivery of the agent to the coronary arteries in its concentrated state. Patients with impaired cardiac function, such as right or left ventricular dysfunction or valvular incompetence, can compromise the contrast delivery and should be recognized by the clinician prior to contrast injection.
Gadolinium-based chelates are among the safest injectable contrast agents in current medical use and have a reputation for being safer than their X-ray contrast counterparts. Mild adverse reactions such as nausea and hives are among the most common adverse reactions and are self-limited. Despite its safety record, there are reports of serious adverse reactions, including life-threatening anaphylactic reactions with a rate between 1 in 200,000 and 1 in 400,000. Nephrogenic systemic fibrosis (NSF) is a very rare irreversible disease linked with gadolinium administration in the setting of advanced renal function impairment. Strict screening protocols of renal function prior to gadolinium administration have been put in place to eliminate occurrence of this disease.

Pharmacologic stressors

Perfusion defects are more readily detected during stress conditions. First-pass imaging is commonly performed during chemical stimulation, which is used to increase blood flow to the myocardium. Physical stress is not a practical method of cardiac stress for CMR imaging due to limited space within the magnet bore and risk of creating motion artifacts.

Stenotic coronary vessels are unable to respond to the vasodilatory stimulation to the same degree as normal vessels, exaggerating regional differences in myocardial blood flow. The differences in regional signal intensity can be caused by loss of distal myocardial perfusion and redirection of flow to the epicardial layer. Generalized vasodilation may also impair high resistance collateral flow.

Historically, adenosine and dipyridamole have been the most commonly used pharmacologic stressors for vasodilatation. A newer agent approved by the FDA in 2008, Lexiscan® (regadenoson), has gained popularity. Adenosine acts on the vascular smooth muscle surface to cause vasodilation. Dipyridamole inhibits the cellular uptake and metabolism of adenosine thereby causing an increase in the interstitial adenosine concentration. Lexiscan® is an adenosine receptor agonist. These agents give rise to a super-physiologic increase in vascular flow as opposed to the approximate two-fold increase of vascular flow seen with dobutamine or exercise.

Contraindications to administering adenosine and adenosine agonists include asthma, high-grade AV block, sinus arrhythmia, stenotic valvular disease, and carotid artery stenosis. Several substances are competitive inhibitors of adenosine including aminophylline, theophylline, and other xanthine containing foods, such as coffee, tea, cocoa products, and soft drinks. These should be restricted for approximately 24 hours prior to the study. Due to the medications’ actions, patients can become symptomatic reporting nausea, dizziness, flushing, and chest discomfort. Indications for stopping the infusion and terminating the scan include bronchospasm, ventricular arrhythmia, new onset AV block, and bradycardia. An antidote to both adenosine and dipyridamole of IV aminophylline should be on hand for immediate administration.

Dobutamine has also been used in CMR stress and perfusion imaging. Dobutamine increases heart rate, blood pressure and contractility similar to exercise. Using progressively increasing doses of dobutamine, the heart can be imaged to look for systolic dysfunction at high heart rates. Considering the progressive cardiac changes to ischemia, systolic dysfunction will precede both electrocardiographic changes and angina. Dobutamine has also been used in conjunction with adenosine for more complex stress CMR protocols. Dobutamine can also be used for evaluation of wall motion abnormalities. Studies have demonstrated dobutamine CMR to be a reliable tool in the decision making process to proceed to invasive procedures versus continuing with medical management.

Adenosine has an extremely short half-life of 10-30 seconds. This characteristic makes it a more favorable agent in the setting of adverse reactions. Since becoming generic, adenosine has become less expensive. The protocol calls for giving adenosine over a 4-minute infusion. Dipyridamole has a half-life of 30 minutes. Adverse reactions have the potential to continue even after the administration of aminophylline. Lexiscan® has an intermediate biologic half-life and is injected over a 10-second duration. Dobutamine has a half-life of approximately 2 minutes. Side effects usually subside rapidly. Beta blockers and theophylline should be on hand to potentially treat a prolonged adverse event.
Imaging Protocol

Patients undergo first-pass contrast-enhanced CMR perfusion using a body coil or specialized cardiac coil. Scout imaging and cine short axis/long axis slices are performed initially to determine the cardiac position and geometry. The scouts are then used to plan the subsequent scans.

Imaging is performed at stress and rest during intravenous injection of the gadolinium-based contrast agent via a power injector at a rate of 5 mL per second. A single-shot gradient echo sequence with saturation-recovery magnetization preparation for T1 weighting and linear k-spacing is used for the first pass. Simulated stress imaging is performed with the infusion of a stress agent, as described previously. The scan is repeated at rest after adequate time for the effects of the stress agent to subside. (Movie 1, Figure 1).

Perfusion is determined in at least 3 short-axis slices of the left ventricle located at the base, middle, and apex. Additional long axis slices can be obtained if heart rate allows. The patient is asked to perform shallow breathing during the exam to minimize respiratory motion.

Delayed enhancement imaging is completed 10-15 minutes after the injection of gadolinium. The infarct information gained from this sequence has an additive diagnostic effect when used with both stress and rest perfusion imaging (Figure 2).

Image Post Processing

Contrast-enhanced magnetic resonance imaging can be used to evaluate myocardial perfusion patterns. Ideally, first-pass imaging with gadolinium-based contrast agents should result in images with signal intensity directly proportional to gadolinium concentration, allowing for accurate perfusion measurements. Perfusion can be qualitatively assessed or quantified using computer analysis of changes in signal intensity (SI) over time. Both relative and absolute flood blows can be quantified by the first-pass method. Quantification requires a rapid bolus of contrast by a power injector, producing a single sharp spike determined at time zero.

The heart is divided into 3 major segments – base, middle, and apex. The base and middle are divided into six sectors while the apex is divided into four (Figure 3). The apical cap is sometimes included if long axis perfusion is performed. Coronary distribution is assigned to their respective sectors using the 17-segment model for tomographic imaging of the heart (Figure 4).4,5 A comparison of the SI curve for each sector should be made with the left ventricular blood pool. This semi-quantitative image can be placed in a polar plot for quick review (Figure 5).

The initial amplitude of the SI curve corresponds with the absolute myocardial blood flow. The myocardial perfusion reserve can be calculated as the ratio of myocardial blood flow at stress over the myocardial blood flow at rest.

Applications

Conventional coronary angiography is the gold standard in evaluating the severity of obstructive coronary disease. However, the invasive nature, expense, and ionizing radiation involved with conventional coronary angiography make it an ineffective tool for screening purposes in patients with
Figure 2. Selected short axis images from an abnormal MRI perfusion scan showing associated mid anteroseptal and anterior wall motion abnormality, rest and stress perfusion abnormality (black arrows), and myocardial delayed enhancement (white arrows) consistent with infarct. (A) Short axis cine end diastole, (B) Short axis cine end systole, (C) Rest perfusion, (D) Adenosine stress perfusion, (E) Delayed enhancement.

Figure 3. Mid chamber short axis perfusion image divided into cardiac segments based on a 17-segment model. (1) Mid anterior, (2) Mid anterolateral, (3) Mid interolateral, (4) Mid inferior, (5) Mid inferoseptum, (6) Mid anteroseptum.

Figure 4. Mid chamber short axis perfusion image divided into coronary perfusion territories. Individual patients may demonstrate variability of these locales. (LAD) Left anterior descending coronary artery, (CFX) Circumflex coronary artery, (RCA) Right coronary artery.
suspected CAD. Other imaging modalities are available for risk stratification among these patients. A meta-analysis performed in 2007 showed CMR to have a sensitivity and specificity of approximately 85% for the detection of myocardial ischemic reactions in the setting of obstructive coronary lesions evaluated by conventional angiography. A study looked at CMR as the sole clinical decision maker whether to proceed with invasive procedures versus continuing with medical management with results similar to baseline. A study performed by M. Costa et al suggests that quantitative CMR can be safely used to determine the hemodynamic significance of coronary stenosis and to exclude the presence of significant CAD with a high degree of accuracy. CMR has shown the ability to provide robust risk stratification for patients who present with symptoms of ischemia. Coronary artery disease is a major cause of morbidity and mortality in patients with diabetes mellitus. A study by Coelho-Fiho et al in 2011 evaluated diabetic patients referred for suspicion of myocardial ischemia. They showed a correlation of a three-fold increase of a major adverse cardiac event in those that demonstrated evidence of ischemia on CMR perfusion. In a separate study, the authors also showed robust prognostic information for risk of major adverse cardiac events beyond the presence of scar, left ventricular ejection fraction, and clinical and ECG markers of cardiac prognosis.

SPECT imaging has been a noninvasive workhorse in evaluating patients for suspected significant coronary artery disease. A single-center study out of Europe published in 2008, and a multi center follow on study in 2012, found CMR to be as effective as SPECT in detection of significant CAD and proposed CMR as a viable alternative to SPECT imaging for the workup of patients with known or suspected disease.

Multiple studies have shown utilization of CMR to...
evaluate for reperfusion in patients status post revascularization.\textsuperscript{11,12} The increased perfusion correlated with regions of perfusion defects seen in preprocedural scintigraphy\textsuperscript{12} and coronary stenosis seen in prior angiography.\textsuperscript{11}

Summary

CMR has the potential of being a one-stop shop when it comes to imaging evaluation of the heart. In contrast to other perfusion imaging modalities, CMR can offer noninvasive examination of the anatomy, function, and perfusion of the heart, all without the use of ionizing radiation. Contraindications for CMR include similar factors as those for other MR imaging. Newer MR safe cardiac pacers make it possible for pacer-dependent patients to receive a magnetic resonance imaging exam.

Studies continue to show the utility of CMR as a valuable imaging tool in the assessment of myocardial ischemia. Although more work needs to be done, CMR has a promising future in the comprehensive examination of myocardial perfusion.

The views expressed in this material are those of the author, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Army or Air Force.

References