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Detecting Left Ventricular Myocardial Ischemia During Intravenous Dobutamine with Cardiovascular Magnetic Resonance Imaging (MRI)

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ABSTRACT

Advances in computer software, scanner hardware, and hemodynamic monitoring equipment have permitted the development of cardiovascular stress testing protocols for use during intravenous Dobutamine infusions within magnetic resonance imaging (MRI) scanners. Recent studies have documented that the safety profile and clinical utility of Dobutamine/Atropine cardiac stress testing during MRI compares favorably with other noninvasive stress imaging modalities and is particularly useful in patients not well suited for stress echocardiograms.

Although exercise testing is used widely to identify inducible myocardial ischemia, many patients are limited in their ability to perform exercise due to peripheral arteriosclerotic vascular disease, disabling arthritis, history of stroke, orthopedic constraints, or chronic pulmonary disease (1). In these patients, inotropic (Dobutamine, Dopamine, Epinephrine, and Isoproterenol) or vasoactive (Dipyridamole or Adenosine) agents, or transcatheter pacing, is substituted for exercise to provide cardiovascular stress (1). Dobutamine, a synthetic catecholamine that increases left ventricular (LV) myocardial contractility in normal subjects (2,3), is the most commonly used inotropic agent. It is relatively inexpensive, its onset of action is within 2 minutes, and it achieves

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a maximal effect on contractility in normal subjects at a relatively low dose (10 μg/kg/min) (4,5). In addition, Dobutamine has a positive chronotropic effect that occurs at a 20 μg/kg/min dose (6). The chronotropic response is important because several studies have documented improved diagnostic accuracy for identifying inducible ischemia when a heart rate response of $\geq$85% of the maximum predicted heart rate response (MPHRR) for age is achieved during stress testing (7). When 85% MPHRR is not achieved with Dobutamine administration, Atropine (a parasympatholytic drug) may be administered in 0.3 mg increments every 30 seconds up to a total dose of 1.5 mg to augment heart rate response. Combined Dobutamine/Atropine pharmacologic stress protocols have a sensitivity and specificity of 80% and 84%, respectively, for detecting inducible ischemia (a diagnostic accuracy that is similar to exercise testing) (8).

The detection of left vertricular (LV) contractile abnormalities induced during Dobutamine stress echocardiography has proven clinical utility for detecting inducible ischemia. Unfortunately, approximately 5–15% of patients undergoing stress echocardiograms exhibit relatively poor acoustic windows—particularly those with large body habitus, severe obstructive airway disease, or prior cardiothoracic surgery (8). In our echocardiography laboratory, this represents 0 to 20% of patients referred for dobutamine echocardiography on a given day. Cine gradient-echo magnetic resonance imaging (MRI) can be used to visualize the endocardium of the left ventricle in any tomographic plane with the spatial and temporal resolution necessary to assess LV thickening. The most common qualitative method used during echocardiography to assess endocardial thickening is based on a 16-segment model developed by the American Society of Echocardiography (9). Since the apical posterior and anterior septal walls are seen with MRI, an 18-segment model incorporating three apical and three short-axis (base, middle, and apex of the left ventricle) views is available. Importantly, the MRI community has standardized neither the 18-segment model nor any of the MRI views. Like echocardiography, a four-point scoring system, in which 1 is normal, 2 is hypokinetic, 3 is akinetic, and 4 is dyskinetic, is used to assess LV endocardial thickening. Ischemia is identified when a deterioration of $\geq$1 in score occurs during stress testing, or a hypokinetic segment at rest fails to improve contractility or displays a biphasic response (Fig. 1) (10).

Since 1992, several investigators have documented the utility of using cine gradient-echo magnetic resonance imaging (MRI) during Dobutamine infusions to detect LV regional wall motion abnormalities indicative of ischemia (11–13). In Table 1, the sensitivity and specificity of MRI testing for detecting coronary arterial luminal narrowings is shown. It is important to note that in the first three studies the severity of coronary artery arteriosclerosis was known prior to MRI testing, wall motion was assessed at baseline and at peak stress (and not visualized continuously throughout the course of testing), and LV wall motion was not assessed during rapid heart rates at high levels of pharmacologic stress (particularly 85% MPHRR by age). These factors, and the perception of poor patient tolerance for stress testing during MRI, limited widespread clinical application of these early reported techniques.

Recent software and hardware modifications have enabled investigators to overcome some of these limitations. Specifically, scans incorporating shorter repetition times, (in the order of 7 to 15 msec) and phase-encoding grouping have allowed for acquisition of images with high temporal resolution that permit clear delineation of the LV endocardial surface at end systole during rapid heart rates (10,14). Using phased-array surface coils that yield images with high signal to noise (thereby permitting image acquisition with increased spatial resolution), crisp image

Table 1

Sensitivity and Specificity of Dobutamine MRI for Detection of Coronary Arterial Luminal Narrowings

	n	Coronary Artery % Luminal Stenosis	Peak Dosage Dobutamine	Atropine	Sensitivity (%)	Specificity (%)	Sensitivity (%)		
							1 vss	2 vss	Multi vss
Pennel, et al.	25	$\geq$50	20	No	91	N/A	N/A	N/A	N/A
Baer, et al.	28	$\geq$70	20	No	85	77	73	N/A	100
vanRugge, et al.	35	$\geq$50	20	No	91	80	88	91	100
Nagel, et al.	208	$\geq$50	40	Yes	86	86	74	84	98
Hundley, et al.	153	$\geq$50	40	Yes	83	83	75	82	92

n = Number of participants, vss = Coronary artery (ies).

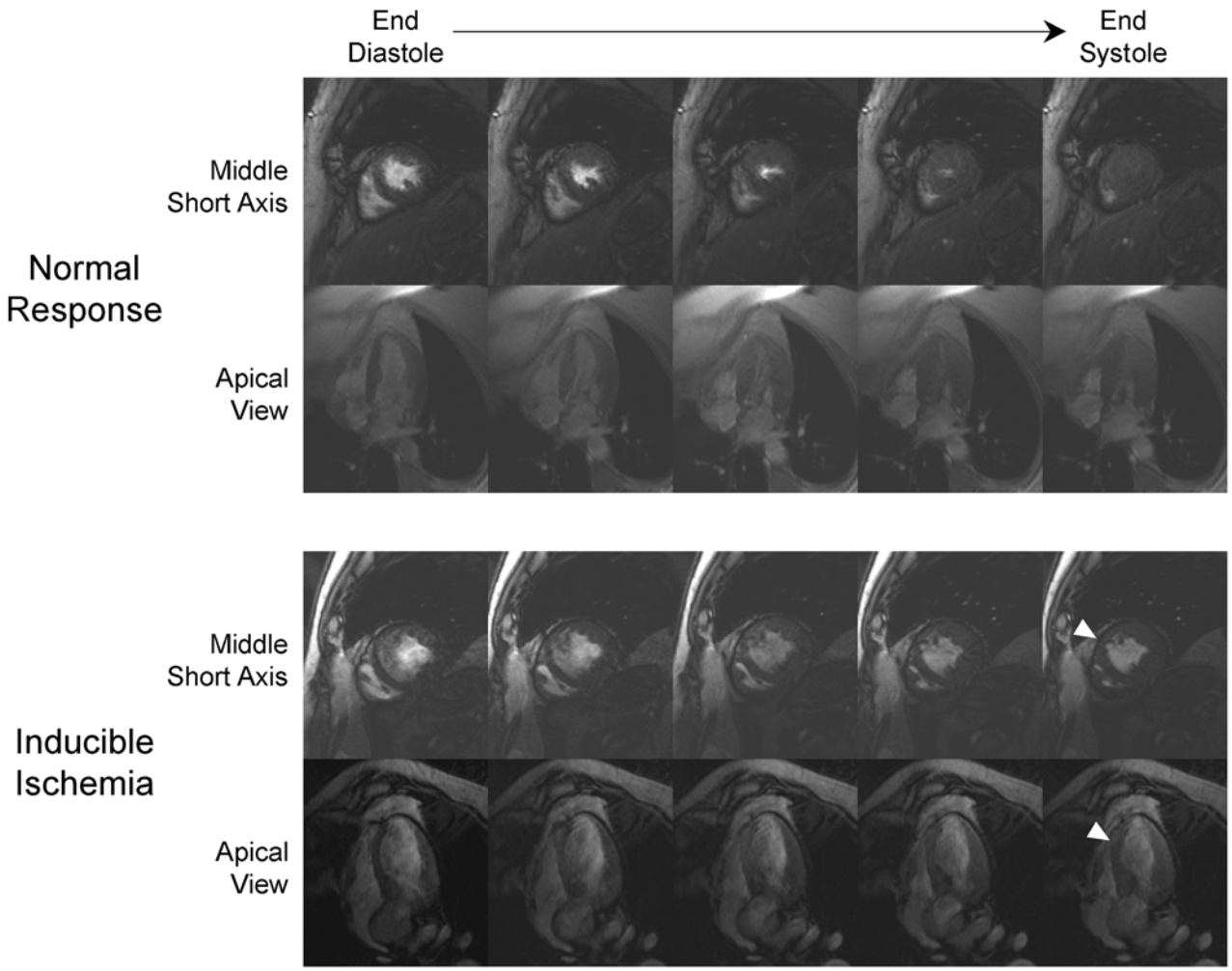

Figure 1. Peak Dobutamine infusion cine MR images of the left ventricle (LV) are shown in the middle short axis and the apical LV outflow tract views. Several images from end diastole (left) to end systole (right) are displayed in a patient with a normal contractile response (top panels), and evidence of inducible ischemia (bottom panels). Inducible ischemia is identified by the development of hypokinesis in the middle and apical segments of the anteroseptum at end systole (white arrows).

quality is routinely available in all tomographic planes of the LV (15). Finally, the introduction of hemodynamic monitoring (heart rate, oxygen saturation, blood pressure) and intravenous administration equipment as well as wall motion visualization have allowed physicians safely to monitor patients during the course of stress testing (10). Monitoring LV systolic thickening for ischemia is particularly important because ST segments are altered by the magnetic field gradient within the bore of the scanner, and monitoring the electrocardiogram (ECG) for ischemia during stress testing is not feasible (16).

Recently, two studies have highlighted the utility of these technical advancements for the widespread clinical use of MRI in cardiovascular stress testing. In the first, Nagel et al. (16) compared ischemia-induced wall motion abnormalities between Dobutamine MRI (DMRI) and Dobutamine stress echocardiography (DSE) with harmonic imaging. DSE and DMRI were performed on 208 consecutive patients with suspected CAD prior to cardiac catheterization. During MRI, Dobutamine was infused at doses of 5, 10, 20, 30, and 40 μg/kg/min in 3-minute stages. Atropine was also given if <85% MPHRR was not achieved. DMRI provided better sensitivity (89% vs 74%) and specificity (86% vs 70%) for detecting CAD ($\geq$50% coronary stenosis by coronary angiography) compared with DSE. It was felt by the investigators that this

was due to improved visualization of the left ventricular endocardial surface.

In a second study (10), Hundley et al. addressed the utility of DMRI in 163 patients who failed second harmonic transthoracic echocardiography. In general, these referrals were relatively heavy (mean weight of 89 kg, range 39–135 kg) and short (average 170 cm in height; range 140–196 cm). Forty-one of the patients weighed >150% of the ideal body weight. The bore diameter of the MR scanner used in this study was 60 cm. At baseline, 97 patients had abnormal and 56 had normal LV wall motion at rest. Thirty-four percent had prior myocardial infarction, 32% had prior coronary surgical revascularization, and 25% had prior percutaneous coronary interventions. Electrocardiograms were abnormal in >50% of the referred patients. When compared to contrast coronary angiography, the sensitivity and specificity were both 83% for detecting coronary arterial luminal narrowings of >50%. Patients who had normal wall motion at rest and no evidence of inducible ischemia had a very good prognosis, with a negative predictive value of 93%.

The study protocol used by Hundley et al. included the following: (a) before study, a 12-lead ECG was performed outside of the magnet; (b) after intravenous access was established, patients were positioned supine on the MR scanning table with a phase-array surface coil, ECG monitoring, brachial blood pressure cuff attached. During testing, a registered nurse and physician continuously monitored heart rate and rhythm, blood pressure, oxygen saturation, and respiratory rate; (c) baseline images were obtained and then repeated every 5 minutes during dobutamine infusions of 5, 10, 20, and 40 μg/kg/min ($\pm$atropine); and (d) after 10 minutes of recovery, additional images and a 12-lead ECG were obtained to confirm wall motion and that the patients' ST segments had returned to baseline.

The fast imaging/display technique implemented by Hundley et al. allows for the visualization of LV endocardial thickening throughout the course of a pharmacologic stress test. This enhances the clinical utility of MR stress testing in several respects. First, as shown in stress echocardiography studies, the physician's diagnostic accuracy is significantly higher when images are reviewed throughout the course of testing (17). Second, inducible ischemia may be identified when patients develop chest discomfort during the course of testing. In a review of 2,246 patients who had undergone DSE, 20% of subjects developed chest discomfort during Dobutamine/Atropine infusion, but only 2–4% of subjects developed wall motion abnormalities indicative of myocardial ischemia (8). Thus, by viewing wall motion during testing, premature test termination can be avoided in patients that do not develop LV wall motion abnormalities indicative of ischemia. Finally, since results are interpreted immediately, rapid facilitation of patient management, such as same-day preoperative risk assessment, can occur.

Pharmacologic stress testing with MRI has limitations and there are several areas that deserve further study:

1. It is important to note that patients with claustrophobia, intracranial metal, pacemakers, or cardiac defibrillators are not candidates for stress testing with MRI.
2. The efficacy of Dobutamine MRI in patients with marked ventricular ectopy or atrial fibrillation is not established.
3. Thus far, patients studied with Dobutamine MRI possess a relatively high pre-test probability of coronary disease and application of MRI to screen other patient populations has not been performed.
4. The utility of this form of testing in patients with left ventricular hypertrophy is not clear.
5. The ability to identify inducible ischemia in myocardial segments that are persistently hypokinetic throughout the course of stress testing is not established. Perhaps combining myocardial perfusion with wall motion testing would be useful in these subjects.
6. Finally, most methods performed to date utilize qualitative physician interpretation. Quantitative analysis techniques, including myocardial tagging and velocity encoded phase mapping, may yield superior results (18,19).

CONCLUSIONS

In conclusion, pharmacologic stress testing during Dobutamine MRI can be used to diagnose inducible ischemia in patients with suspected coronary atherosclerosis. Recent results suggest this technology may be particularly useful for patients unable to undergo stress echocardiography due to poor acoustic windows. The safety profile and clinical utility of Dobutamine/Atropine MR compares favorably with other widely-accepted noninvasive imaging modalities. Further research is required to determine if supplementation of wall motion testing with other techniques, such as MR perfusion or coronary artery imaging, would improve the clinical efficacy of MRI testing in patients with reduced LV systolic function at rest, as well as in patients with LV hypertrophy.

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