Dobutamine Stress MRI for the Assessment of Coronary Artery Disease: Initial Clinical Experience in Israel

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ABSTRACT: **Background:** Over the past few years dobutamine stress magnetic resonance (DSMR) has proven its efficacy as an integral part of the diagnosis of coronary artery disease (CAD).
Objectives: To present the feasibility and safety of DSMR in Israel.
Methods: Thirty patients with suspected or known CAD were studied. DSMR images were acquired during short breath-holds in three short axis views and four-, two-, and three-chamber views. Patients were examined at rest and during a standard dobutamine-atropine protocol. Regional wall motion was assessed in a 16-segment model and the image quality was evaluated using a four-point scale for the visibility of the endocardial border.
Results: In 28 patients (93.4%) DSMR was successfully performed and completed within an average of 55 ± 6 minutes. One patient could not be examined because of claustrophobia and another patient, who was on beta-blockers, did not reach the target heart rate. Image quality was excellent and there was no difference between the rest and stress images in short axis (3.91 ± 0.29 vs. 3.88 ± 0.34, $P = 0.13$, respectively) and long axis (3.83 ± 0.38 vs. 3.70 ± 0.49, $P = 0.09$, respectively) views. Segmental intra-observer agreement for wall motion contractility at rest and stress cine images was almost perfect ($\kappa = 0.88$, 95% confidence interval = 0.93–0.84, and $\kappa = 0.82$, 95% CI = 0.88–0.76) respectively. No serious side effects were observed during DSMR.
Conclusion: The present study confirms the feasibility, safety and excellent image quality of DSMR for the diagnosis of coronary artery diseases.

IMAJ 2013; 15: 273–277

KEY WORDS: dobutamine stress magnetic resonance (DSMR), magnetic resonance imaging (MRI), ischemia, viability, coronary artery disease (CAD)

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Dobutamine stress magnetic resonance imaging is an established clinical method with high diagnostic and prognostic value for the evaluation of coronary artery disease [1-5]. Because of the high intrinsic contrast between intracavitary blood and the endocardium, DSMR allows, without the use of contrast agents, an accurate delineation of the endocardial border and therefore an accurate and reproducible assessment of wall motion contractility. In addition, DSMR has a high spatial and temporal resolution, which facilitates a complete tomographic cine loop acquisition within short acquisition intervals (e.g., 12 heart beats). Therefore, identical pharmacological stress protocols can be implemented for dobutamine stress echo and MRI. At each stress level, several highly reproducible views can be acquired [Figure 1] that are highly reproducible because the coordinates rather than visual assessment are used for repetitive imaging.

The assessment of ischemia and viability by MRI (dobutamine and adenosine stress MRI) has become an integral part of the diagnostic imaging modalities in cardiology [2]. Until recently, to the best of our knowledge these tests have not been performed in Israel. We report our initial experience with DSMR in a tertiary care hospital in Israel.

PATIENTS AND METHODS

We prospectively studied 30 consecutive patients; written informed consent was obtained from all patients before the DSMR. Patients were eligible if they had suspected or known CAD (with or without prior percutaneous or surgical revascularization) but were not considered for study inclusion if they had typical contraindications for MRI or administration of dobutamine [Table 1]. The clinical indications for DSMR were: a) evaluation of ischemia in 17 patients (61%), b) preoperative risk assessment of major non-cardiac surgery in 9 patients (32%), and c) viability assessment in 2 patients (7%). All patients were instructed to stop taking beta-blockers and anti-anginal medication at least 24 hours before the DSMR study. The study was conducted in accordance with the local institutional review board.

DSMR = dobutamine stress magnetic resonance imaging
CAD = coronary artery disease

Figure 1. Time course of DSMR

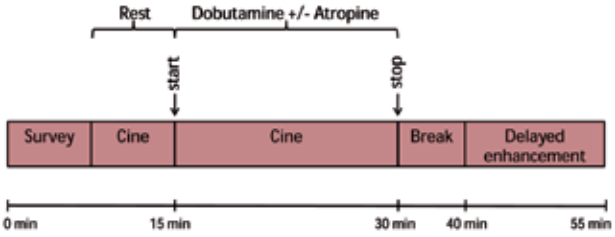


Table 1. Baseline characteristics of the study population

Characteristic	Value
Age (yr) Range	54.5 ± 14.5 17–82
Gender, male, n (%)	24 (86)
Body mass index (kg/m²)	26.9 ± 3.8
Risk factors	
Hypertension, n (%)	22 (79)
Diabetes, n (%)	15 (54)
Hypercholesterolemia, n (%)	22 (79)
Current cigarette smoking, n (%)	9 (32)
Family history of CAD < 55 yr, n (%)	15 (54)
Known CAD, n (%)	14 (50)
Previous myocardial infarction, n (%)	7 (25)
Prior percutaneous coronary intervention, n (%)	12 (43)
Beta-blocker premedication, n (%)	17 (61)
LVEF (%)	58 ± 10
LVEDV (ml)	117 ± 45
LVESV (ml)	50 ± 32

CAD = coronary artery disease, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume

DSMR STUDY

MRI was performed with a 1.5 Tesla scanner (Signa Excite, GE Healthcare, USA) and a dedicated eight-channel cardiac phased-array coil. Cardiac synchronization was performed with four electrodes placed on the left anterior hemithorax (vector electrocardiogram).

The following MRI protocol was applied: a) acquisition of survey images in three orthogonal planes (transverse, coronal, sagittal) to localize the heart within the chest; b) acquisition of rest cine short axis views (apical, mid, and basal short axis) in addition to long axis views in four-, two-, and three-chamber orientations using a balanced steady-state free precession (bSSFP) sequence (repetition time/echo time/flip angle 1.3 ms/3.2 ms/45° retrospective gating, 30 phases/cardiac cycle field of view 300 mm, matrix 128 × 256, and slice thickness 8 mm); c) acquisition of short axis covering the whole myocardium.

DSMR examination was carried out using the standard high dose regimen (up to 50 μg/kg/min) plus atropine (up to 2 mg), if needed, to reach the target heart rate. Dobutamine was infused intravenously at 3 minute stages at doses of 10, 20, 30, 40, and 50 mg/kg per minute and stopped when ≥ 85% of age-predicted heart rate was reached. At every stage, three short axis (apical, mid, and basal) and three long axis views (four-, two-, and three-chamber), with the same geometry as the rest images, were repeated. Termination criteria were severe chest pain, significant arrhythmia, hypertension (blood pressure > 240/120 mm Hg), systolic blood pressure drop of > 40 mmHg, and any intolerable side effect regarded as associated with dobutamine [6]. For assessment of viability a low dose dobutamine protocol was used: 5 and 10 μg/kg per min for 3 minutes. The test was indicative of viability when there was an improvement of wall motion contractility at either the 5 or the 10 μg/kg per min dose. At the end of DSMR myocardial late gadolinium enhancement scar imaging in short and long axis orientations was obtained 10 minutes after intravenous administration of gadolinium (0.2 mmol/kg, gadopentetate dimeglumine, Magnevist, Bayer Schering, Germany).

IMAGE ANALYSIS

The MRI dataset was transferred to a dedicated MRI workstation MASS (QMass MR version 7.2, Medis, Leiden, The Netherlands) for review with a 16-segment model [7] for analysis of regional left ventricular wall motion and myocardial delayed enhancement images. Ischemia was defined as one or more segments showing inducible wall motion abnormality or if a biphasic response was demonstrated in areas with resting wall motion abnormalities. For volume measurements, endocardial borders were traced manually at end-diastole and end-systole in the short axis projection with papillary muscles excluded from the analysis; the most basal section of the left ventricle was defined for end-diastole and end-systole as the slice of which at least 50% of the LV myocardial circumference was visible.

The image quality of each standard view (long and short axis) was rated on a 4-point scale for the visibility of the endocardial border (1 = poor or non-diagnostic, 2 = partial or moderate visibility, 3 = good visibility, 4 = excellent visibility) [8].

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Windows; for all continuous parameters, mean ± standard deviation is given. The paired Student *t*-test was used to assess statistical significance of continuous variables. Intra-observer variability for the assessment of wall motion contractility was evaluated in 10 randomly selected study subjects using Cohen κ to allow quan-

LV = left ventricular

titative measure of agreement by using the following grading: κ grades of 0–0.2 = poor agreement, 0.21–0.40 = fair agreement, 0.41–0.6 = moderate agreement, 0.61–0.80 = substantial agreement, and 0.81–1.0 = nearly perfect agreement. For κ values, the respective 95% confidence intervals are given [9]. The Wilcoxon signed-rank test was used to evaluate the statistical correlation between the visual score of cine images at rest and at maximum stress. $P \leq 0.05$ was considered statistically significant.

RESULTS

The study group consisted of 30 patients with suspected or known CAD. In 28 of them (93.4%) DSMR was successfully performed. One patient could not be examined because of claustrophobia and another patient, who was on beta-blockers, did not reach the target heart rate. The average dosage of dobutamine was 41.4 ± 10.2 μg/kg per minute, and atropine was infused to nine patients at an average dosage of 0.2 ± 0.3 mg. The mean duration of DSMR including rest cine imaging and delayed enhancement was 55 ± 6 minutes [Figure 1]. All patients tolerated DSMR without incidence of death, myocardial infarction, ventricular fibrillation, or other serious side effects; one patient with moderately reduced ejection fraction (34%) developed nonsustained ventricular tachycardia which resolved spontaneously. Reasons for test termination included achieving the target heart rate (22 patients), improvement of myocardial contractility in patients sent for low dose DSMR for viability assessment (2 patients), and development of inducible ischemia (4 patient).

DSMR

Two patients (out of 17) sent for evaluation of ischemia had positive DSMR results. One patient developed mild hypokinesia at the maximal dobutamine dose in one of the segments. Due to atypical symptoms and known anaphylactic shock to iodinated contrast agent in previous invasive coronary angiography no further evaluation was performed. In another patient with positive DSMR results (ischemia in anterior wall) and known significant lesion in the distal left anterior descending artery, invasive coronary angiography was not performed. Representative examples of negative and positive DSMR results are shown in Figure 2.

Two patients (of nine) sent for preoperative risk assessment of major non-cardiac surgery had positive DSMR results but were clinically asymptomatic and therefore did not undergo coronary angiography. All nine patients sent for preoperative risk assessment did not experience any cardiac event (death, myocardial infarction, congestive heart failure) during surgery or during their postoperative course.

Two patients with three-vessel disease and severe LV dysfunction sent for low dose DSMR had a positive test result for viability and coronary artery bypass surgery for complete revascularization was therefore performed.

Table 2. Average image quality score in short and long axis

	Visual score		
Short/long axis	**Rest**	**Stress**	***P* value**
Base	3.95 ± 0.23	3.92 ± 0.31	0.43
Mid	3.92 ± 0.27	3.90 ± 0.29	0.58
Apex	3.82 ± 0.38	3.78 ± 0.42	0.13
Two-chamber view	3.83 ± 0.38	3.71 ± 0.46	0.37
Three-chamber view	3.79 ± 0.41	3.64 ± 0.49	0.25
Four-chamber view	3.86 ± 0.35	3.75 ± 0.52	0.37

Three patients without a history or ECG or echocardiographic evidence of previous myocardial infarction had subendocardial LGE consistent with the diagnosis of myocardial infarction. An additional patient, hospitalized in another hospital with diagnosed acute myocardial infarction, had epicardial LGE consistent with the diagnosis of previous myocarditis.

IMAGE QUALITY AT REST AND MAXIMUM DOBUTAMINE STRESS

All DSMR studies were diagnostic. The image quality did not differ between the rest and stress images in short axis and long axis views [Table 2].

INTRA-OBSERVER AGREEMENT

Segmental intra-observer agreement for myocardial wall motion contractility at rest and stress cine images were almost perfect (κ = 0.88, 95% CI = 0.93–0.84, and κ = 0.82, 95% CI = 0.88–0.76), respectively.

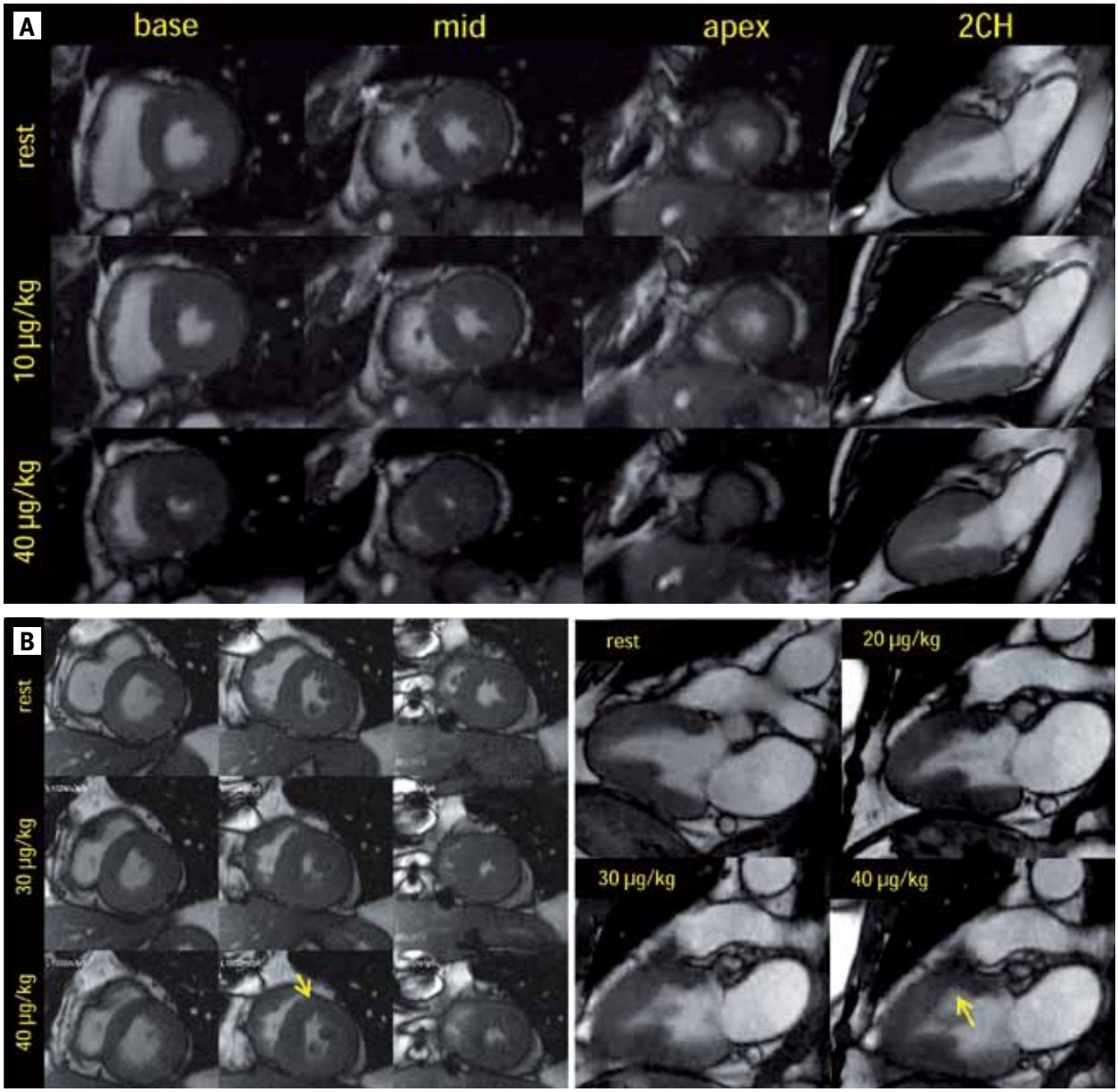
DISCUSSION

In recent years DSMR has become a worldwide robust modality for identifying ischemia, evaluating viability, assessing prognosis and predicting complications. This novel imaging modality, however, has never been performed in Israel. We believe we are the first to demonstrate its different clinical applications, feasibility and safety in Israel.

Nagel et al. [6] were the first to validate DSMR for the detection of CAD. DSMR performed better than stress echocardiography in the identification of CAD, using at least 50% stenosis on coronary angiography as the gold standard. MRI sensitivity and specificity in this study of 208 patients were 88.7% and 85.7%, respectively. Since then many validation studies have been performed and have reported similar results. Nandalur and co-authors [10] pooled the data from 14 studies and 724 patients and confirmed good sensitivity (83%, 95% CI 79–88%) and specificity (86%, 95% CI 81–91%)

LGE = late gadolinium enhancement
CI = confidence interval

Figure 2. [A] Representative example of negative DSMR study: improvement of myocardial contractility with increasing dobutamine dose in short (base, mid, apex) and long axis (two-chamber and three-chamber) views. Note the high natural contrast between blood and myocardium as well as the clear definition of the endocardial and epicardial border. **[B]** Representative example of positive DSMR study: clearly visible hypokinesia in the mid-anterior (arrows) segments at high dose dobutamine (40 µg/kg/min)



of stress-induced wall motion abnormalities against X-ray coronary angiography for the detection of CAD. In addition, in patients unable to undergo stress echocardiography with clinical predictors suggesting an intermediate risk for the development of a cardiac event during non-cardiac surgery, DSMR may be used to identify those at high and low risk for cardiac death, myocardial infarction, or congestive heart failure during or after non-cardiac surgery [11]. In the present study all nine patients sent for preoperative risk assessment and having a negative DSMR or mild ischemia did not experience any cardiac event.

In addition to the assessment of ischemia using high dose DSMR, viability assessment is achieved using low dose DSMR (functional response) and/or LGE scar imaging (morphological assessment of viability) [12]. A comparison between positron-emission tomography and low dose DSMR demonstrated similarities between the two techniques for the assessment of viability with DSMR sensitivity of 88% and specificity of 87%

compared with PET [13]. Wellnhofer et al. [14] compared DSMR and LGE for the prediction of viability in 29 patients and found DSMR to be slightly superior in predicting recovery after revascularization. LGE predicted 73% of hibernating segments correctly, compared with 85% correctly predicted by low dose DSMR.

High dose DSMR is both safe and effective. In a series of 1000 patients, 28 adverse events included 1 case (0.1%) of sustained and 4 cases (0.4%) of non-sustained ventricular tachycardia, 16 cases (1.6%) of atrial fibrillation, and 2 cases (0.2%) of transient second-degree atrioventricular block [15]. In the present study all patients tolerated DSMR without incidence of serious events; one patient with moderately reduced ejection fraction developed non-sustained ventricular tachycardia which resolved spontaneously.

CLINICAL APPLICATIONS

Coronary revascularization has a central role in the management of patients with stable CAD; however, despite extensively published literature, the appropriate selection of patients and lesions for revascularization in stable CAD continues to be an area of controversy. Considering coronary anatomy alone, which can also be evaluated using MRI [16], while ignoring the physiology when selecting patients and lesions for revascularization oversimplifies a complex disease. In addition to the assessment of ischemia, DSMR provides other valuable data such as evaluation of LV volumes and function (MRI is the gold standard for volume measurements [17]), diagnosis of undetected previous myocardial infarction (as shown in three patients in the present study), and even alternative diagnoses as shown in one patient in the present study. Therefore, DSMR may direct and even change the management of the complex CAD.

CONCLUSIONS

The present study confirms the feasibility, safety and excellent image quality of DSMR for the diagnosis of CAD. Our initial data show that DSMR is an important addition to the present diagnostic armamentarium for accurate evaluation of ischemia, viability, as well as etiology of myocardial damage. The assessment of myocardial ischemia and viability by DSMR should play an integral part in diagnostic imaging modalities in cardiology in Israel.

PET = positron-emission tomography

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"In a completely rational society, the best of us would be teachers and the rest of us would have to settle for something less, because passing civilization along from one generation to the next ought to be the highest honor and the highest responsibility anyone could have"

Lee Iacocca (b. 1924), American automobile executive