High-Dose Dobutamine Stress Cardiac MR Imaging for Detection of Myocardial Ischemia

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Introduction

Stress induced impairment of regional left ventricular function is a reliable indicator of transient myocardial ischemia [1, 13]. Therefore, the analysis of wall motion abnormalities by echocardiography in conjunction with a variety of different stress modalities has grown to a clinically established non-invasive test for the assessment of myocardial ischemia [2]. However, optimal echocardiographic image acquisition depends on the skill of the operator and the presence of an adequate acoustic window. Approximately 15% of patients admitted to stress-echo yield suboptimal or non-diagnostic images [3, 4, 5, 6]. Formerly these patients were referred to myocardial scintigraphy performed in single-photon emission computed tomography (SPECT) technique. High-dose dobutamine stress cardiac magnetic resonance imaging (CMR) emerged as an alternative high-resolution and noninvasive method for the detection of stress induced myocardial ischemia, which does not expose the patient to radiation and provides a diagnostic accuracy for the detection and localization of functional significant coronary artery disease (CAD) comparable to stress echocardiography and SPECT technique [6, 16]. Various studies have shown that CMR permits acquisition of images with high-spatial and improved temporal resolution in any tomographic plane [7] and allows accurate determination of left ventricular function in terms of wall motion and wall thickening at rest and during pharmacological stress [8, 9]. High dose dobutamine stress testing can be safely performed with a standard dobutamine/atropine stress proto-

col similar to stress echocardiography studies and proved to be a clinically feasible tool for the assessment of hemodynamically significant coronary artery stenoses [6, 10, 11, 12, 14, 22, 23, 26].

Dobutamine stress cardiac MR imaging

Due to its high spatial resolution and good tissue contrast, CMR has been shown to be the most accurate imaging modality for determination of wall thickening and volume measurements [13, 14, 15]. Recent technical developments, providing stronger gradient systems with new ultrafast sequences and fast data reconstruction procedures providing "near real-time" imaging facilitate clinically feasible cardiac MRI stress testing. Cine CMR with retrospective ECG-gating displays myocardial contractility of the entire cardiac cycle and permits evaluation of global and regional function [17].

MR sequence

The image quality of gradient echo techniques, which offer a shorter acquisition time as spin-echo sequences, depends on flow effects and may decrease depending on impaired regional or global ventricular function. Steady-state free precession sequences (e.g. TrueFISP) provide much higher signal intensity and signal-to-noise ratio (SNR) [18]. They enable rapid data acquisition and a high contrast between blood and myocardium without flow artifacts. Because of the distinguished delineation of anatomic structures steady-state free precession sequences are ideally suited for evalua-

The diagnostic accuracy of dobutamine stress MRI is comparable to stress echocardiography and SPECT.

TrueFISP cine sequences provide rapid image acquisition and high contrast between blood pool and myocardium.

tion of wall motion and wall thickening. Parallel imaging techniques reduce imaging time even more, but there is a partial loss of SNR depending on the accelerating factor. Currently, steady state free precession sequences in combination with parallel image acquisition and retrospective gating are state of the art. New real-time imaging sequences with improved spatial and temporal resolution will lead to further improvement in cardiac MR imaging especially during stress testing [17].

Image acquisition

Primary rapid multi-slice localizing images are acquired to define the cardiac axes. By means of single-angulated tomograms intersecting the mitral valve and the cardiac apex on a transverse view double-angulated long-axis tomograms that also intersect the mitral valve plane and the apex are planned. Based upon these images contiguous true short-axis cine scans are acquired to cover the whole left ventricle. In addition, three long-axis tomograms – two chamber view, four chamber view and three chamber view – are acquired according to the equatorial short axis orientation. Scanning by breath-holding in end-expiration reduces breathing artifacts. True short-axis and long-axis cine images are obtained at each stress level.

Standard high-dose dobutamine protocol

As a primarily beta1-adrenergic catecholamine with positive inotropic and positive chronotropic effect, dobutamine increases the myocardial oxygen consumption. Coronary arteries with severe stenosis do not allow adequate increase of blood flow to compensate elevated myocardial oxygen consumption under stress conditions. Myocardial ischemia leads to impairment of regional myocardial function, depressed systolic contractility and loss of systolic wall thickening. ECG changes and clinical symptoms manifest later and inconsistently in the "cascade of ischemia" [13].

For stress testing dobutamine is infused intravenously during 3-minute stages at doses of 10, 20, 30 and 40 µg per kilogram of body weight per minute under continuously monitoring of heart rhythm, blood pressure and symptoms. If the submaximal stress level described by a target heart rate of $((220\text{-age}) \times 0.85)$ is not reached, additional fractionated atropine doses of 0.25 mg every 60 seconds up to a maximal dose of 1.0 mg are administered intravenously. The same true short-axis and long-axis cine images are obtained at each stress level as acquired at rest (Figure 1). Immediately after acquisition images are displayed

iPAT (integrated Parallel Acquisition Techniques) allow fast acquisition of cine images in multiple orientations.

Dobutamine stress MRI is performed using the same incremental dobutamine protocol as known from stress echocardiography.
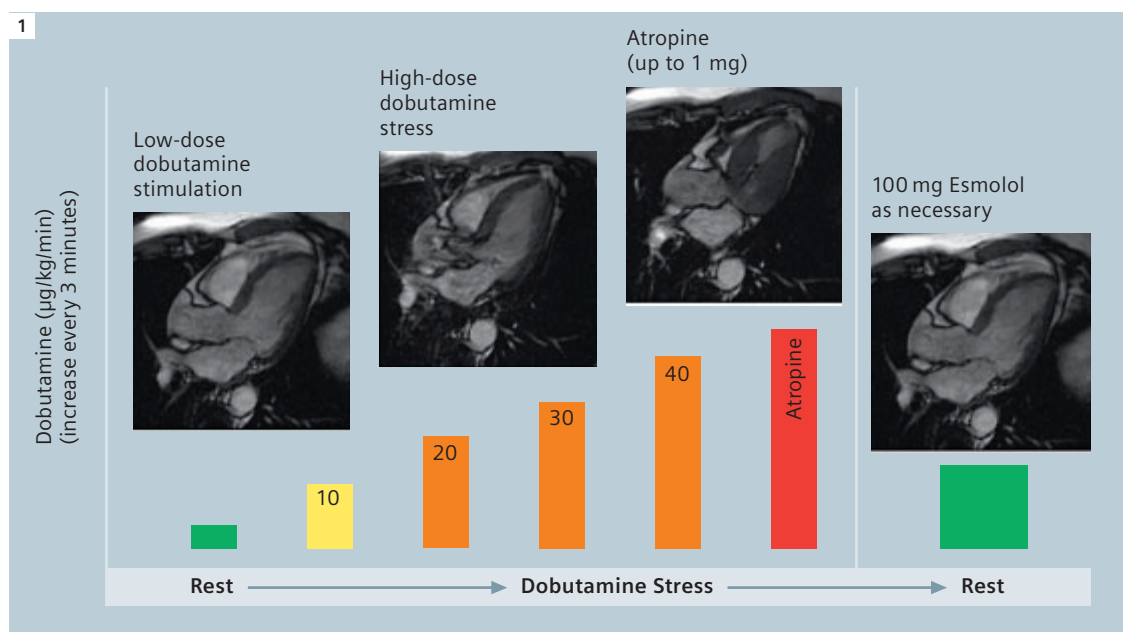
1 Schematic illustration of a dobutamine stress CMR examination consisting of cine imaging at rest, dobutamine stress and rest imaging.

Table 1: Contraindications to dobutamine stress MRI

- Unstable angina pectoris
- Left main coronary artery disease
- Higher-grade aortic stenosis
- Hemodynamically relevant obstructive hypertrophic cardiomyopathy
- Myocarditis, endocarditis, pericarditis
- Aortic dissection / higher-grade aortic aneurysm
- Higher-grade complex ventricular arrhythmia
- History of sudden death
- Mobile left ventricular / left atrial thrombus
- Severe systemic hypertension (systolic blood pressure > 240 mmHg and/or diastolic blood pressure > 120 mmHg)
- Intractable anxiety / claustrophobia

Contraindications to atropine

- Advanced heart block
- Glaucoma
- Pyloric stenosis
- Prostatic hypertrophy

Table 2: Side effects during dobutamine / atropine stress:

- Mild complications (10–50%): Anxiety, nausea and vomiting, palpitations, heat sensations, tachypnoea, angina pectoris, hypertension, hypotension, premature ventricular beats, atrial and ventricular arrhythmia, atrial fibrillation, transient atrioventricular blocks
- Severe complications (0.1–0.3%): Sustained ventricular tachycardia, ventricular fibrillation and myocardial infarction

Table 3: Termination criteria for dobutamine stress MRI

- Target heart rate reached ((220 – age) × 0.85)
- New or worsening wall-motion / thickening abnormalities
- Complex cardiac arrhythmias
- Systolic blood pressure increase > 240 mmHg and/or diastolic blood pressure > 120 mmHg
- Blood pressure decrease > 20 mmHg below baseline systolic blood pressure and/or decrease > 40 mmHg from a previous level
- Severe chest pain or other intractable symptoms

for observation of new wall motion abnormalities. If clinically relevant symptoms of arrhythmia or angina occurs or if the age predicted target heart rate or a systolic blood pressure over 240 mmHg or a diastolic blood pressure over 120 mmHg is reached, the dose of dobutamine must not increased further. An advantage of dobutamine is its rapid onset of action and short half-life of about 120 seconds allowing for gradual drug titration. After stress termination, dobutamine side effects can be reversed by administration of a beta-blocker. To increase the sensitivity of the test, it is recommended to stop beta-blocker treatment 24–48 h prior to the examination [20].

Contraindications to dobutamine stress CMR, side effects, and termination criteria are listed in Tables 1, 2 and 3, respectively.

Due to the risk of severe side effects of stress testing, patients have to be closely monitored for their safety. Resuscitation equipment and trained personnel must be available.

Diagnostic criteria and image analysis

For standardized assessment and documentation of CMR the use of the 17-segment model of the American Heart Association is recommended [21]. It is generally accepted and enables comparability to other imaging modalities. The left ventricle will be divided into a

- basal,
- mid-cavity and
- apical short axis section.

With regard to the circumferential location, the basal and mid-cavity slices are further subdivided into six segments of 60° each, named

- anterior,
- anteroseptal,
- inferoseptal,
- inferior,
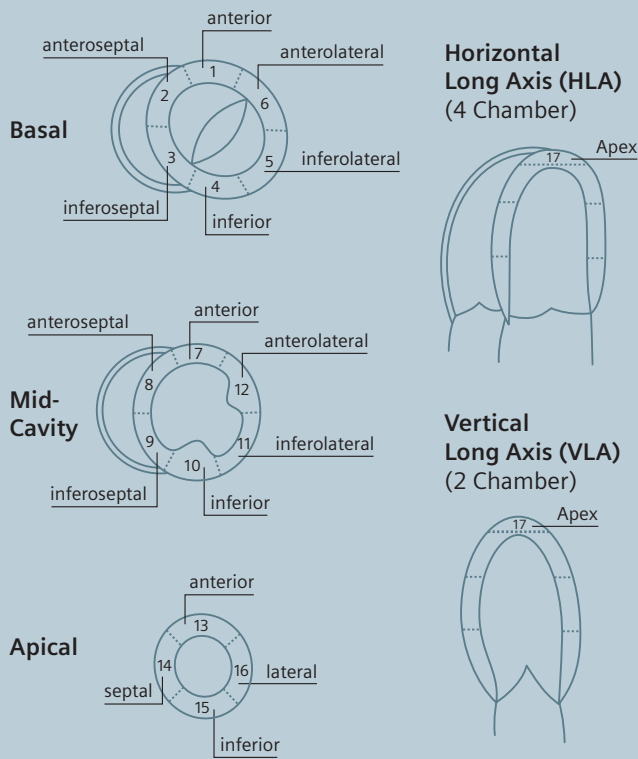- inferolateral,
- anterolateral

and numbered anticlockwise from 1 (basal anterior) to 6 (basal anterolateral) respectively from 7 (mid anterior) to 12 (mid anterolateral). The apical slice is subdivided into four segments, named

- anterior,
- septal,
- inferior and
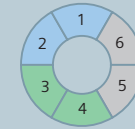- lateral

and numbered anticlockwise from 13 (apical ante-

2A

Short Axis (SA)

Basal
- anteroseptal
- anterior
- anterolateral
- 1
- 2
- 6
- 3
- 5
- inferolateral
- 4
- inferoseptal
- inferior

Mid-Cavity
- anteroseptal
- anterior
- anterolateral
- 7
- 8
- 12
- 9
- 11
- inferolateral
- 10
- inferoseptal
- inferior

Apical
- anterior
- 13
- 14
- 16
- lateral
- septal
- 15
- inferior

Horizontal Long Axis (HLA) (4 Chamber)

17 — Apex

Vertical Long Axis (VLA) (2 Chamber)

17 — Apex

2B

Coronary Artery Territories

Short Axis (SA)

Basal
- 1
- 2
- 6
- 3
- 5
- 4

Mid
- 7
- 8
- 12
- 9
- 11
- 10

Apical
- 13
- 14
- 16
- 15
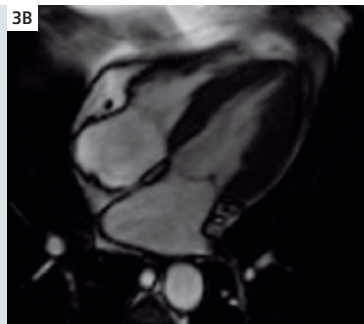
Vertical Long Axis

Mid
- 17

☐ LAD   ☐ RCA   ☐ LCX

2 Recommendation of the American Heart Association for standardized myocardial segmentation and nomenclature in cardiac imaging. (Adapted from Cerqueira et al. [21])
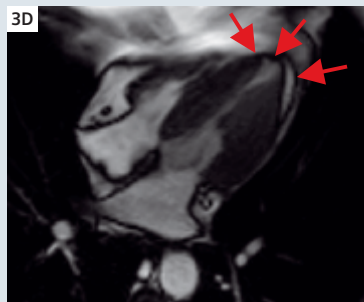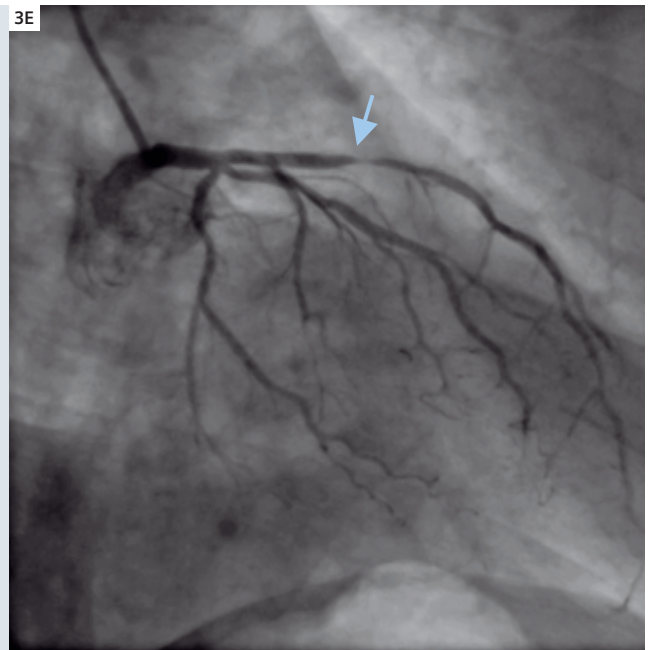
3A

3B

3C

3D

3E

3 **(A–D):** CMR images at rest (top) and at peak dobutamine stress (bottom) showing LV end-diastolic (l.), and end-systolic (r.) frames from a four-chamber view in a patient with normal contraction at rest and with inducible ischemia clearly visible as hypokinesia apical (red arrows). **(E):** Corresponding angiogram of the left coronary artery showing a high-grade LAD stenosis (blue arrow) in the same patient.
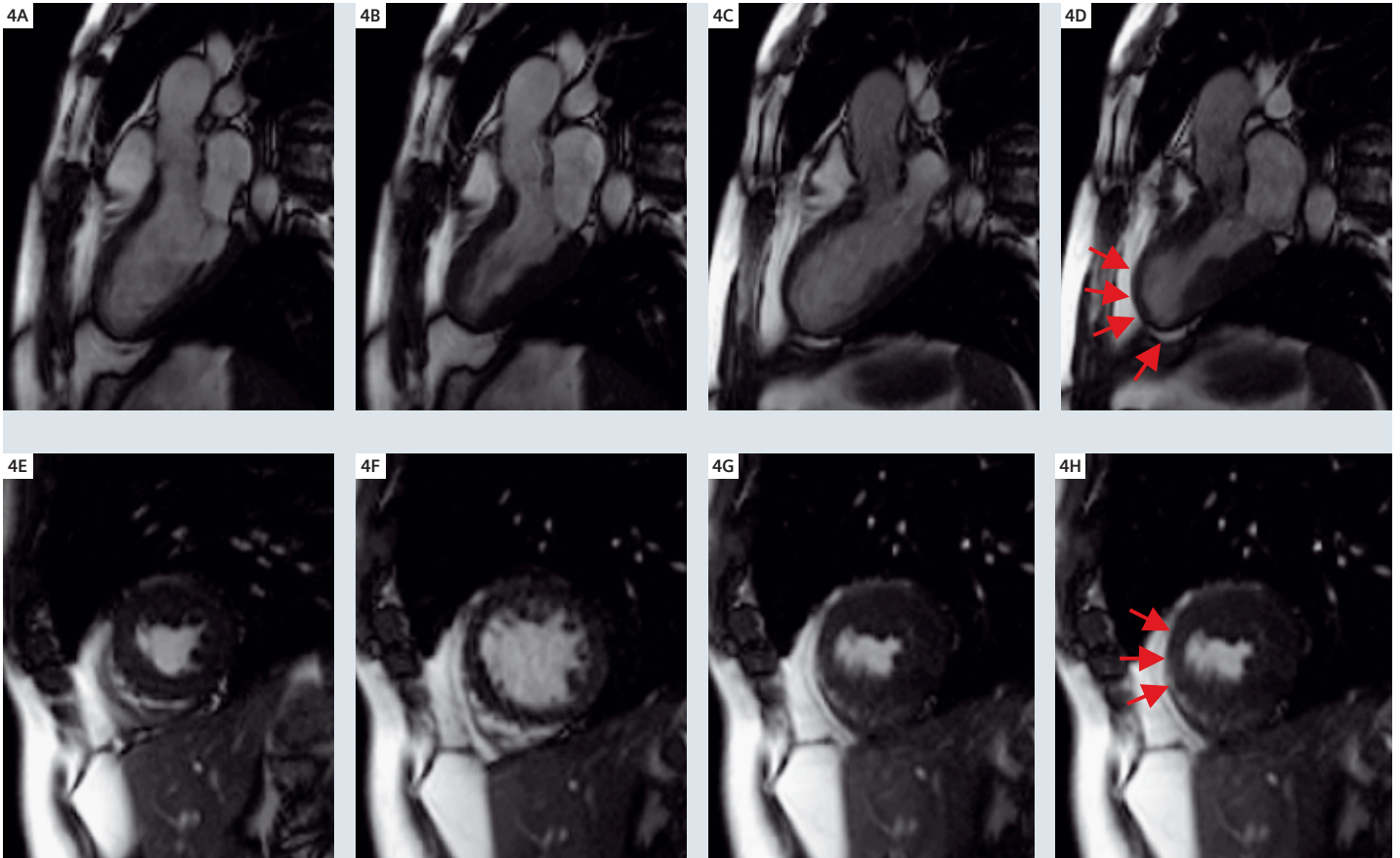
4 **(A–D):** End-diastolic and end-systolic frames from an apical long-axis view of the left ventricle (three chamber view) and **(E–H):** midventricular shortaxis view at rest (left) and at peak dobutamine stress (right) in a patient with inducible ischemia. Red arrows mark the region from anteroseptal midventricular to the apex that shows an impaired contractile response with pronounced wall motion abnormality and reduced thickening.
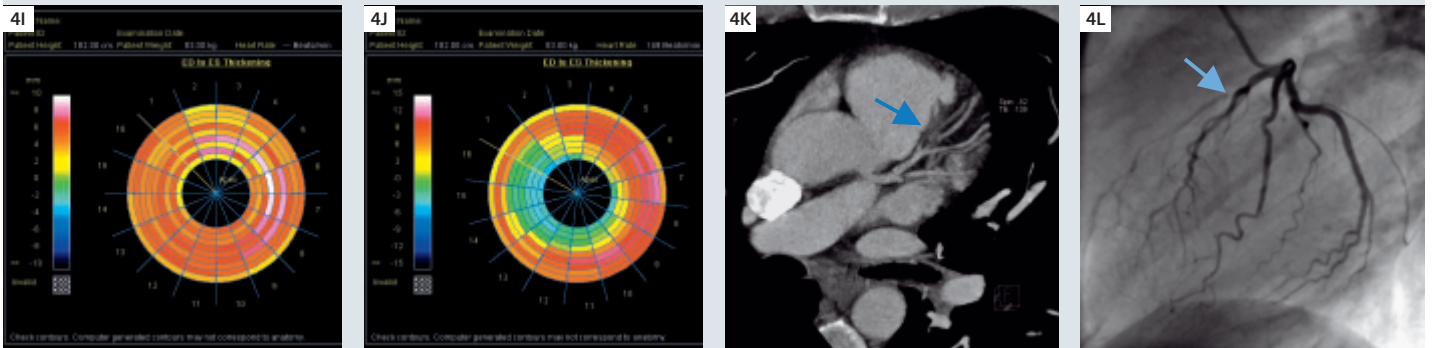
4 **(I–J):** Bulls eye plots of enddiastolic to endsystolic thickening at rest (left) and at peak dobutamine stress (right) in the same patient.

4 **(K–L):** Dual source computed tomography (DSCT) coronary angiography (left) and conventionally coronary angiography (right) reveal a subtotal stenosis of the LAD (blue arrows).

rior) to 16 (apical lateral). The apical cap represents the muscle at the tip of the ventricle and is defined as segment 17, called the apex (Figure 2). During high-dose dobutamine stress CMR all 17 left ventricular segments should be analyzed. Therefore, the acquisition of not less than three short-axis slices (basal, mid-cavity, apical) and at least one additional long-axis plane (two- , four- or three-chamber view) is recommended for evaluation of the apical region. At all stress levels an assessment of regional myocardial contractility is performed, including rest and post-stress phase. A **normal** wall motion response at dobutamine stress CMR is defined as development of hyperkinetic wall motion or preservation of the resting contraction pattern during dobutamine infusion. A pathologic response is characterized by transient wall motion abnormalities in at least one segment that was graded normal at rest (Figure 3). Segmental wall motion is graded **hypokinetic**, if endocardial inward movement and systolic wall thickening appeared decreased but not absent. A segment is graded **akinetic** if it shows lack of inward endocardial motion and absence of systolic wall thickening. A segment is graded **dyskinetic**

if it demonstrated paradoxical systolic outward movement of the endocardial border or systolic wall thinning [2].
The location of segments with normal and pathologic wall motion are compared to the perfusion territory of the main epicardial coronary arteries which are defined by the AHA recommendations [21]. Wall motion abnormalities in anterior, anteroseptal, and septal segments are usually attributed to the left anterior descending artery (LAD), those in inferior and inferoseptal segments to the right coronary artery (RCA), and those in lateral segments to the circumflex artery (RCX). A coronary artery is considered as significantly stenosed if at least one of the segments located in its territory was abnormal at dobutamine stress CMR (Figure 4). If no segment was abnormal, the corresponding coronary artery is graded to have no relevant stenosis.

Discussion

High-dose dobutamine stress CMR is currently an established method for the assessment of stress inducible regional left ventricular wall motion abnormalities due to its high diagnostic accuracy, feasibility and versatility (Table 4).

A coronary artery is considered as significantly stenosed if at least one of the segments located in its territory was abnormal at dobutamine stress CMR.

Table 4: Dobutamine stress MRI for detection of significant CAD compared with conventional coronary angiography.

Author	Year	Sensitivity	Specificity	Number of patients
Pennell et al.	1992	91%	–	25
van Rugge et al.	1993	81%	100%	45
Baer et al.	1994	84%	–	35
van Rugge et al.	1994	91%	80%	39
Nagel et al.	1999	86%	86%	172
Hundley et al.	1999	83%	83%	41
Kuijpers et al.	2003	96%	95%	68
Paetsch et al.	2004	89%	80%	79
Wahl et al.	2004	89%	84%	160
Syed et al.	2005	89%	100%	19

Dobutamine stress MRI is a reliable, clinically safe and robust method to evaluate the functional significance of coronary lesions with high diagnostic accuracy.

Previous studies have demonstrated the clinical feasibility of CMR in conjunction with pharmacological stress testing for the detecting of relevant CAD [6, 10, 12, 14]. Pennell et al. [10] reported the first use of dobutamine stress in conjunction with CMR in 25 patients with chest pain by using an intermediate dose of dobutamine (up to 20 µg/kg/min). He found a 91% incidence of dobutamine–induced reversible wall motion abnormalities in patients with CAD.

Baer et al. [11] and van Rugge et al. [12] have shown that dobutamine MRI detects overall CAD with a sensitivity of 85% and 91%, respectively by using moderate doses of dobutamine up to 20 µg/kg/min.

Nagel et al. provided the first report on the efficacy and safety of high-dose dobutamine (up to 40 µg/kg/min and additional use of atropine as needed) combined with CMR for the detection of CAD in a larger patient population. In this study dobutamine stress CMR proved to be superior to dobutamine stress echocardiography in terms of sensitivity (86% vs. 74%) and specificity (86% vs. 70%) in 172 patients. The superior results of CMR were attributed to its better overall image quality, which was graded good or very good in 82%, but only in 51% of echocardiography studies [6].

Hundley et al. performed high-dose dobutamine CMR for the detection of ischemia in 41 patients who were not well suited for second harmonic stress echocardiography because of poor acoustic windows and reported a sensitivity and specificity of 83% for the detection of a coronary stenosis > 50% luminal diameter [22].

Wahl et al. performed high-dose dobutamine-atropine stress CMR after coronary revascularization in 160 consecutive patients with pre-existing wall motion abnormalities at rest. CMR displayed good results, with sensitivity of 89% and specificity of 84% for detection of significant CAD [23].

Using TrueFISP or SSFP cine sequences Paetsch et al. found high-dose dobutamine stress CMR to be superior to adenosine stress perfusion MR for detection of significant CAD, with sensitivities and specificities of 89% and 80% and 91% and 62%, respectively in 79 patients without history of prior infarction [26].

Syed et al. had shown a high interstudy reproducibility (p = 0.91) and a low interobserver variability (kappa = 0.81) of dobutamine stress MRI in 19 patients with severe coronary disease [27].

The overall sensitivity and specificity for the assessment of ischemia induced wall motion abnormalities for detecting CAD achieved with dobutamine stress CMR is in good agreement with stress echocardiography studies yielding sensitivities of 78% to 96% and specificities of 66% to 85% [28–32].

Conclusion

Dobutamine stress CMR using a state of the art fast imaging sequence is a reliable and clinically safe and robust method to evaluate the functional significance of coronary lesions by detecting ischemic induced wall motion abnormalities.

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References and recommended reading

1 Sugishita J, et al. Dissociation between regional myocardial dysfunction and ECG changes during myocardial ischemia induced by exercise in patients with angina pectoris. Am Heart J 1883;106:1–8.

2 Geleijnse ML ,et al. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30(3):595–606.

3 La Canna G, et al. Echocardiography during infusion of dobutamine for identification of reversibly dysfunction in patients with chronic coronary artery disease. J Am Coll Cardiol 1994;23:617–26.

4 Hoffmann R, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996;27:330–6.

5 Zoghbi AW, Barasch E. Dobutamine MRI: A serious contender in pharmacological stress imaging? Circulation 1999;99:730–2.

6 Nagel E, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose Dobutamine Stress MRI: Comparison with dobutamine stress echocardiography. Circulation 1999;99:763–70.

7 Sechtem U, et al. Cine MR imaging: potential for the evaluation of cardiovascular function. AJR 1987;148:239–46.

8 Pflugfelder PW, et al. Quantification of regional myocardial function by rapid cine MR imaging. AJR 1988;150:523–9.

9 Reichek N. Magnetic resonance imaging for assessment of myocardial function. Magn Reson 1991;Q 7:255–74.

10 Penell DJ, et al. Magnetic resonance imaging during dobutamine stress in coronary artery disease. Am J Cardiol 1992;70:34–40.

11 Baer FM, et al. Coronary artery disease: Findings with GRE MR Imaging and Tc-99m-Methoxyisobutyl-Isonitrile SPECT during simultaneous dobutamine stress. Radiology 1994;193:203–9.

12 Van Rugge FP, et al. Magnetic resonance imaging during dobutamine stress for detection and localization of coronary artery disease: quantitative wall motion analysis using a modification of centerline method. Circulation 1994;90: 127–38.

13 Pennell DJ, et al. Dipyridamole magnetic resonance imaging: a comparison with thallium-201 emission tomography. Br Heart J 1990;64(6):362–9.

14 Pennell DJ, et al. Magnetic resonance imaging during dobutamine stress in coronary artery disease. Am J Cardiol 1992;70(1):34–40.

15 Baer FM, et al. Feasibility of high-dose dipyridamole-magnetic resonance imaging for detection of coronary artery disease and comparison with coronary angiography. Am J Cardiol 1992;69(1):51–6.

16 Jochims, et al.Dobutamine stress magnetic resonance imaging: a reliable alternative to stress echocardiography in patients with insufficient image quality? Eur Heart J 1999;20:678 (abstract).

17 Finn, et al. Cardiac MR Imaging: State of the Technology. Radiology 2006;241(2):338–54.

18 Barkhausen J, et al. MR evaluation of ventricular function: true fast imaging with steady-state precession versus fast low-angle shot cine MR imaging—feasibility study. Radiology 2001;219:264–9.

19 Nesto RW, et al. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographicand symptomatic expressions of ischemia. Am J Cardiol 1987;59(7):23C–30C.

20 Nagel E, et al. Stress cardiovascular magnetic resonance: consensus panel report. J Cardiovasc Magn Reson 2001;3(3):267–81.

21 Cerqueira, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Int J Cardiovasc Imaging 2002;18(1):539–42.

22 Hundley WG, et al. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited forsecond harmonic stress echocardiography. Circulation 1999;100(16):1697–702.

23 Wahl A, et al.High-dose dobutamine-atropine stress cardiovascular MR imaging after coronary revascularization in patients with wall motion abnormalities at rest. Radiology 2004;233 (1):210–6.

24 Secknus MA, et al. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. J Am Coll Cardiol 1997;29(6):1234–40.

25 Wahl A, et al. Safety and feasibility of high-dose dobutamineatropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25(14):1230–6.

26 Paetsch I, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. Circulation 2004;110 (7):835–42.

27 Syed MA, et al.Reproducibility and inter-observer variability of dobutamine stress CMR in patients with severe coronary disease: implications for clinical research. J Cardiovasc Magn Reson 2005;7(5):763–8.

28 Marcowitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. Am J Cardiol 1992;69:1269–73.

29 Mazeika PK, et al. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol 1990;19:1203–11.

30 Sawada SG, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83:1605–14.

31 Segar DS, et al. Dobutamine stress echocardiography: Correlation with coronary lesion severity as determined by quantitative angiography. J Am Coll Cardiol 1992;19:1197–202.

32 Takeuchi M, et al. Comparison of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed tomography for detecting coronary artery disease. J Am Soc Echocardiogr 1993;6:539–602.

33 Kuijpers D, et al. Dobutamine cardiovascular magnetic resonance for the detection of myocardial ischemia with the use of myocardial tagging. Circulation 2003;107(12):1592–7.

34 Strach K, et al. Cardiac stress MR imaging with dobutamine. Eur Radiol 2006;16: 2728–38.

35 Mandapaka S, et al. Dobutamine Cardiovascular Magnetic Resonance: A Review. J. Magn. Reson. Imaging 2006;24:499–