Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases

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Aims To determine the safety of high-dose dobutamine-atropine stress cardiovascular magnetic resonance (stress-CMR), which recently emerged as a highly accurate modality for diagnosis of inducible myocardial ischaemia.

Method and results From 1997 to 2002, 1000 consecutive stress-CMR examinations were performed. Images were acquired at rest and during a high-dose dobutamine-atropine protocol in 3 short-axis, a 4- and a 2-chamber view. Stress testing was discontinued when >85% of age-predicted heart rate was reached, on patient request, maximum pharmacologic infusion, or when new or worsening wall motion abnormalities, severe angina, dyspnoea, increase or decrease in blood pressure, or severe arrhythmias occurred. Stress-CMR was successfully performed in all but four patients (0.4%; insufficient ECG-triggering). Target heart rate was not reached in 95 cases (9.5%), due to maximum pharmacologic infusion in submaximal negative examinations in 21 cases (2.1%), and limiting side effects in 74 (7.4%). Side effects included one case (0.1%) of sustained and four cases (0.4%) of non-sustained ventricular tachycardia, 16 cases (1.6%) of atrial fibrillation, and two cases (0.2%) of transient second degree AV block.

Conclusion The safety profile of stress-CMR is similar to other methodologies using dobutamine infusions. Patients must be closely monitored, and resuscitation equipment and trained personnel must be available.

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Introduction

Recently, high-dose dobutamine-atropine stress cardiovascular magnetic resonance (stress-CMR) emerged as a highly accurate modality for diagnosis of inducible myocardial ischaemia. However, its safety has not yet been sufficiently documented. Therefore, the purpose of the present study was to determine the incidence of adverse events associated with stress-CMR in a large consecutive patient population.

Methods

Patient population

From July 1997 to June 2002, 1075 consecutive stress-CMR examinations were attempted in 1035 consecutive patients. The study protocol was approved by the institutional Ethics committee and all patients gave prior written informed consent. Patients were excluded in case of non-MR-compatible metallic implants such as pacemakers, unstable angina, severely depressed left ventricular ejection fraction (<25%), severe aortic stenosis, hypertrophic obstructive cardiomyopathy, left ventricular thrombus, and severe arterial hypertension (P>220/120 mm Hg). In order to assess the overall feasibility of stress-CMR in an unselected population, patients unable to undergo CMR due to claustrophobia or severe obesity (bore diameter 60 cm) were not excluded from the study population. To ensure an adequate heart rate response to dobutamine, patients were requested to withhold beta-blockers on the day of the stress examination. Other anti-anginal medications were not discontinued.

CMR examination

Patients were examined with a 1.5 T whole body tomograph (ACS NT, Philips, Best, The Netherlands), with a phased array cardiac coil placed around their chest (Fig. 1). Stress-CMR images were acquired at rest and during a standardised high-dose dobutamine-atropine protocol during short breath-holds in three short-axis views (apical, midventricular and basal), a 4-chamber and a 2-chamber view. The time sequence of the examination is shown in Fig. 2. From 1997 to 2000, a single-slice segmented turbo gradient echo technique (TR/TE/flip 5.6/1.9/25; spatial resolution ≤1.6 × 1.6 × 8 mm) was used. With increasing heart rate this would result in shorter breath-holds and fewer images per cardiac cycle. Therefore, for higher heart rates the k-space segmentation was increased, in order to attain higher temporal resolution during stress, while keeping the breath-hold length constant. Thus, 20 phases per cardiac cycle were acquired for a heart rate of 60 beats per minute, yielding a temporal resolution of 50 ms, while 12 phases per cardiac cycle were acquired for a heart rate of 150 beats per minute, yielding a temporal resolution of 34 ms. From 2001 on, a steady state free precession technique (TR/TE/flip 3.0/1.5/55; spatial resolution ≤1.4 × 1.4 × 8 mm) was used, allowing for better endocardial delineation, especially in the long axis views. Using this sequence, 25 phases were acquired per cardiac cycle, independently of heart rate. This gives a temporal resolution of 40 ms for a heart rate of 60 beats per minute and of 16 ms for a heart rate of 150. Pertinent medical history, haemodynamic data, CMR-findings and adverse effects were gathered using a standardised reporting form. Data were entered in a computerised database retrospectively for 1997–1999 and prospectively from 2000 onwards. ECG-rhythm and symptoms were monitored.
continuously, and blood pressure was determined every 3 min. Dobutamine was infused intravenously during 3 min stages at doses of 10, 20, 30, and 40 μg kg⁻¹ min⁻¹, until ≥85% of age-predicted heart rate was reached. If at peak dobutamine dose target heart rate was not achieved and the stress test was still negative, 0.25 mg fractions of atropine (maximal dose 2 mg) were administered in the absence of contraindications such as narrow-angle glaucoma or symptoms of prostatic obstruction. During stress testing, images were displayed on the operator console approximately 10 s after acquisition for determination of new wall motion abnormalities. Stress testing was discontinued when ≥85% of age-predicted heart rate was reached, on patient request, maximum pharmacologic infusion, or when new or worsening wall motion abnormalities in ≥2 segments, severe chest pain or dyspnoea, intolerable non-cardiac symptoms, decrease in systolic blood pressure >40 mm Hg, severe hypertension (>240/120 mm Hg), or severe arrhythmias occurred. Esmolol (25–100 mg iv) and nitroglycerin (0.4–0.8 mg sublingual) were administered when clinically indicated.

Image analysis

All digital stress-CMR images were displayed as continuous synchronised cineloops using a multiple screen format to compare corresponding rest, increasing stress and peak stress levels. Regional wall motion was assessed using a 16 segment model. Segmental wall motion was semi-quantitatively graded by a four-point scoring system (1: normal; 2: hypokinetic; 3: akinetic and 4: dyskinetic). Stress-CMR was defined as positive for ischaemia in case of development of a new wall motion abnormality in ≥1 segment with normal wall motion at rest, or of a worsening wall motion abnormality or a biphasic response in ≥1 segment with abnormal wall motion at rest. In the absence of ischaemia, failure to attain ≥85% of age-predicted maximal heart rate was identified as a non-diagnostic result.

Statistical analysis

Continuous variables are expressed as mean value ± one standard deviation. Non-continuous, categorical variables are given as counts and percentages. Student’s paired t-test was used to assess hemodynamic differences at baseline and during stress-CMR. Statistical significance was assumed with a p-value < 0.05.

Results

Feasibility of stress-CMR

In 75 out of 1035 consecutive patients (7%), CMR could not be performed due to claustrophobia (n = 64; 6%) or severe obesity (n = 11; 1%). Thirty two patients underwent two, and 4 patients underwent three successful stress-CMR examinations, with an interval of 13 ± 16 (range 1–58) months. Thus, 1000 stress-CMR examinations in 960 patients were available for analysis. Patient demographics are summarised in Table 1. Stress-CMR was successfully performed in all but four cases (in four patients; 0.4%), in which the examination had to be aborted for technical reasons (insufficient ECG-triggering). The hemodynamic response is shown in Table 2. The mean maximal dose of dobutamine was 36 ± 7 μg kg⁻¹ min⁻¹. Atropine (mean dose 0.7 ± 0.4 mg) was administered in 54% of cases. Sixty percent of the patients with positive test results received atropine and 52% of the patients with negative test results required atropine to reach target heart rate. Chest pain occurred in 50% of cases and dyspnoea in 14%. The reasons for test termination are shown in Table 3. In the absence of ischaemia, target heart rate was not reached in 95 examinations (9.5%). This was due to maximum pharmacologic infusion in submaximal negative examinations in 21 cases (2.1%) and limiting side effects in 74 cases (7.4%). Image quality was non-diagnostic in six cases (0.6%), due to breathing or motion artifacts. Thus, stress-CMR was diagnostic (either positive for ischaemia or negative with an at least submaximal heart rate response) in 89.5% of cases. Four hundred and twenty (42%) showed a new or worsening wall motion abnormality, or a biphasic response, while 475 (47.5%) did not. An example from a positive examination is shown in Fig. 3.

Safety of stress-CMR

The total number of side effects, including those described above and leading to interruption of the test, is shown in Table 4. The only major complication consisted of one case (0.1%) of sustained ventricular tachycardia with haemodynamic compromise requiring successful external defibrillation after imaging at peak dobutamine dose in a 60-year-old patient with three-vessel disease and a left ventricular ejection fraction of 35%. There was no death, nor myocardial infarction. Other significant arrhythmias included four cases (0.4%) of non-sustained ventricular tachycardia (four beats only), 16 cases (1.6%) of paroxysmal atrial fibrillation with rapid ventricular rate, and two cases (0.2%) of transient second degree AV block. Side effects, especially arrhythmias, were not correlated with atropine administration, and their incidence was similar in patients with known or suspected coronary artery disease.

Discussion

Stress-CMR has been shown highly accurate for the diagnosis of inducible myocardial ischaemia, both in
patients with suspected coronary artery disease, with sensitivities and specificities between 83% and 86%, as compared with quantitative invasive coronary angiography. Stress-CMR has also been shown superior to dobutamine stress echocardiography in patients with suspected coronary artery disease, a difference mainly attributed to superior image quality. However, its routine clinical use is currently limited, in part due to safety concerns, as well as to the perception of a limited patient tolerance. Indeed, extensive prior experience with other methodologies using dobutamine infusions, particularly during high-dose protocols in patients with advanced coronary artery disease, has shown that severe complications occur in 0.25–0.6% of patients including sustained ventricular tachycardia, myocardial infarction, ventricular fibrillation and even death. Significant arrhythmias have been reported to be more frequent in patients with a history of ventricular arrhythmias or left ventricular dysfunction at rest. Thus, similar complication rates might be expected during stress-CMR, the main concern being the occurrence of malignant ventricular arrhythmias. In addition, during CMR, observation of the patient is hampered by confinement within the magnet, and ST-segment analysis is precluded by distortion caused by the magnetic field. However, verbal communication can be maintained throughout the procedure, either via intercom, or personally, and CMR allows monitoring of cardiac rhythm and, thus, on-line assessment of stress-induced arrhythmias. During stress-CMR, monitoring the patient within the magnet is mandatory, and requires the same precautions and equipment as any other stress examination. Monitoring can be done either by using MR-compatible equipment, or by placing standard equipment outside the scanner room, which is connected to the patient using special extensions through a waveguide in the radiofrequency cage. Currently, a variety of MR-compatible devices are commercially available to record virtually every important physiologic parameter. A trained physician, a defibrillator and emergency medications must be at the CMR site.

The present study of 1075 consecutive cases in 1035 consecutive patients documents the safety, feasibility and side effects of stress-CMR, as the technique evolved over five years at a single-center. In this population with a rather high pre-test probability of inducible ischaemia, stress-CMR was mostly well tolerated, with major adverse effects occurring in only one patient. Since the introduction of MR imaging in the 1980s, an estimated 100 million diagnostic procedures have been performed with relatively few major incidents involving patients, personnel or equipment, the few serious injuries or deaths reported having been mostly attributed to the inadvertent presence of ferromagnetic implants and objects or cardiac pacemakers. With regard to CMR safety, it is important to keep in mind that the magnetic

Table 2 Haemodynamic data (n = 1000)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak stress</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per minute (range)</td>
<td>69 ± 12 (40–120)</td>
<td>138 ± 17 (60–185)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (range)</td>
<td>131 ± 22 (74–211)</td>
<td>154 ± 34 (59–243)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (range)</td>
<td>72 ± 11 (42–118)</td>
<td>74 ± 16 (33–134)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg min⁻¹</td>
<td>9081 ± 2357</td>
<td>21191 ± 5217</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3 Reasons for test termination (n = 1000) and list of limiting side effects

<table>
<thead>
<tr>
<th>Reasons for termination</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tests</td>
<td></td>
</tr>
<tr>
<td>Positive for ischaemia</td>
<td>895 (89.5%)</td>
</tr>
<tr>
<td>With heart rate ≥ 85%</td>
<td>420 (42%)</td>
</tr>
<tr>
<td>With heart rate &lt; 85%</td>
<td>322 (37%)</td>
</tr>
<tr>
<td>Negative (heart rate ≥ 85%)</td>
<td>98 (23%)</td>
</tr>
<tr>
<td>Non-diagnostic tests</td>
<td></td>
</tr>
<tr>
<td>Technical reasons (Insufficient ECG-triggering)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Insufficient image quality</td>
<td>6 (0.6%)</td>
</tr>
<tr>
<td>Maximum pharmacologic infusion in submaximal negative</td>
<td>21 (2.1%)</td>
</tr>
<tr>
<td>Limiting side effects</td>
<td></td>
</tr>
<tr>
<td>Patient request</td>
<td>74 (7.4%)</td>
</tr>
<tr>
<td>Severe chest pain</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Severe dyspnoea</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Decrease in systolic blood pressure &gt; 40 mm Hg</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Ventricular extrasystoly</td>
<td>8 (0.8%)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>5 (0.5%)</td>
</tr>
</tbody>
</table>

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field of a CMR scanner is permanently active. In case of medical emergency within the magnet room for which emergent medical intervention is required, Safe Practice Guidelines from the American College of Radiology recommend that appropriately trained MR-personnel should immediately initiate basic life support and/or cardio-pulmonary resuscitation as required by the situation, while the patient is being emergently removed from the magnet room to a predetermined magnetically safe location, where full resuscitative efforts are to continue. While the magnet can be switched off (quenching, i.e., emergent evacuation of the liquid helium contained in the cooling circuit, with ensuing loss of superconductivity and dissipation of the magnetic field), intentional quenching of the magnet is not routinely advised for a medical emergency, since quenching the magnet itself and having the magnetic field dissipate could easily take more than a minute, a time interval more wisely used to initiate life support measures while removing the patient to a location where the strength of the magnetic field is insufficient to be a medical concern. Using manual table release and a trolley permanently placed under the table, this manoeuvre, which is trained every 3 months at our institution, can be performed by two staff members in less than 30 s. Accordingly, the patient presenting a sustained ventricular tachycardia with haemodynamic

<table>
<thead>
<tr>
<th>Side effects</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>16 (1.6%)</td>
</tr>
<tr>
<td>Transient second degree AV block 2:1</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Severe increase in blood pressure (&gt;240/120 mm Hg)</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Decrease in systolic blood pressure &gt;40 mm Hg</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (3.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>64 (6.4%)</td>
</tr>
</tbody>
</table>

Fig. 3 Four-chamber and midventricular short axis views at rest, and at intermediate- and peak-dose dobutamine stress (steady state free precession technique). Both end-diastolic (ED) and end-systolic (ES) frames are shown. Note the development of mid-lateral akinesia (arrows) at peak dobutamine stress. In this patient, invasive coronary angiography demonstrated a left circumflex coronary artery stenosis.
compromise was first recovered from the magnet room and then successfully cardioverted using a defibrillator placed in the preparation room.

If no general contraindications to CMR were applied, stress-CMR yielded a high number of diagnostic examinations (89.5% were either positive for ischaemia or negative with an at least submaximal heart rate response). These figures are comparable with dobutamine stress echocardiography, where around 10% of patients will have non-diagnostic submaximal negative test results because of an insufficient haemodynamic response to dobutamine-atropine administration or limiting side effects.8

Hundley et al.2 performed stress-CMR in 153 patients with poor acoustic windows that prevented adequate transthoracic echocardiographic imaging. However, in the 143 patients who received dobutamine, the test was prematurely terminated due to side effects in 26 patients (18%), including two cases of ventricular tachycardia (1.4%) and one case (0.7%) of atrial fibrillation. In addition, 29 patients (20%), 42% of those taking beta-blockers and 8% of those who did not, failed to reach submaximal age-predicted heart rate despite maximal pharmacological stress, thus yielding a large number of non-diagnostic examinations. The same authors also published a retrospective review of their extended experience on 469 examinations. The same authors also published a retro-

pective stress, thus yielding a large number of non-diagnostic examinations (89.5% were either positive for ischaemia or negative with an at least submaximal heart rate response). These figures are comparable with dobutamine stress echocardiography, where around 10% of patients will have non-diagnostic submaximal negative test results because of an insufficient haemodynamic response to dobutamine-atropine administration or limiting side effects.8

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tively similar baseline characteristics, our larger number of diagnostic examinations were most likely due to withholding of beta-blockers prior to testing and more frequent administration of atropine (54% versus 27%), allowing the achievement of a higher heart rate response (138 ± 17 versus 123 ± 18 or 119 ± 2319 beats per minute).

All examinations were performed by at least one MR technologist and one physician. While specific training is obviously required for adequate image acquisition and interpretation, as well as patient care during pharmacological stress.4,16 Specific training recommendations for stress-CMR have not been issued so far. Beyond the ability to actually perform the scan, these should include reviewing the resting images before dobutamine administra-
tion, interpretation of the images immediately after acquisition during pharmacological stress in order to stop testing once ischaemia has been detected, and adequate reaction to adverse effects such as severe angina pectoris, arrhythmias or cardiac or respiratory arrest. Most importantly, since ECG ST-T changes are not diagnostic within the scanner, termination of the stress test de-

pends solely on symptoms and on the detection of new or worsening wall motion abnormalities. Thus, wall motion has to be assessed on-line rapidly and decisions on termi-
nation of the test or patient safety have to be made immediately. The presence of a physician who is expe-
renced in stress testing and especially in on-line wall motion analysis, usually a cardiologist, is therefore ab-
solutely mandatory.

The importance of reviewing resting images before administering dobutamine has been shown by Hundley et al.2 After baseline imaging, 10 out of 153 patients (7%) did not receive dobutamine, among them one patient with previously unidentified aortic dissection and two patients with a mobile left ventricular thrombus. As for dobutamine stress echocardiography,7,10 the interruption of the test once new or worsening wall motion abnormalities have been detected, even if these are neither severe nor extensive, might improve safety compared to an approach using only maximal dose or achievement of target heart rate as endpoints. In a retrospective review of 469 consecutive stress-CMR results, Hamilton et al.19 determined that evidence of inducible ischaemia oc-
curred in 39 of 102 patients (38%) with positive results before receiving high doses of dobutamine. In our study, among the examinations with positive results, stress testing was stopped before administration of the highest dobutamine dose in 24%. If some positive tests were continued to reach target heart rate despite positivity, the incidence of side effects may have risen, although in some large dobutamine stress echocardiography studies with similar safety records,8,13,15 stress testing was not interrupted after new wall motion abnormalities were detected, unless these were severe and extensive.

In most stress-CMR studies as well as in clinical prac-
tice, wall motion is assessed only semi-quantitatively. This allows for immediate on-line analysis with termi-
nation of the test once ischaemia has been detected, and for rapid off-line analysis and reporting. For visual analysis of stress-CMR studies, a temporal resolution <40 ms is considered sufficient to visualise end-systole.4 Re-
cently, small regional delays in the onset of myocardial motion (myocardial asynchrony) emerged as an early marker of ischaemia, preceding changes in either the amplitude of motion or subsequent wall thickening or thinning changes. Thus, in the future, the accurate identification and quantification of ischaemia-induced delays of approximately 30 ms, which are not recogni-
sable visually in a moving image, may improve the de-
tection of ischaemia using wall motion studies. However, the temporal resolution required for quantitative analy-
sis of such small delays, which can be afforded by newer echocardiographic techniques with parallel processing and digital monitors,20 is currently out of reach for an-
giographic, nuclear and CMR techniques.

Finally, concerning data storage and the ability of the referring physicians to access the images, complete stress-CMR datasets (approximately 150 MB) can be stored on a single CD in a vendor-independent stan-
dardised DICOM-format. For multiple screen analysis how-
ever, dedicated software is required.

Limitations

Since nearly all patients had diagnostic image quality, the major limitation of stress-CMR is the exclusion of patients due to general contraindications to CMR, espe-
cially claustrophobia, which precluded the examination of 6% of patients in the present study. In 1226 consecu-
tive patients referred for clinical CMR imaging, Francis et al.21 reported an initial refusal rate due to claustro-
phobia of 4.4%, which could be reduced to 1.6% after mild sedation. In addition, in many instances such
patients may be able to undergo imaging if adequate non-pharmacological measures to overcome claustrophobia and anxiety are implemented. Nevertheless, these proportions are similar to the 5–10% exclusion rate from echocardiographic studies due to a poor acoustic window. In a previous study from our institution comparing stress-CMR with dobutamine stress echocardiography for diagnosis of ischaemia in patients with suspected coronary artery disease, a similar number of patients had to be excluded from both modalities, with claustrophobia, severe obesity and metallic implants precluding CMR in 8.2%, and insufficient image quality hampering stress echocardiography in 8.7% of patients.

Conclusions

The results of this single-centre study of 1075 consecutive cases over a period of five years confirm that high-dose stress-CMR is safe and feasible in patients with suspected or known coronary artery disease. The overall safety profile and frequency of adverse events of stress-CMR are in agreement with previous reports of other well established methodologies using similar dobutamine-atropine stress protocols. However, these results underscore that patients must be closely monitored for their safety, and that resuscitation equipment and trained personnel must be available.

Acknowledgements

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References