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Dobutamine Cardiovascular Magnetic Resonance

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Abstract

Dobutamine stress cardiovascular magnetic resonance (CMR) is a new diagnostic tool for the noninvasive detection of coronary artery disease. With technological advances, CMR has evolved to become an adequate alternative to standard cardiac stress tests such as ECG exercise stress testing, stress echocardiography, and perfusion scintigraphy. Magnetic resonance imaging technology is widely available, possible in nearly every patient, and not associated with exposure to ionizing radiation. Its high reproducibility and high image quality of the anatomical features of the left ventricle and left ventricular function at rest and during stress make it an ideal technique for the comprehensive evaluation of patients with suspected coronary artery disease. Besides its ability to detect myocardial ischaemia, CMR has proved to be diagnostic for myocardial viability as well. A recent technical refinement in CMR using myocardial tagging has improved the diagnostic accuracy for myocardial ischaemia even further. This article reviews the pathophysiology and methodology of dobutamine stress CMR. The recent literature is discussed.

Introduction

Dobutamine stress CMR is used to identify wall motion abnormalities of the left ventricle in patients with proven or suspected coronary artery disease (1–4). The ability of CMR to visualize wall motion, especially changes in systolic wall thickening of the left ventricle, enables the detection of wall motion abnormalities, indicative of myocardial ischaemia (1–4). Dobutamine stress CMR has emerged as a highly accurate and safe diagnostic modality not only for the assessment of myocardial ischaemia, but also for the assessment of myocardial viability (5). Although exercise ECG is the most widely used noninvasive test for patients with chest pain syndromes, its sensitivity and specificity are limited (especially in women and patients with left ventricular hypertrophy), and it does not provide direct information about the localization and the extent of coronary artery disease (6, 7). Dobutamine stress echocardiography is currently the preferred method for ascertaining left ventricular wall motion abnormalities (8, 9). However, dobutamine stress echocardiography has several limitations. Reproducibility is poor, and the examination yields no diagnostic information in up to 15% of patients because of an inadequate acoustic window in obese patients (10, 11). The weakness of stress echocardiography is also that its use by the occasional user may be attended with loss of accuracy (12).

The first study to report the application of dobutamine stress CMR was that by *Pennell* and coworkers (1). Subsequently, additional low-dose (13–15) and high-dose (2–4) dobutamine stress CMR studies have been reported. Recently, the use of high-dose dobutamine CMR in combination with the myocardial tagging technique has been reported, with excellent diagnostic results. The use of this new technique and the clinical applications are discussed.

Pathophysiology

Pharmacological exercise normally provokes an increase of regional wall motion and thickening, with an increment of ejection fraction of the left ventricle caused by a reduction of systolic dimensions. Regional systolic dysfunction is usually caused by coronary artery disease; however, cardiomyopathies may show regional wall motion abnormalities as well. The presence of resting wall motion abnormalities is mostly the result of prior myocardial infarction, which could be viable or nonviable myocardial tissue. Residual viable tissue is more common in hypokinetic than in akinetic myocardial segments. In the ischaemic cascade (Fig. 1), regional systolic changes generally precede ECG changes and chest pain but follow the onset of malperfusion and

changes in diastolic function. Myocardial ischaemia can be defined as a new or worsening wall motion abnormality in at least two segments at consecutive planes of the left ventricle. The presence of inducible wall motion abnormalities implies a significant limitation of blood flow at peak stress and corresponds to a coronary artery stenosis of >50% diameter. In the case of a relatively mild coronary artery stenosis, the provocation of ischaemia depends on the performance of maximal stress. Inducible wall motion abnormalities recover rapidly after peak stress but may be persistent if ischaemia is severe and stunning is induced (12).

Methods and Results

Cardiac stress testing

The primary indication for pharmacological stress is the inability to exercise or to identify viable myocardium. Dobutamine is a synthetic beta-agonist and the most commonly used pharmacological stressor up to a peak dose of 40 μg/kg/min. Dobutamine increases myocardial oxygen consumption through increments in inotropic state, heart rate, and blood pressure. Dobutamine is competitively antagonized by beta blockers and well suited to analyse wall motion and global ventricular studies, where myocardial ischaemia is more reliably provoked by increased myocardial oxygen demand. In our institution, dobutamine stress CMR is performed in patients with an inconclusive diagnosis of myocardial ischaemia by means of history, ECG recording at rest or during bicycle exercise test. Currently, in our hospital, 50% of the patients who performed an exercise ECG stress test have an inconclusive result. We do not perform stress echocardiography or perfusion scintigraphy in these patients but examine them directly with dobutamine stress CMR. Contraindications for dobutamine stress CMR are: patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120 mmHg), complex cardiac arrhythmias, MRI-incompatible metallic implants, and known claustrophobia.

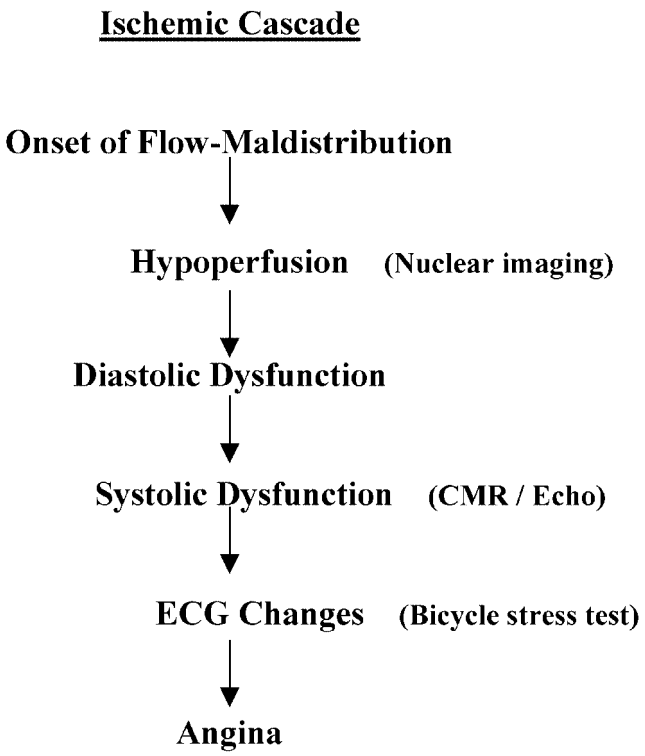

Fig. 1. Ischaemic cascade.

Antianginal medication, atropine and infusion time

To ensure cardiac response to dobutamine, antianginal medication is stopped 1 to 4 days prior to the dobutamine stress CMR examination (2–4). In many cardiac stress centres, atropine is given to increase heart rate in patients who fail to reach the target rate. In the study by *Kuijpers* et al. (4), all antianginal medication was stopped 4 days prior to the stress test, infusion time of dobutamine was prolonged from 3 to 6 min, and no atropine was given. The target-rate rule, which forms the basis of applying this drug (target rate: 85% of maximum; men: 220 minus age; women: 200 minus age), was not applied in that study. It is known that the addition of atropine can enhance sensitivity for detecting coronary artery disease (16). However, the target-rate rule has been questioned in several reports (17–19). The peak-rate pressure product in the study by *Kuijpers* et al. (4) was similar to that reported by others (2), which indicates that in that study the same stress level was reached at the end of the test. Because of the side effects of atropine, patients are unable to drive a car after the study, which is a disadvantage for an outpatient procedure. So, to obviate the need for atropine and to obtain an adequate response to dobutamine, the infusion time of each dose of dobutamine was prolonged, to 6 min (4).

Both approaches have their advocates and there is as yet no clear consensus, which probably indicates that both approaches will function in daily practice.

CMR imaging protocol

Before the patient enters the MR suite, the presence of an acute coronary syndrome is ruled out by a physician. After the patient is positioned on the MR scanning table, intravenous access is established via an antecubital vein. At present, in our institution we start with a 0.1 mmol/kg intravenous injection of gadolinium to detect nonviable myocardium and to optimize imaging contrast for myocardial tagging. Imaging of the contrast-enhanced myocardium of the left ventricle takes place about 20 min after the injection of gadolinium.

ECG monitoring leads, a phased-array surface coil covering the heart, and a brachial blood pressure cuff are applied. The entire procedure, including positioning and ECG monitoring, takes 10–15 min per patient.

A single-lead ECG is continuously monitored on the MRI console. Systolic and diastolic blood pressures are recorded, using an automatic device (Welch Allyn, Emro Medical), at baseline and every 3 min throughout the procedure. Blood pressure and heart frequency are recorded throughout the study by technicians. After acquisitions at rest, dobutamine is infused intravenously using a digital pump injector situated outside the scanner room. In case an evident wall motion abnormality is detected at rest, infusion is started at 5 μg/kg/min, after which the dobutamine dose is increased to 10, 20, 30, and 40 μg/kg/min. If no wall motion abnormality is detected at baseline (rest), the study is started at 10 μg/kg/min. In the study by *Kuijpers* et al. (4), imaging began 6 min after each dose increase, and required 3 min per dose increase. Imaging consisted of acquiring three short-axis cine images (basal, midventricular and apical) without, and two short-axis cine images (basal and midventricular) with, myocardial tagging. Long-axis images were acquired when additional information was needed about a regional wall motion abnormality at the apex of the left ventricle. Other studies (2, 3) use 3 min per dose increase, which limits the length of the study significantly.

During the infusion of dobutamine, the radiologist and cardiologist are present in the MR suite to monitor the condition of the patient and to evaluate the images directly. A physician trained in cardiovascular emergencies (ventricular fibrillation) and resuscitation needs to be at the scanner. In our experience, it is advisable to test safety and emergency procedures regularly, together with the MR technicians.

Dobutamine termination criteria

Criteria for ending the dobutamine CMR examinations are:

1. Development of new wall motion abnormalities indicative of myocardial ischaemia,
2. Fall of systolic blood pressure of >40 mmHg,
3. Marked hypertension >240/120 mmHg,
4. Severe chest pain,
5. Ventricular arrhythmias, and
6. Intolerable side effects of dobutamine (nausea, vomiting).

CMR imaging technique

To assess wall motion, cine imaging of the heart is required with gradient-echo or segmented *k*-space turbo-gradient-echo sequences. Faster image acquisition is possible by the use of echo planar imaging, which allows either reduced scan time or improved temporal resolution. Most of the studies reported use 1.5-T magnetic resonance systems, but other field strengths are used as well. In the tagging study (4), CMR was performed using a standard 1-T MRI system. An ECG-triggered segmented gradient-echo pulse sequence was used: FLASH/TR: 90 ms; TE: 6.1 ms; α: 25°; FOV: 325–350 mm; slice thickness: 8 mm; matrix: 256×256. Tagging was performed using a standard FLASH grid sequence: TR: 96 ms; TE: 4.4 ms; α: 15°; FOV 325–350 mm; slice thickness: 8 mm; matrix: 256×256. The basal plane was taken 1.5 cm below the mitral valves. The midventricular and apical short-axis views were divided equally over the remaining part of the left ventricle. Each cine breath-hold acquisition took 15–19 heartbeats and was made during maximum inspiration. If the heart rate reached 100 beats per minute, the number of phases per acquisition was decreased to optimize temporal resolution. The lack of temporal resolution is a disadvantage of 1-T MRI systems. The use of a higher field strength increases temporal resolution, and even a further reduction of acquisition time is possible with real-time imaging (20). However, until now only limited data on real-time imaging have been available.

Myocardial tagging

Myocardial tagging is an imaging method that uses a sequence of radiofrequency pulses to presaturate thin planes of the myocardium just prior to imaging. These 'tags' persist in the myocardial wall during the heart cycle and can be used to analyse the wall motion of the left ventricle by acquiring images perpendicular to the tagging planes. In the study by *Kuijpers* et al. (4), tagging was performed with a standard FLASH grid sequence. Nonselective radiofrequency pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients were used to achieve tag spacing of 8 mm. This technique is the most frequently used tagging sequence for CMR, which generates two orthogonal sets of parallel planes of magnetic saturation (grid tagging) by a sequence of nonselective radiofrequency pulses (21). The quantitative harmonic-phase tagged image processing method is based on the use of isolated spectral peaks in SPAMM-tagged MR images (22). Until now, quantitative assessment of myocardial strains in a single slice has taken a few minutes, making it almost applicable for wall motion analysis during the stress study. The additional value of quantitative analysis in the diagnosis of myocardial ischaemia is probably limited, because the semiquantitative method has already shown excellent results (2–4). In the future, quantitative tagging analysis may be an important adjunct of the standard semiqualitative breath-hold technique, perhaps in combination with real-time imaging as well.

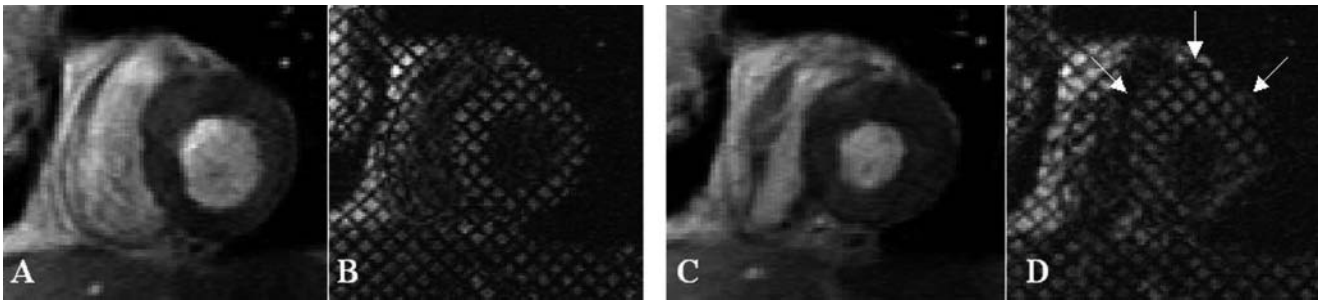

Fig. 2. Short-axis basal views at baseline (rest) and peak-dose dobutamine (40 μg), before and after tagging. 2a (without tagging) and 2b (with tagging) show a diastolic phase of a normal left ventricle at rest. 2c shows an early systolic phase of the same left ventricle at peak-dose dobutamine. The wall contraction pattern (wall thickening) appears to be normal. 2d same phase as 2c. Preservation of tagging lines at the wall of the left ventricle. There is akinesia of three segments: septal, anterior-septal, anterior (arrows), which indicate myocardial ischaemia. Coronary angiography shows a significant stenosis in the left anterior descending coronary artery. (Printed with permission of CIRCULATION).

Interpretation of CMR cine images

Gradient-echo images provide high natural contrast between flowing blood and the myocardium, as well as between the myocardium and the surrounding structures. These signals allow a reliable delineation of the endo- and epicardial border. Until now, interpretation of the cine images has occurred qualitatively, according to the (new) guidelines of the American Heart Association (23). Short-axis images are divided into multiple segments, with six segments in the basal and midventricular and four segments in the apical image. According to the new guidelines, 17 instead of 16 segments can be assigned to the left ventricle. An additional segment is added at the apex of the vertical long axis of the left ventricle, to optimize analysis of wall motion

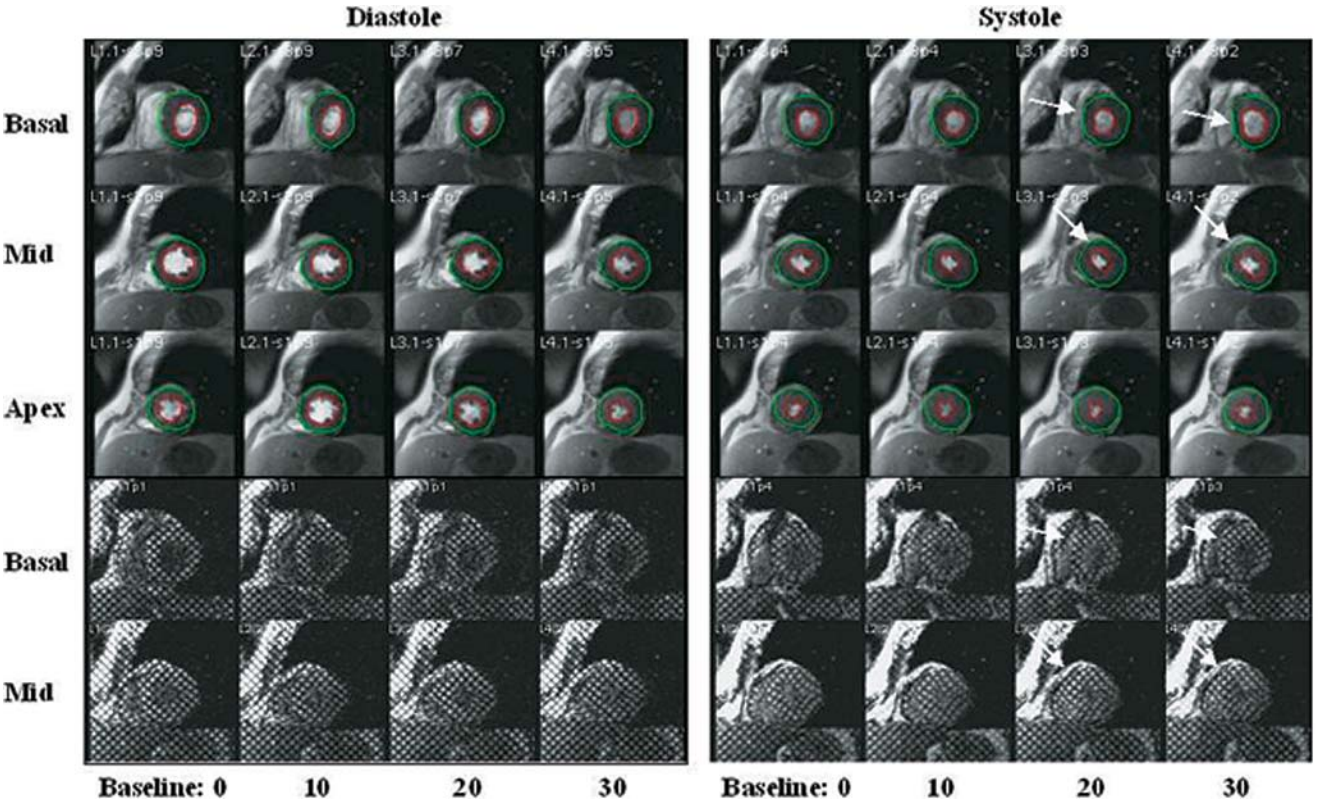

Fig. 3. Overview of dobutamine CMR images during diastole and systole. On the *x*-axis, the dobutamine levels: 0 (baseline), 10, 20 and 30 μg dobutamine. On the *y*-axis, the short-axis planes of grid-tagged images (basal and midventricular planes) and nontagged images (basal, midventricular and apical planes). At 20 and 30 μg dobutamine, there is matching ischaemia between nontagged and tagged images (arrows) of the inferior and septal walls on the basal and midventricular short-axis planes of the left ventricle. (Printed with permission of CIRCULATION).

abnormalities in this area. All the images can be scored using a four-point scale, in accordance with these guidelines: Per segment, wall motion is graded as 1 (normal or hyperkinesia), 2 (hypokinesia), 3 (akinesia), or 4 (dyskinesia). The wall motion score index (WMSI) is derived from the mean score of all segments ($N=17$) of all images. If wall motion abnormalities are already observed at rest and improve during low-dose dobutamine stress but worsen during peak stress, then these wall motion abnormalities are considered diagnostic of inducible myocardial ischaemia. All dobutamine CMR images are magnified (2×) and displayed as continuous cine loops on high-resolution grey-scale monitors. The cine images are analysed directly after each series of images during the examination to rule out new or worsening wall motion abnormalities, indicative of myocardial ischaemia.

Figures 2 and 3 show two patients with chronic airway disease and inability to perform a bicycle exercise stress test. Figure 2d shows preservation of tagging lines at the anterior wall of the left ventricle. There is akinesia of three segments: septal, anterior-septal, anterior (arrows), which indicate myocardial ischaemia. Coronary angiography shows a significant stenosis in the left anterior descending coronary artery. The tagging images clearly depict the wall motion abnormality at the anterior wall. Figure 3 shows a matching ischaemia at 20 and 30 μg between nontagged and tagged images (arrows) of the septal wall on the basal and midventricular short-axis planes of the left ventricle.

Dobutamine CMR in the literature

Several reports have described the use of high-dose dobutamine CMR for the detection of coronary artery disease (2–4). In a recent study, 211 consecutive patients with chest pain and an inconclusive diagnosis of myocardial ischaemia underwent high-dose dobutamine CMR with the use of myocardial tagging, which was successfully performed in 194 patients (4). In this study, dobutamine CMR without tagging detected new wall motion abnormalities in 58 patients, while with myocardial tagging 10 additional patients were detected. Coronary angiography showed coronary artery disease in 65 (96%) of these 68 patients. This study demonstrates that the use of myocardial tagging with high-dose dobutamine CMR is a specific diagnostic technique in the analysis of ischaemic heart disease. These data show that 96% of the patients with inducible new wall motion abnormalities had significant coronary artery disease. Two other studies have reported results of dobutamine CMR (6, 7), but no myocardial tagging was used. *Nagel* et al. (6) compared dobutamine CMR and dobutamine stress echocardiography in 172 patients referred for coronary angiography. Dobutamine CMR provided better sensitivity (86% vs. 74%) and specificity figures (86% vs. 70%) for the detection of new wall motion abnormalities compared to stress echocardiography. For both tests, 18 patients could not be examined. For echocardiography, the main reason was poor image quality; for CMR, claustrophobia and obesity were the main problems. The image quality of CMR was demonstrated to be a major issue in the confidence of interpretation of stress testing in general. This issue was further validated by *Hundley* et al. (7), who reported the use of dobutamine CMR in patients who failed dobutamine stress echocardiography, and showed a sensitivity and specificity of 83% each.

These data can be compared with the data of the traditional stress tests, such as stress echocardiography and myocardial perfusion scintigraphy. Recently, a pooled analysis was reported of 17 direct comparison studies (stress echocardiography vs. perfusion imaging) with different stressors (nine studies with dobutamine) (24). Pooling of the data of 1405 patients showed an overall sensitivity of 80% for stress echocardiography and 84% for perfusion imaging; the specificity was 86% and 77%, respectively. Perfusion imaging showed a lower accuracy, especially in women and patients with hypertension. These data are comparable with the reported data of standard high-dose dobutamine stress CMR tests. However, the additional use of myocardial tagging increased the number of positive dobutamine CMR studies with 17% in the study by *Kuijpers* et al. (4). The addition of myocardial tagging to high-dose dobutamine stress CMR increases diagnostic accuracy, as it simplifies the interpretation of the images. Technical refinements in myocardial tagging and further improvements in spatial and temporal resolution will determine the future development of this new diagnostic tool.

Conclusions

Dobutamine CMR using myocardial tagging is a promising new diagnostic tool in the initial assessment of patients suspected of myocardial ischaemia. Follow-up studies are needed to evaluate the prognostic value and safety of this imaging technique.

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