Dobutamine stress tagging and gradient-echo imaging for detection of coronary heart disease at 3 T

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Objective: The purpose of this study was to evaluate the feasibility and diagnostic accuracy of a combined spoiled gradient-echo (sGRE) and tagged gradient-echo (SPAMM-GRE) protocol for detection of coronary artery disease (CAD) during high-dose dobutamine stress at 3 T.

Method: The study protocol was approved by the local ethics committee. For stress testing, a standard high-dose dobutamine protocol was employed. Image quality at the highest stress level and diagnostic accuracy of the sGRE and SPAMM-GRE sequences were compared. The final study population consisted of 37 patients.

Results: The mean image quality score was 2.6 ± 0.6 for the sGRE sequence and 2.4 ± 0.6 for the SPAMM-GRE sequence ($p > 0.05$). Sensitivity, specificity and diagnostic accuracy were 0.81, 0.86, 0.84 and 0.88, 0.86, 0.86 for the sGRE and SPAMM-GRE, respectively. In three cases with new wall motion abnormalities (WMAs), detected by sGRE and SPAMM-GRE, WMAs were detected at a lower stress level by tagging.

Conclusion: The combined sGRE and SPAMM-GRE high-dose dobutamine protocol at 3 T is feasible and delivers good diagnostic accuracy. Tagging increases the sensitivity of high-dose dobutamine stress testing for detection of CAD and may allow for detection of new WMAs at lower stress levels compared with sGRE alone.

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During recent years there has been an increasing distribution of 3 T scanners worldwide. With their increasing use in clinical routine, 3 T MR systems are also used more and more for cardiac applications [1–6]. Many theoretical advantages of high-field imaging directly translate into improved image quality for cardiac applications, e.g. myocardial perfusion [4, 7] and viability imaging [5, 8]. Myocardial tagging has been shown to benefit from 3 T imaging because of an increased signal-to-noise ratio (SNR) and prolonged T_1 relaxation time, resulting in better tag definition and longer tag persistence in healthy volunteers [3, 9]. However, other applications, such as steady-state-free-precession (SSFP) cine imaging, impose a challenge in daily practice [10–12]. This has led to a resurgence of the spoiled gradient-echo (sGRE) sequence for cine imaging, which has demonstrated a better SNR and contrast-to-noise ratio (CNR) at 3 T than at 1.5 T and is more robust against off-resonance artefacts than SSFP at 3 T [11, 13]. So far, very little has been published regarding the use of cine sGRE sequences or myocardial tagging at 3 T in routine clinical practice. In particular, the performance of myocardial tagging and sGRE at 3 T has not been evaluated under high-dose dobutamine stress conditions in patients and at high heart rates.

Thus, the aim of this study was to evaluate the feasibility and diagnostic accuracy of a combined cine sGRE and myocardial tagging high-dose dobutamine stress protocol in patients at 3 T.

Methods and material

Patients

The study population consisted of patients with known coronary artery disease (CAD) (>18 years old), who were referred to our MRI department to rule out significant occlusive CAD by non-invasive high-dose dobutamine stress testing. Patients with unstable angina pectoris, severe arterial hypertension (>220/120 mmHg), obstructive cardiomyopathy, ejection fraction <20%, complex cardiac arrhythmias, significant aortic stenosis, pericarditis, myocarditis and endocarditis were excluded from enrolment. Furthermore, patients were excluded if they had known claustrophobia and MR-incompatible metallic implants. All patients discontinued anti-anginal (nitrates) medication and β -blockers ≥ 24 h before the study. Written informed consent was obtained from all patients and the study was approved by the local ethics committee.

Magnetic resonance imaging

All studies were performed on a whole-body 3 T cardiac imaging system (Achieva 3T, Philips Medical Systems, Best, the Netherlands) equipped with 80 mT m⁻¹ maximum field gradients and a 200 T m⁻¹s⁻¹ slew rate using a dedicated six-element cardiac-phased array coil (three posterior elements, three anterior elements). Electrocardiographic gating was performed using a vector-ECG (electrocardiograph) and images were acquired while patients held their breath.

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Figure 1. Time course of the combined stress spoiled gradient-echo (sGRE) and spatial modulation of magnetisation (SPAMM)-GRE protocol.

Imaging protocol

The time course of the stress protocol is given in Figure 1. The cardiac short and long axes were identified using standard scout SSFP sequences. After iv injection of a contrast agent (gadolinium-DTPA, 0.2 mmol kg⁻¹), delayed-enhancement (viability) imaging for the detection of myocardial infarction was performed approximately 15 min later using a standard three-dimensional (3D) inversion recovery sGRE sequence. For the remainder of the study and at each stress level cine images were acquired in the short axis orientation (four slices: apical; midventricular/apical, distal to the papillary muscle insertion; midventricular at the papillary muscle insertion; basal, 1.5 cm below the mitral valve). A retrospectively gated, k-space-segmented sGRE sequence was used during an end-expiratory breath-hold: slice thickness 8 mm, field of view (FOV) 320–380 mm, reconstructed matrix 256 × 256, sense factor 2–2.5, repetition time (TR) 4.8 ms, echo time (TE) 2.6 ms, α 20° and 25 cardiac phases, acquisition window <45 ms. In addition a spatial modulation of magnetisation (SPAMM)-tagged sGRE (SPAMM-GRE) sequence was acquired before or after acquisition (alternating order) of the sGRE sequence in the same short axis slices at rest and during each stress level. Detailed scan parameters were as follows: slice thickness 8 mm, FOV 320–380 mm, reconstructed matrix 256 × 256, sense factor 2–2.5, TR 3.7 ms, TE 2.2 ms, α 10°, 14–16 cardiac phases and 8 mm tag separation using a grid-tag pattern. Images were analysed immediately at each stress level for detection of new or worsening of pre-existing wall motion abnormalities (WMAs).

Stress protocol

Dobutamine was infused at 10, 20, 30 and 40 µg kg⁻¹ min⁻¹ at 3–5 min intervals. If the target heart rate (defined as 85% of age-predicted heart rate (220–age)) was not achieved at the maximum dobutamine level, additional atropine was applied in incremental dose rates of 0.25 mg to a maximum dose of 1.5 mg. Criteria for ending the stress protocol were visual detection of a newly developed or worsening of a pre-existing WMA in the sGRE sequence, achievement of the target heart rate, marked hypertension >240/120 mmHg, fall of systolic pressure >40 mmHg, ventricular arrhythmias, severe chest pain and intolerable side-effects of dobutamine. Heart rate was monitored continuously and blood pressure was measured at 1 min intervals during dobutamine infusion.

Data analysis

All scans were analysed qualitatively by two experienced readers (DT, 7 years of cardiac magnetic resonance imaging (CMR) experience, TS, 12 years of CMR experience) through consensus reading. Readers were blinded to the results of invasive coronary angiography and all other clinical data. sGRE and SPAMM-GRE studies were read on different days and the readers were blinded to the results of either imaging modality.

MR images were displayed as continuous cine loops by use of a quad screen display for analysis (Viewforum, Rel. 5.2., Philips, Best, The Netherlands). A 16-segment model, similar to the AHA segment model, was used for the analysis of regional WMAs. The three standard short axis slices at the level distal to the papillary muscle insertion, at the papillary muscle insertion and below the mitral valve were assigned to segments 1–16 and used for subsequent analysis. Segmental wall motion was visually scored according to the guidelines of the American Society of Echocardiography (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia). A positive finding was defined if ≥ 1 segment showed new WMAs (increase of wall motion score at any stress level) or if a segment showing improvement of wall motion during low-dose dobutamine demonstrated deterioration during higher stress levels. CMR diagnosis of stress-induced ischaemia was defined as true-positive if the involved myocardial

Table 1. Demographic data of patients included in the study

Number of patients	37
Gender (M/F)	31/6
Age	50 ± 5
Risk factors	
Hypertension	31 (84%)
Hypercholesterolaemia	35 (95%)
Diabetes	3 (8%)
Smoking	30 (81%)
Obesity	23 (62%)
Symptoms	
Typical angina	19 (51%)
Atypical angina	5 (14%)
Dyspnoea	19 (51%)
No. of diseased vessels	
1	13 (35%)
2	12 (32%)
3	12 (32%)
Bypass	5 (14%)
Stent	33 (89%)
Myocardial Infarction	18 (49%)

Figure 2. Images of a patient who had undergone bypass grafting 7 years before. The presence of sternal wires, causing typical susceptibility artefacts in the anterior chest wall, does not influence overall image quality. Excellent diagnostic image quality is maintained to the highest stress level (40 μ g dobutamine, 123 bpm). At the highest stress level an inferolateral wall motion abnormality (white arrows), due to stenosis of the venous graft to the circumflex artery, can clearly be seen in both the spoiled gradient-echo (sGRE) (a) and the spatial modulation of magnetisation (SPAMM)-GRE (b) sequence. ED, end diastole; ES, end systole.

segment matched the presumed vascular territory of a significantly diseased coronary artery or the respective diseased bypass vessel at quantitative coronary angiography. Segments or subsegments with myocardial infarction, as defined by CMR late enhancement exhibiting WMAs, were not considered for wall motion analysis.

The image quality of sGRE and SPAMM-GRE was assessed at the maximum stress level using a four-point grading scale, based on the following criteria:

- Grade 1 (excellent): sharp delineation of left ventricular (LV) endocardial borders (in sGRE) and left ventricular tags (in tagging sequences) in all segments ($n=16/16$).

- Grade 2 (good): LV endocardial borders/tag definition in one or more segments slightly blurred or obscured by artefacts but definable in all segments ($n=16/16$).
- Grade 3 (moderate): LV endocardial borders/tag definition in $\leq 3/16$ segments not definable owing to major artefacts.
- Grade 4 (poor): LV endocardial borders/tag definition not definable in $>3/16$ segments owing to major artefacts.

Quantitative coronary angiography

Invasive coronary angiography was performed in multiple projections using the standard Judkins technique. A haemodynamically significant stenosis was

Figure 3. Spoiled gradient-echo (sGRE) (a) and spatial modulation of magnetisation (SPAMM)-GRE (b) stress images of a patient during 30 μ g and 40 μ g dobutamine infusion. Tagging very clearly demonstrates a hypokinetic septal segment at the lower stress level, which extends into the anteroseptal/septal segments at the highest stress level (white arrows). At the same time, the wall motion abnormality is not clearly detectable at the lower stress level, owing to pre-existing asymmetry of the left ventricle, which can even be seen at end diastole (ED). This led to continuation of the dobutamine infusion beyond 30 μ g in this patient; ES, end systole.

defined as a reduction $>50\%$ of the vessel diameter in the main coronary arteries, their first-order branches (≥ 2 mm) or bypass vessels. The stenosis severity was defined quantitatively by an experienced interventionalist blinded to the results of CMR.

Patients with a negative dobutamine CMR, who were not catheterised following the CMR study, were followed-up for ≥ 20 months to assess their clinical status of major adverse cardiac events (MACE), which were defined as myocardial ischaemia, myocardial infarction, heart failure or cardiac death. If no such MACE occurred and the patient was free of angina, the CMR finding was judged as being a true-negative.

Statistical analysis

Analysis was performed on a patient-by-patient basis using standard analytical software (MS Excel 2003, Microsoft Corporation Redmond, WA). Continuous variables are expressed as mean $\pm$ standard deviation. Sensitivity, specificity, accuracy and predictive values (positive and negative) were calculated according to standard definitions.

Results

Safety and feasibility of dobutamine stress CMR at 3 T

A total of 40 consecutive patients were initially included in the study. The examination was terminated upon the patient's request in one case because of severe angina pectoris at a low stress level and low heart rate, and because of the onset of claustrophobia in another patient. A third patient was excluded because of the non-diagnostic image quality during the resting study owing to the patient's inability to breath-hold. Thus, the final study population consisted of 37 patients. In all patients high-dose dobutamine stress was performed successfully. The addition of the tagging sequence extended the imaging time by approximately 1.5–2 min per dose increment and was tolerated well by all patients. Overall, no serious adverse events occurred (*i.e.* severe hypertension $>240/120$ mmHg or decrease in systolic blood pressure >40 mmHg, ventricular tachycardia, myocardial infarction, death). Non-cardiac minor side-effects occurred in 8 (21%) patients, 4 patients suffered from nausea and 4 patients reported severe headache. The resting heart rate was 58 ± 6 bpm and the maximum stress heart rate was 132 ± 15 bpm. The target heart rate was achieved in all patients without new or worsening WMAs ($n=21$). The mean ejection fraction, as determined by CMR under resting conditions, was $60 \pm 4\%$; and the mean left ventricular end-diastolic diameter measured 53 ± 5 mm in the short axis plane. More detailed patient characteristics are given in Table 1.

Image quality

Image quality of the sGRE and the SPAMM-GRE did not differ significantly, with a mean score of 2.6 ± 0.6 for the sGRE sequence and a slightly better score for

the SPAMM-GRE sequence of 2.4 ± 0.6 ($p>0.05$). Considerable flow artefacts as a result of increased blood flow at higher heart rates did not appear to be an issue with the use of the sGRE sequence. One stress study was excluded because of non-diagnostic image quality of the sGRE and SPAMM-GRE sequences at the highest stress level. A diagnostic image quality, allowing clinical assessment of the stress studies (*i.e.* positive or negative finding for ischaemia with achievement of the target heart rate), was achieved in 37 patients, who constituted the final study group (Figure 2).

Diagnostic performance

Significant obstructive CAD, as confirmed by coronary angiography, was present in 16 of 37 patients included in the study (prevalence 43%). Nine of the patients with a negative finding during the stress examination did not undergo subsequent coronary angiography. However, these patients did not have any MACE during the follow-up period of 20 months, nor did they have typical angina, and their subsequent non-invasive stress tests were negative. Thus, these cases were judged true-negative.

The sensitivity and specificity of dobutamine stress sGRE for the detection of significant CAD were 81% and 86%, respectively. sGRE imaging alone correctly identified 13/16 patients as having significant CAD. In addition to the 13 positive patients detected by sGRE alone, SPAMM-GRE correctly classified 1 more patient as having significant CAD (14/16). The overall sensitivity and specificity for the detection of significant CAD by SPAMM-GRE were higher than those by sGRE (sensitivity 88% and specificity 86%). In three true-positive cases, WMAs were detected at a lower stress level by SPAMM-GRE than by sGRE ($30 \mu\text{g kg}^{-1}\text{min}^{-1}$ compared with $40 \mu\text{g kg}^{-1}\text{min}^{-1}$) (Figure 3). The combination of positive findings at both sGRE and SPAMM-GRE did not increase sensitivity. The diagnostic accuracy as well as the positive and negative predictive values are given in Table 2.

Discussion

To the best of our knowledge this is the first study evaluating the feasibility and accuracy of a combined sGRE and SPAMM-GRE high-dose dobutamine stress protocol at 3 T. Our data reveal that the combined

Table 2. Sensitivity, specificity and diagnostic accuracy for the detection of significant coronary artery disease derived from spoiled gradient-echo (sGRE) and spatial modulation of magnetisation (SPAMM)-GRE sequences through consensus reading

	sGRE	SPAMM-GRE
Sensitivity (%)	0.81	0.88
Specificity (%)	0.86	0.86
Accuracy (%)	0.84	0.86
Positive predictive value (%)	0.81	0.82
Negative predictive value (%)	0.86	0.90

protocol using sGRE and SPAMM-GRE is feasible in a clinical context in patients with CAD, providing good image quality and high accuracy for detection of significant CAD. SPAMM-GRE delivers a higher sensitivity for the detection of CAD than sGRE, and in three cases detected WMAs at a lower stress level.

Stress sGRE imaging

In recent years cine SSFP sequences have become the gold standard for the assessment of global and regional myocardial function by CMR owing to improved overall SNR and improved myocardium blood contrast compared with standard cine sGRE imaging at 1.5 T [14, 15]. However, SSFP sequences are more sensitive to off-resonance artefacts, rendering their application in cardiac high-field imaging problematic [10–12]. Frequency shifting strategies and higher order shimming algorithms have demonstrated some benefit in reducing SSFP artefacts [10, 12]. But, specifically with stress studies, which are characterized by a significant increase in heart rate and consequently more complex blood flow patterns, which further deteriorate image quality, most image optimisation strategies are of limited value. It has thus been suggested that sGRE sequences for cine imaging of the heart at higher field strength should be used [11, 13]. In our study, which is comparable with very recently published data [16], sGRE imaging performed very well at 3 T at various heart rates during dobutamine stress testing. Only 1 out of 40 patients had to be excluded because of insufficient image quality. Contrary to Kelle et al [16] we performed viability imaging as the very first step in our study. This allows identification of infarcted segments and determination of infarct transmural extent before the stress study and may facilitate online reading during the stress study. Interestingly, there was no compromise in image quality of the sGRE sequences despite the previous double-dose contrast agent injection. This finding is in agreement with the study of Hamdan et al [13], who suggested contrast agent injection for sGRE imaging to improve overall CNR and to compensate for flow-related artefacts at 3 T [13]. However, their approach has been shown to improve image quality for imaging of the cardiac long axis but not the short axis.

Stress myocardial tagging

The composition of the SPAMM-tagging pre-pulse in this study results in a grid tag pattern on the underlying myocardium. Visual assessment of grid deformation throughout the cardiac cycle allows for evaluation of radial thickening as well as circumferential shortening of the myocardium. Myocardial tagging has been shown to benefit from imaging at high field strength [3, 9]. Owing to a prolonged T_1 relaxation time of myocardium at 3 T compared with that at 1.5 T, the tags will show a longer persistence throughout the cardiac cycle. Consequently, the overall tag myocardium contrast is improved. In our study, the mean image quality was graded as good at the highest stress level, and in just one case graded as non-diagnostic, supporting the previous findings in healthy

volunteers [3, 9]. Although contrast agent injection has not been recommended for tagging at 1.5 T, because of the T_1 shortening effect, preliminary data suggest an advantage of low-dose contrast agent injection for tagging studies at 3 T [17]. We consistently found no disadvantage of contrast agent injection in our study, as the viability imaging was performed prior to the stress study. Given the higher heart rates encountered in high-dose dobutamine stress studies, previous contrast agent injections can be expected to be even more advantageous, since the tag fading effect is less prominent. The increased tag persistence at 3 T may allow for improved assessment of diastolic function [3]. Diastolic dysfunction is known to occur before systolic dysfunction in the ischaemic cascade and may thus be interesting to investigate under stress conditions [18]. However, subtle differences in diastolic function can only be explored through strain analysis using quantitative post-processing software. Although recent improvements in strain analysis software have tremendously facilitated quantitative analysis [19], the post-processing is currently still too time-consuming to be implemented in a clinical stress protocol, where real-time analysis of data is warranted.

Diagnostic performance

While some theoretical advantages of high field imaging directly translate into improved image quality for cardiac applications, SSFP cine imaging imposes a challenge in the daily routine. One way to overcome such a limitation has been the resurgence of the sGRE sequence for cine imaging at 3 T. So far, very little has been published regarding the use of cine sGRE sequences at 3 T in routine clinical practice. Only very recently, Kelle et al [16] reported on the use of high-dose dobutamine stress testing at 3 T in 30 patients. The diagnostic accuracy achieved in our study was nearly identical to that in the study by Kelle et al (sensitivity 80%, specificity 86%). Although contrary to Kelle et al, we also included bypass patients in our study and the overall prevalence of significant obstructive CAD was rather low (43% vs 73.5%) [16]. The low prevalence was because the patients in our study were referred for stress testing because of a clinical indication, based on equivocal findings of other non-invasive stress tests and clinical presentation. This scenario reflects the typical setting, under which routine clinical stress testing usually occurs. Recently, a meta-analysis on high-dose dobutamine stress CMR for detection of CAD was published, reporting an overall sensitivity of 83% (95% confidence interval (CI) 79–88%) and specificity of 0.86 (95% CI 81–91%) on a per-patient basis [20]. Compared with these data and the recent study by Kelle et al, the diagnostic accuracy of our study in a highly selected population with known CAD but a low prevalence of significant obstructive CAD (defined as a reduction of $\geq 70\%$ of the vessel diameter in the main coronary arteries, their first-order branches (≥ 2 mm) or bypass vessels) is similar. The study by Kelle et al and our data support the use of a sGRE sequence for stress wall motion studies at 3 T. However, there appears to be no diagnostic benefit over stress wall motion studies at 1.5 T

[20–22]. Previous studies demonstrated an improved image quality of tagging studies at 3 T compared with that at 1.5 T in healthy volunteers [3, 9]. Consequently, our study sought to investigate the clinical applicability and diagnostic impact of high-dose dobutamine stress myocardial tagging at 3 T in a combined SPAMM-GRE and sGRE protocol. Our study has shown the feasibility of a high-dose dobutamine stress tagging protocol at 3 T. In addition, myocardial tagging increased the sensitivity for detection of significant CAD (14/16 true-positive cases by SPAMM-GRE *vs* 13/16 by sGRE alone) and allowed for the detection of WMAs at a lower stress level in 3 patients. In the study by Kuijpers et al [23], the impact of tagging on the detection of WMAs under dobutamine stress was comparable (68 patients identified with tagging *vs* 58 patients without) with our study. However, Kuijpers et al did not report the maximum dobutamine dose at which the WMAs were detected by either the sGRE sequence or the SPAMM-GRE sequence. The detection of new WMAs at a lower stress level may reduce the stress time and dose of dobutamine needed, and may thus increase patient safety and comfort. However, this finding warrants further investigation in larger patient trials. Paetsch et al [18] performed a quantitative analysis of myocardial complementary spatial modulation of magnetisation (CSPAMM) tagging in patients screened for CAD during low- and high-dose dobutamine. They found that the presence of significant CAD could best be detected during low-dose dobutamine by the diastolic parameter time to peak untwisting. This finding is in agreement with the fact that diastolic dysfunction occurs before systolic dysfunction in the ischaemic cascade. Somewhat unexpected in their study, systolic parameters, more specifically circumferential shortening, did not differ significantly between patients with and without significant CAD at high- or low-dose dobutamine. This would appear, at first glance, to contradict the findings of Kuijpers et al and our findings. However, this can be explained by the fact that Paetsch et al analysed and reported absolute values per slice and not myocardial segment. High-dose dobutamine stress protocols aim at provoking regional WMAs through induction of hypoperfusion, which could have been missed by their analysis. Therefore, for dobutamine stress studies, a myocardial segment-based analysis may be a more promising approach for quantitative image analysis.

Limitations

The true impact of the combined 3 T protocol compared with that at 1.5 T cannot be assessed from our results. A head-to-head comparison would have required exposure of the patient to the potential risks of stress testing twice, which was excluded from this study for ethical reasons.

We did not perform a quantitative analysis of the tagged images, because at present quantitative wall motion analysis is still a time-consuming procedure, which cannot be performed real-time during a stress study. Thus, it cannot be used for immediate diagnostic decisions, *i.e.* stopping the dobutamine stress study because of detected ischaemia. In the future, post-processing

software may allow real-time display of quantitative myocardial tagging data at the end of every stress level, which could pave the way for the implementation of quantitative analysis into clinical routine.

Our study scenario represents a typical clinical setting under which non-invasive CMR stress testing usually is performed. Consequently, based on the overall findings, 9 of the 37 patients included did not undergo subsequent coronary angiography. However, these patients were followed up for at least 20 months and no MACE occurred. Finally, the number of patients in this study is rather limited, which allows only a preliminary statement on the feasibility and diagnostic accuracy of the combined stress testing protocol.

Conclusion

The combined sGRE and SPAMM-GRE high-dose dobutamine protocol at 3 T is feasible, providing good image quality and diagnostic accuracy in a patient group with a low prevalence of obstructive CAD. The addition of stress tagging increases the sensitivity of high-dose dobutamine stress studies for the detection of CAD and may allow for the detection of ischaemia-induced WMAs at lower dobutamine stress levels than for cine sGRE sequences. Thus, myocardial tagging in addition to sGRE cine imaging at 3 T is a very promising tool for high-dose dobutamine stress testing and non-invasive diagnosis of significant CAD. The results of Kuijpers et al and our own result support the need for further post-processing software development, allowing the full potential of myocardial tagging to be exploited for stress testing in the future.

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