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MYOCARDIAL PERFUSION

# Myocardial Perfusion Imaging Using OMNISCAN: A Dose Finding Study for Visual Assessment of Stress-Induced Regional Perfusion Abnormalities

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## ABSTRACT

*Background:* Different doses of contrast agent are applied for magnetic resonance perfusion studies and mainly semiquantitative approaches have been reported for analysis. We aimed to determine the optimal dose for a visual detection of perfusion defects. *Methods:* 49 patients ($59 \pm 8$ years; 33 male) scheduled for invasive angiography were examined at stress (0.14 mg adenosine/kg body weight/minute) and rest using a TFE-EPI hybrid sequence (Philips ACS NT; 1.5 T). Patients were assigned to three different dose groups of gadodiamide (0.05, 0.1, and 0.15 mmol/kg body weight) injected as a bolus via a peripheral vein. Visual assessment was used to detect a regional reduction of peak signal intensity or speed of contrast agent inflow at stress in comparison to rest. *Results:* Prevalence for coronary artery disease was 67%. The highest diagnostic accuracy was reached for a dose of 0.1 mmol gadodiamide/kg body weight (86% $p$ = nonsignificant vs. 0.15 and 0.05 mmol gadodiamide/kg). At this dose, no major artifacts related to the contrast agent were found. *Conclusions:* Visual assessment of myocardial perfusion using a high-flow rate contrast agent bolus injection and a TFE-EPI sequence can be best achieved with a dose of gadodiamide 0.1 mmol/kg bodyweight.

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## INTRODUCTION

The assessment of myocardial perfusion with magnetic resonance (MR) techniques has received increasing attention over the last years. Using different imaging techniques, such as turbo gradient echo, echo planar imaging, or hybrid techniques, several slices are imaged every or every second heartbeat, usually at rest and after vasodilation using dipyridamole or adenosine. From these images, the first pass of a bolus of an extracellular contrast agent on gadolinium basis is followed through the left ventricle and the myocardium (Wilke et al., 1994). Three different strategies to analyze the data have been suggested. First, a visual assessment mainly looking at signal differences between normal and hypoperfused myocardium; second, a semiquantitative assessment using parameters, such as the upslope of the signal intensity over time curve or the peak signal intensity (Al-Saadi et al., 2000); and third, a quantitative approach using a deconvolution procedure and mathematical approaches (Jerosch-Herold and Wilke, 1997). Since only with small contrast agent concentrations can a linear relationship between signal intensity and contrast agent concentration be found, and high contrast agent concentrations cause susceptibility artifacts, most authors have used relatively small doses of contrast agents for their studies, ranging from 0.025 to 0.05 mmol/kg body weight (Al-Saadi et al., 2000; Cullen et al., 1999; Ibrahim et al., 2002; Panting et al., 2002; Sensky et al., 2000; Wilke et al., 1999). However a few authors have also used higher doses (Schwitter et al., 2001). High doses of contrast agent may, however, be advantageous for visual assessment. Up to now, no dose finding study has been reported.

The aim of the present study was to compare three different doses of gadodiamide (gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide, Gd-DTPA-BMA) injected via a peripheral vein for their value to assess myocardial perfusion on a visual basis.

## METHODS

### Patients

The study population consisted of 49 patients (59±8 years; 33 male) who were referred for coronary angiography. Written informed consent was obtained from all study participants.

Patients were excluded if they were <18 years old, had a history of prior myocardial infarction or presented with unstable angina, hemodynamic relevant valvular disease, ventricular extrasystoly ≥Lown III, atrial fibrillation, ejection fraction <30%, blood pressure >160/95 mmHg or <100/70 mmHg, obstructive pulmonary disease, known claustrophobia, or a general contraindication for a MR-examination such as incompatible metal implants. Antianginal medication was stopped at least 12 hours before the examination.

### Coronary Angiography

After the MR examination, all patients underwent left-sided cardiac catheterization and biplane selective coronary angiography in Judkins technique. Coronary stenoses were filmed in the center of the field from multiple projections, and as much as possible overlap of side branches and foreshortening of relevant coronary stenoses was avoided. Coronary angiograms were visually assessed by two experienced observers blinded to the MR examination for high-grade coronary artery stenoses (≥75%); disagreement regarding stenosis interpretation was settled in a consensus reading.

### Magnetic Resonance Perfusion Measurements

All patients were examined in the supine position (1.5 Tesla MR tomograph, ACS-NT, Philips, the Netherlands) using a five-element phased-array cardiac coil placed around the chest of the patient. After three rapid surveys to determine the exact axis and length of the left ventricular cavity, three short-axis planes were imaged. The distance between each plane was 1/4th of the end-diastolic length of the left ventricular cavity. A single shot segmented k-space turbo-gradient-echo/echo-planar-imaging (EPI) hybrid technique (TE/TR/flip: 3.3/12.5/30, turbo factor: 4, EPI factor: 11, spatial resolution: 1.7–2.2 mm × 1.9–2.4 mm, slice thickness: 8 mm, 3 images/heartbeat) was used. After the infusion of 0.14 mg adenosine/kg body weight/min for 4 min under continuous electrocardiogram (ECG) and blood pressure monitoring images were acquired for 10 heartbeats before and 60 heartbeats during the first pass of a randomly assigned dose of 0.05 mmol ($n$=20), 0.1 mmol ($n$=14), or 0.15 mmol ($n$=15) gadodiamide/kg body weight (Omniscan™; Nycomed Amersham, Oslo, Norway) flushed with 20 ml 0.9% NaCl (flow rate: 8 ml/sec; Medrad, Spectris®, USA) using a previously described breathing scheme (Nagel et al., 2003). A 15-minute break allowed for myocardial clearance of the first contrast agent bolus while the patient remained in position. After the break, the

*Table 1.* Diagnostic performance for different dose levels.

| Dose | All ($n=49$) | 0.05 ($n=20$) | 0.1 ($n=14$) | 0.15 ($n=15$) |
|---|---|---|---|---|
| Sensitivity | 78.8 | 61.5 | 88.9 | 90.9 |
| Specificity | 75 | 85.7 | 80 | 50 |
| NPV | 63.2 | 54.5 | 80 | 66.7 |
| PPV | 86.7 | 88.9 | 88.9 | 83.3 |
| Accuracy | 77.6 | 70 | 85.7 | 80 |

examination was continued using the identical protocol as before without adenosine-induced vasodilation.

Termination criteria for the adenosine infusion were patient request, chest discomfort indicative of progressive or severe angina, dyspnea, decrease in systolic pressure >40 mmHg, severe supraventricular, or ventricular arrhythmias.

### Image Analysis

Two independent, experienced readers blinded to the contrast agent dose and the results of invasive coronary angiography visually analyzed the MR perfusion images. In the case of disagreement consensus was reached during a combined review. The results given were calculated on a per-patient basis.

A patient was classified as pathologic, if lower peak signal intensity in at least one segment in comparison to other segments was found at stress but not at rest or if the speed of myocardial contrast enhancement was reduced at stress in comparison to the resting study.

Image artifacts were classified as contrast agent related (susceptibility) or nonrelated (fold-over, breathing motion, EPI-streaks) and their effect on making a diagnosis (no, minor effect, major effect) was determined.

### Statistical Analysis

Continuous variables are expressed as mean value ± one standard deviation. The paired Student's T-Test was used to assess statistical significance of continous variables. Group differences for categorical variables were tested with the $\chi^2$ or Fisher's exact test. All tests were two tailed; $p < 0.05$ was considered significant.

Sensitivity, specificity, accuracy, and predictive values (positive and negative) were calculated according to standard definitions and accuracy was compared between groups ($\chi^2$ or Fisher's exact test).

## RESULTS

### Patient Population

MR imaging could be successfully completed in all patients. In most patients, minimal side effects, such as flush, warmth, or headache, were observed resolving within 30 sec without any further intervention after stopping the adenosine infusion. No patient required medical treatment due to side effects.

### Diagnostic Accuracy

Hemodynamically relevant coronary artery disease was present in 33 of 49 patients (prevalence: 67%). Twenty patients had 1-vessel disease, 8 patients had 2-vessel disease, and 5 patients had 3-vessel disease. The results of the perfusion measurements compared with angiography are shown in Table 1. A tendency toward higher diagnostic accuracy was found for a dose of 0.1 mmol/kg body weight; however, it did not reach statistical significance in comparison to the two other dose groups ($p$=ns).

*Table 2.* Number of artifacts for different dose levels.

| Dose | All ($n=49$) | 0.05 ($n=20$) | 0.1 ($n=14$) | 0.15 ($n=15$) |
|---|---|---|---|---|
| No artifacts | 21 (43%) | 14 (70%) | 7 (47%) | 0 (0%) |
| Minor artifacts | 16 (33%) | 5 (25%) | 6 (40%) | 5 (33%) |
| Contrast agent–related | 8 | 0 | 3 | 5 |
| % of minor artifacts | 50% | 0% | 50% | 100% |
| Major artifacts | 12 (24%) | 1 (5%) | 1 (7%) | 10 (67%) |
| Contrast agent–related | 10 | 0 | 0 | 10 |
| % of major artifacts | 83% | 0% | 0% | 100% |

### Artifacts

Imaging artifacts were found in 28 patients; however, in most cases (16) they had no or only a minor effect on diagnosis. At the highest dose, significantly more contrast agent related artifacts with major effect on making a diagnosis were found ($p = 0.02$; see also Table 2).

## DISCUSSION

The optimal dose for visual assessment of myocardial perfusion using gadodiamide is 0.1 mmol/kg body weight using a peripheral venous injection. With this dosage, a sensitivity of 89% with a specificity of 80% was reached, yielding a diagnostic accuracy of 86%. With a smaller dose (0.05 mmol/kg body weight of gadodiamide) more false negative results occurred, leading to a mildly higher specificity with lower sensitivity. The highest dose of 0.15 mmol gadodiamide yielded a similar sensitivity in comparison to the optimal dose. However, specificity was low, mainly due to susceptibility artifacts rendering interpretation of myocardial contrast pattern difficult. Yet, we could not demonstrate a statistically significant difference between the three contrast agent dose levels with regard to the diagnostic accuracy. It is noteworthy that with the dose of 0.1 mmol/kg, artifacts were found in 53% of patients. However, in only one patient did a noncontrast agent–related artifact influence diagnostic decision making. On the contrary, with the highest dose, all artifacts were primarily related to the contrast agent and had a major influence on diagnostic decision making in 67% of the patients (Fig. 1).

The optimal dose found in this study is higher than used in most previous studies (Al-Saadi et al., 2000, 2002; Nagel et al., 2003); whereas for quantitative or semiquantitative analysis it is important to achieve a linear relationship between signal intensity and contrast agent concentration, this aspect may not be of importance for visual assessment. Such a linear correlation can only be found at low contrast agent concentrations, which have, thus, been applied for most (semi-) quantitative approaches (Al-Saadi et al., 2000; Cullen et al., 1999; Ibrahim et al., 2002). A dose of 0.1 mmol gadodiamide may be too high for quantification, as myocardial perfusion and especially perfusion reserve will be underestimated as the effect of nonlinearity is more pronounced at high than at low flow states. However, for visual assessment a large difference in myocardial signal intensity over time between ischemic and nonischemic areas is advantageous and can be better achieved with 0.1 mmol gadodiamide in comparison to 0.05 mmol. Although contrast may be even higher at a dose of 0.15 mmol gadodiamide, diagnostic accuracy was lower with this dose, most probably related to the susceptibility artifacts introduced by the administration of the contrast agent (e.g., Fig. 2).

In most studies published to date, data from semiquantitative analysis have been used to derive the diagnostic accuracy: according to a meta-analysis from

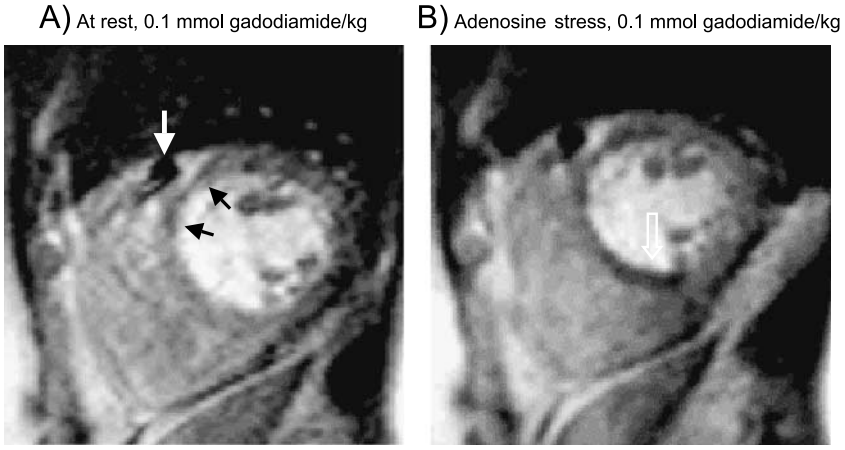


***Figure 1.*** Perfusion image at rest (A) and stress (B) using a dose of 0.1 mmol/kg gadodiamide. At rest, a small defect in the anterior wall can be seen (black arrows), which is also found at stress, demonstrating a small myocardial infarction. In addition, at stress a distinct subendocardial defect of the inferior septal segment can be appreciated (open white arrow). A stent-related artifact is visible in the left anterior descending coronary artery (closed white arrow).


***Figure 2.*** Perfusion image at rest (A) and stress (B) using a dose of 0.15 mmol/kg gadodiamide. At rest, there is normal, homogeneous signal enhancement in all myocardial segments. Under stress, an inducible and clearly demarcated regional perfusion deficit in the inferior segment with 100% transmurality can be appreciated (open white arrow). Note the occurrence of susceptibility around the papillary muscles and in the anterior and lateral myocardial segments (white arrows).

Wilke et al. (1999), sensitivity and specificity for MR perfusion measurements are approximately 82% and 88%. Our data are in a similar range, with a slightly better sensitivity but a lower specificity for the optimal dose group. In a recent study by Sensky et al. (2002), visual assessment was used for the detection of significant coronary artery disease in a group of patients with very high prevalence of significant stenoses and a sensitivity of 93% with a specificity of 60% was achieved using a dose of 0.025 mmol gadodiamide.

An important factor in the visual assessment of myocardial perfusion is to take the inflow of the contrast agent into account. In a study by Al-Saadi et al. (2001), several parameters were compared for the discrimination between ischemic and nonischemic myocardium. The alteration of the upslope induced by vasodilation was the best discriminator, followed by the alteration of the peak signal intensity. Thus, visual assessment should not only be based on the peak signal intensity achieved during vasodilation, but should also

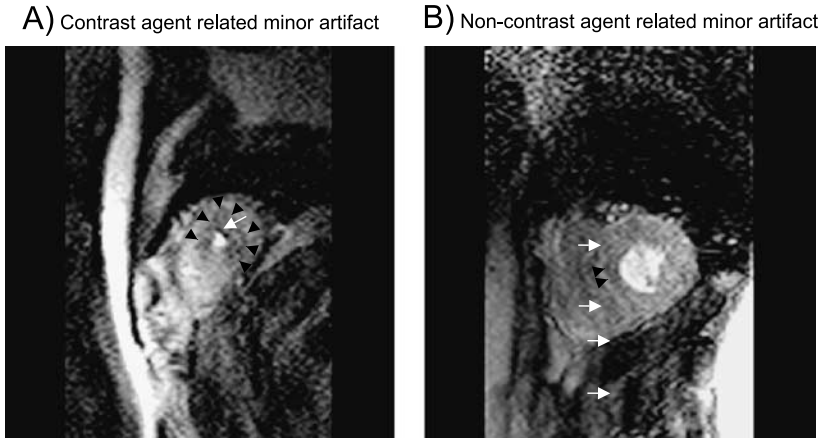


***Figure 3.*** Minor artifacts. (A) Contrast agent related: Clearly visible, nearly circumferential perfusion deficit with varying transmurality of 50 to 100% (black arrowheads). Note the small contrast agent related susceptibility artifact at the endocardial border (white arrow, dosage: gadodiamide 0.1 mmol/kg), which had no influence on the confidence of the reader. (B) Noncontrast agent related: EPI streaks resulting from breathing motion (white arrows). The observer diagnosed a perfusion deficit in the anterior/antero-septal segments (black arrowheads), although an influence of the EPI streaks on the signal intensity pattern of the septum could not be fully ruled out.

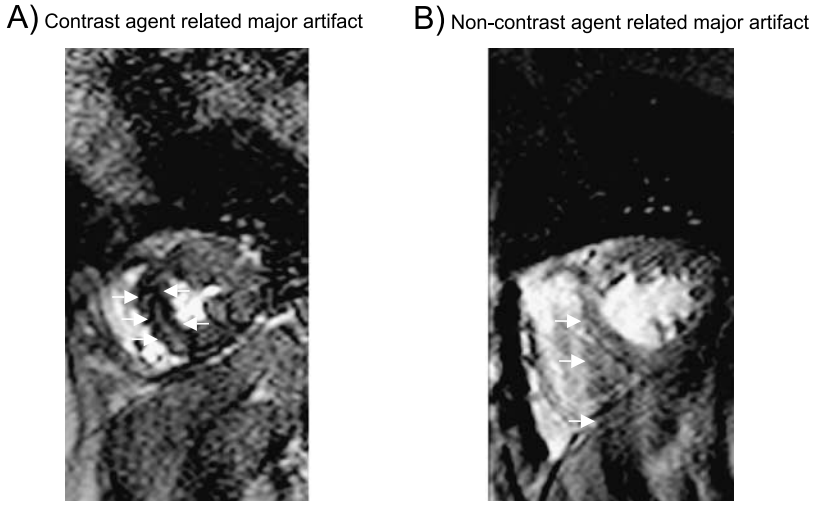


***Figure 4.*** Major artifacts. (A) Contrast agent related: Severe susceptibility due to high contrast agent concentrations (dosage: 0.15 mmol/kg gadodiamide) at the right and left ventricular endocardial borders of the interventricular septum. (B) Noncontrast agent related: Multiple, extensive EPI streaks occurring in the phase encoding direction: the disturbance of the magnetization in the septum had a major influence on the confidence of the reader.

take in account the speed of the wash-in of the contrast agent bolus. In addition, the observer should carefully evaluate the changes of the myocardial contrast pattern between the examination at rest and during stress in order to account for regional inhomogeneities independent of ischemia.

A potential disadvantage of a higher contrast agent dose is the influence of the first study (rest or stress) on the second (stress or rest), as the concentration of the remaining contrast agent in the myocardium is higher with higher doses and longer equilibration times between the two scans may have to be accepted. This may negatively influence semiquantification, as well as the visual assessment, since contrast between underperfused and normally perfused areas might be reduced.

In this study, we used a TFE-EPI hybrid sequence. This sequence allows both high-spatial resolution as well as good temporal coverage. Thus, three short-axis views were imaged every heartbeat with an in-plane spatial resolution of below $2.5 \times 2.5$ mm. Such a high spatial resolution facilitates the detection of small subendocardial defects and may, thus, be advantageous in comparison to other sequences allowing only for a lower spatial resolution. The use of EPI, on the other hand, introduces some artifacts (see Figs. 3B and 4B), which might influence the assessment of the images. A direct comparison of different sequence types is required to solve this issue.

## Limitations

The results from this trial cannot be extended to other sequence types, as images acquired without EPI and shorter TE will be less sensitive to susceptibility artifacts and may, thus, profit from higher doses.

In our study, the accuracy was not significantly higher for the optimal dose (0.1 mmol/lkg) in comparison to the two other dose groups; yet, the combination of a tendency toward higher accuracy with a minimum of contrast agent–related imaging artifacts was favorable.

In principle, the readers were blinded to the amount of contrast agent administered. This may have influenced the results: a scan with a lower contrast agent dose may be falsely interpreted as being positive for overall hypoenhancement. Even though this cannot be fully excluded, sensitivity rather than specificity was reduced with the lower contrast agent dose. Second, an experienced reader can easily determine the given amount of contrast agent from the signal response in the right and left ventricular cavities and, thus, can adapt the reading.

## CONCLUSIONS

Visual assessment of myocardial perfusion using a high-flow rate contrast agent bolus injection and a

TFE-EPI sequence can be best achieved with a dose of gadodiamide 0.1 mmol/kg body weight.

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