Chapter 7

Comparison of dual to single contrast bolus magnetic resonance myocardial perfusion imaging for detection of significant coronary artery disease

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ABSTRACT

Purpose: To investigate the incremental diagnostic value of dual bolus over single contrast bolus first pass magnetic resonance myocardial perfusion imaging for detection of significant coronary artery disease (CAD).

Materials and Methods: Patients (n=49) with suspected CAD underwent first pass adenosine stress and rest magnetic resonance myocardial perfusion imaging and invasive coronary angiography (ICA). Gd-DTPA was injected with a pre-bolus (1 ml) and a large bolus (0,1 mmol/kg). For the single bolus technique, the arterial input function (AIF) was obtained from the large contrast bolus. For the dual bolus technique, the AIF was reconstructed from the pre-bolus. Absolute myocardial perfusion was calculated by Fermi-model constrained deconvolution. Receiver operating characteristic (ROC) analysis was used to investigate diagnostic accuracy of MR myocardial perfusion imaging for detection of significant CAD on ICA at vessel based analysis.

Results: The area under the curve of the minimal stress perfusion value for the detection of significant CAD using the single and dual bolus technique was 0.85 ± 0.04 (95% CI: 0.77-0.93) and 0.77 ± 0.05 (95% CI: 0.67-0.86), respectively.

Conclusion: In this study the dual bolus technique had no incremental diagnostic value over single bolus technique for detection of significant CAD with the used contrast concentrations.

INTRODUCTION

Absolute myocardial perfusion can be determined using first pass gadolinium magnetic resonance myocardial perfusion imaging (MR-MPI) using the Fermi-model deconvolution technique (1-3). In this model, a linear relationship between contrast concentration and signal intensity is assumed. However, it has been shown that at high contrast concentration this linear relation disappears (4). As low contrast concentrations have limited contrast to noise ratio, a dual bolus technique has recently been introduced (5) and applied by several research groups (6-10). For calculation of the arterial input functional (AIF) the small pre-bolus is used to limit signal saturation effects. The large contrast bolus that is used to determine the myocardial response provides adequate signal to noise ratio. The implementation of the pre-bolus has shown to provide absolute perfusion values comparable to perfusion values determined by microspheres in animals (5,6) and positron emission tomography (PET) in healthy volunteers (7). Kurita et al. showed that regional myocardial perfusion reserve determined by using dual bolus MR-MPI correlated well to coronary flow reserve by intracoronary Doppler flow wire in patients with suspected CAD (11). Ibrahim et al. (12) performed dual bolus MR-MPI in healthy volunteers and found that semi-quantitative perfusion values correlated well to PET values. However, no absolute quantitative perfusion values were calculated.

In clinical practice, MR-MPI is used as a diagnostic tool to investigate patients with suspected coronary artery disease (CAD). Several studies have shown that MR-MPI can accurately predict the presence and extent of CAD assessed on invasive coronary angiography (13,14). This study compared dual bolus absolute perfusion values to values obtained from the single contrast bolus technique in patients with no or only mild CAD, as a reproduction of earlier studies. The main objective was to investigate the incremental diagnostic value of dual bolus over single contrast bolus technique for detection of significant CAD, using invasive coronary angiography (ICA) as standard of reference.

MATERIALS AND METHODS

Patient population

Patients with chest pain and suspected CAD who were referred for MR-MPI and underwent both MR-MPI and ICA within 2 months, were included prospectively. Referral for ICA was on the basis of symptoms or non-invasive test results (exercise electrocardiography, multi-detector computed tomography coronary angiography, single photon emission computed tomography or MR-MPI). Exclusion criteria were any prior history of CAD (prior documented myocardial ischemia, myocardial infarction, percutaneous coronary intervention or cardiac surgery), any change of clinical status between MR-MPI and ICA, significant arrhythmia, pregnancy, renal insufficiency (serum creatinine > 110 μmol/L), known allergy to ionated contrast material, any absolute contra-indication for magnetic resonance imaging (e.g. cerebral clips), claustrophobia and asthma. The study protocol was

approved by the local ethics committee and written informed consent was obtained from all patients.

Magnetic resonance myocardial perfusion imaging

All imaging was performed on a 1.5T whole body MRI scanner (Sonata/Avanto, Siemens, Erlangen, Germany) with the patient in supine position using an eight-element phased array cardiac receiver coil. Patients were instructed to refrain from caffeinated drinks and other competitive antagonists of adenosine 24 hours before the examination. All images were acquired with electrocardiographic triggering and expiration breath holding. First pass myocardial perfusion was assessed using a dynamic single shot saturation recovery gradient-echo planar pulse sequence, accelerated by parallel imaging with a factor two using TSENSE, during the administration of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany). To suppress signal of epicardial fat, a frequency selective fat saturation RF pulse was applied before imaging. Typical scan parameters were: TR/TE = 5.6/1.1 ms, saturation time 110 ms, flip angle 18^{o}, echo-planar factor 4, matrix-size 160 x 144 and voxel size 2.5 x 2.5 x 10 mm^{3}. First, a small bolus of 1 ml was injected followed by a 15 ml saline chaser during the first breath hold. During a second breath hold, a larger contrast bolus of 0.1 mmol/kg body weight followed by 15 ml saline chaser was injected. All contrast agent and saline chaser was injected at a rate of 3 ml/sec. Every heartbeat, 3 left ventricle short axis slices (basal, mid and apical) were acquired. The stress scan was acquired after three minutes of continuous intravenous infusion of adenosine (140 µg/kg/min); the adenosine was stopped immediately after completion of the scan. Blood pressure and heart rate were monitored during adenosine infusion. The rest scan was acquired at least ten minutes after the stress scan, with identical scan parameter settings, contrast dose and slice positions.

Image analysis

Endo- and epicardial contours were drawn and manually corrected for cardiac motion by an observer blinded to clinical and MR-MPI data. Subsequently, the myocardium was divided in 18 segments (6 segments per basal, mid and apical short axis orientation) and signal intensity - time curves for each segment were obtained using standard software (Mass 5.1, Medis, Leiden, the Netherlands). A small region of interest was drawn in the left ventricle cavity of the pre- and large bolus basal slice images and signal intensity - time curves were obtained to determine the AIF. Using in-house built software (Matlab R14, The Mathworks, Massachusetts, USA), perfusion values were calculated using Fermi-model constrained deconvolution (1). A locally linear normalization was applied to correct for the distance-dependent attenuation pattern resulting from the surface coil inhomogeneity over all segments. For this normalization, the baseline signal intensity in the myocardium prior to the arrival of the contrast agent was used. Normalization was performed both between segments in one slice and between the 3 different slices. After normalization, offset correction was applied using the pre-contrast baseline signal. The arterial input function from the single bolus (AIF-sb) was derived from the signal intensity - time curve of the

large bolus images in the left ventricle cavity. The arterial input function of the dual bolus (AIF-db) was reconstructed from the pre-bolus data. The main bolus can be considered as multiple pre-boluses, each shifted in time by the duration of the injection of 1 ml (0.33 s). Therefore, the reconstructed AIF-db can be created by the summation of multiple pre-bolus blood pool signal intensity - time curves, each shifted in time by 0.33 s (7).
The myocardial segments were allocated to 3 coronary artery territories according to a 18 segment model modified from the 17 segment AHA model (15). In this model each slice was divided into 6 segments. Inferoseptal and inferior segments were allocated to the right coronary artery. Anteroseptal and anterior segments were allocated to the left anterior descending coronary artery and anterolateral and inferolateral segments to the circumflex coronary artery. Several perfusion parameters were calculated from rest and stress images: mean perfusion per vessel (defined as the mean perfusion value of all segments of 1 coronary territory), minimal perfusion per vessel (defined as the smallest perfusion per segment of all segments within 1 coronary territory), mean myocardial perfusion reserve (MPR) per vessel (defined as the ratio between mean stress and rest perfusion per vessel) and minimal MPR per vessel (defined as the ratio between minimal stress and rest perfusion per vessel).

Invasive coronary angiography

Conventional coronary angiography was performed according to standard clinical protocols. An interventional cardiologist blinded to the clinical and MR-MPI data evaluated the angiograms. The coronary tree was divided according to a 16-segment coronary artery model modified from the American Heart Association (16). All segments that were estimated visually as having at least one diameter stenosis > 20% were quantitatively analyzed using quantitative coronary analysis (QCA) software (Inturis, CIVP, Philips, Best, the Netherlands). Vessels with no or mild CAD were classified when no CAD was present or the diameter stenosis was visually scored below 20%. Significant CAD was defined as >50% diameter stenosis in two orthogonal directions on QCA.

Statistical analysis

All data are presented as mean ± standard deviation for continuous data. Statistical analysis was performed using a standard software package, SPSS version 15.0 (SPSS, Chicago, IL, USA). Single and dual bolus mean rest, stress and MPR values of patients with no or mild CAD were compared using a paired t-test. Inter- and intra-individual relative standard deviations of these parameters were compared in patients with no or mild CAD using an F-test. Receiver operating characteristic (ROC) analysis was used to investigate diagnostic accuracy of MR-MPI for detection of significant CAD at vessel based analysis. An additional analysis was performed to investigate the diagnostic accuracy for detection of ≥ 75% diameter stenosis on QCA. ROC curves were compared by a z-score test. A p-value of < 0.05 was defined as a significant difference.

Table 1. Patient characteristics

Patients, n	49
Gender (male)	35 (71)
Mean age (yrs)*	57 ± 9
Symptoms:	
non-anginal chest pain	14 (29)
atypical chest pain	29 (59)
typical chest pain	6 (12)
Risk factors for CAD:	
Diabetes	8 (16)
Hyperlipidaemia	12 (24)
Hypertension	22 (45)
Familiy history	14 (29)
Smoking	12 (24)
Observed CAD per vessel:	
No or mild CAD (QCA <20%)	80 (54)
Non-significant CAD (QCA 20% - 50%)	28 (19)
Significant CAD (QCA >50%)	39 (27)

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses.
* Mean ± standard deviation. CAD, coronary artery disease; QCA, quantitative coronary analysis

RESULTS

MR-MPI and ICA were performed successfully in all 49 patients. Thus, 49 patients and 147 coronary arteries were included in the analysis. Mean time interval between MR-MPI and ICA was 31 ± 14 days, median 30 days. Patient characteristics are described in table 1.

In 2 patients the aortic outflow tract was visible on the basal short axis slice due to shift of the level of expiration breath hold. Thus, in these patients the antero- and inferoseptal basal myocardial segments were not visualized. These 4 segments were excluded from the analysis. An example of signal intensity - time curves using the single and large bolus and the reconstructed AIF by convolution of the pre-bolus signal intensity - time curve is shown in figure 1. Less saturation was observed in the AIF using the pre-bolus signal. The degree of saturation can be defined by the area under the curve of the AIF-db divided by the area under the curve of the AIF-sb. This resulted in a ratio at rest and during stress of 3.4 ± 1.8 and 2.2 ± 1.7, respectively.

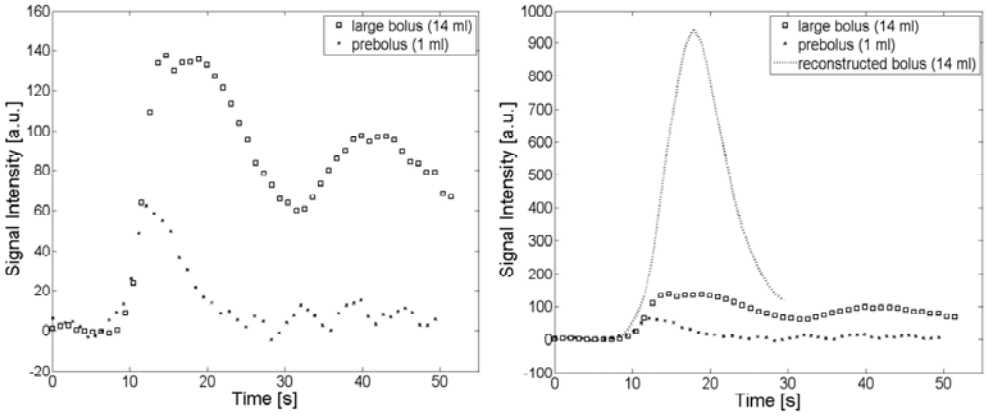

Figure 1. Example of the signal intensity time curves in the blood pool, used for the arterial input function. On the left side, the curves are shown for the large bolus (squared) and the re-bolus (cross). On the right, the same two curves are presented together with the convolved arterial input function reconstructed from the pre-bolus.

Myocardial perfusion values

Mean rest perfusion in patients with no or only mild CAD on ICA (n=15) for single and dual contrast bolus technique were 2.2 ± 0.9 ml/g/min and 0.5 ± 0.2 ml/g/min, respectively ($p<0.001$). Mean stress perfusion values using single and dual bolus technique were 4.1 ± 1.1 ml/g/min and 1.4 ± 0.6 ml/g/min, respectively ($p<0.001$). Mean MPR values using single and dual bolus technique were 2.0 ± 0.5 and 3.1 ± 1.3, respectively ($p<0.001$), see figure 2. There was a trend towards a higher inter-individual relative standard deviation of dual versus single bolus stress perfusion values, 27% and 44%, respectively ($p=0.08$). There was no significant difference between the intra-individual standard deviation of the dual and the single bolus technique, 26% and 33%, respectively ($p=0.4$)

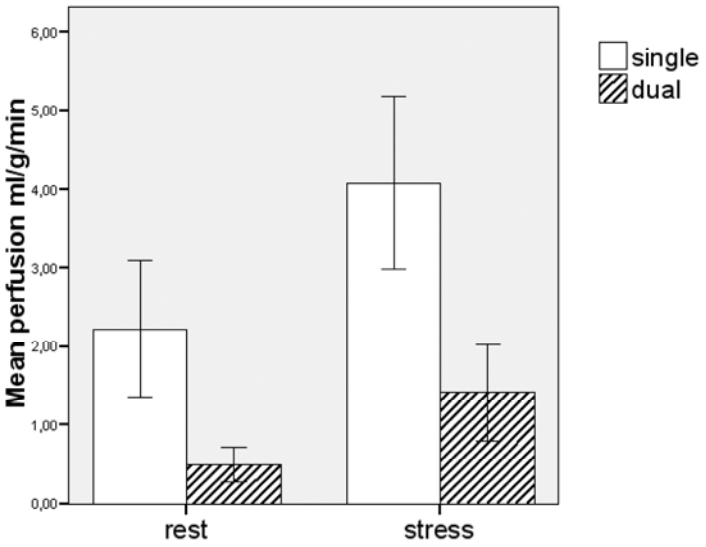

Figure 2. Single and dual bolus rest and stress perfusion values (mean ± SD) in patients without or only mild coronary artery disease on invasive coronary angiography. Dual bolus values were significantly lower than single bolus values ($p<0.001$).

Invasive coronary angiography

No or only mild CAD was observed in 15 of 49 (31%) patients and 80 of 147 (54%) vessels. Intermediate CAD (20-50%) was observed in 12 (24%) patients and 28 (19%) vessels. Significant CAD was observed in 22 (45%) patients and 39 (27%) vessels. Single vessel disease was present in 10 (20%) patients, 7 (14%) had two-vessel disease and 5 (11%) had three vessel disease. In 4 (8%) patients and 5 (3%) vessels ≥ 75% diameter stenosis was found on ICA.

Diagnostic accuracy

ROC analysis of minimal stress perfusion value per coronary territory for detection of significant CAD using single or dual bolus technique is shown in figure 3. The area under the curve (AUC) of single bolus technique, 0.85 ± 0.04 (95% CI: 0.77-0.93) was significantly larger than dual bolus technique 0.77 ± 0.05 (95% CI: 0.67-0.86), p<0.015.

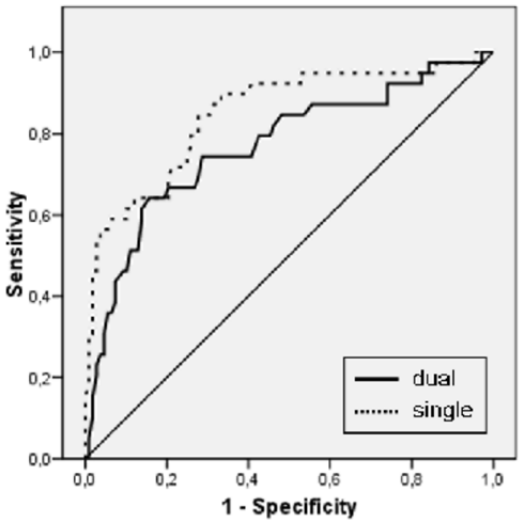

Figure 3. ROC curves of single and dual bolus minimal stress perfusion value for detection of significant coronary artery disease at vessel based analysis. The area under the curve of single bolus technique, 0.85 ± 0.04 (95% CI: 0.77-0.93) was significantly larger than dual bolus technique, 0.77 ± 0.05 (95% CI: 0.67-0.86), p<0.015.

ROC analysis of minimal MPR per coronary territory for detection of significant CAD using single or dual bolus technique is shown in Fig. 4. For the MPR, the AUC of dual bolus technique, 0.63 ± 0.05 (95% CI: 0.53-0.73) was not significantly different from the AUC of the single bolus technique, 0.71 ± 0.05 (95% CI: 0.62-0.81), p=0.05. Additionally, there was no significant difference between the AUC of the dual bolus and the AUC of the single bolus technique for detection of ≥75% diameter stenosis: for stress perfusion 0.95 ± 0.03 (95% CI: 0.89-1.0) versus 0.97 ± 0.01 (95% CI: 0.94-1.0), respectively (p=0.5) and for MPR 0.87 ± 0.04 (95% CI: 0.78-0.95) versus 0.85 ± 0.06 (95% CI: 0.73-0.97), respectively (p=0.8).

For both single and dual bolus technique, the AUC of minimal stress perfusion was significantly larger than the AUC of the minimal MPR value for detection of significant CAD (p<0.003).

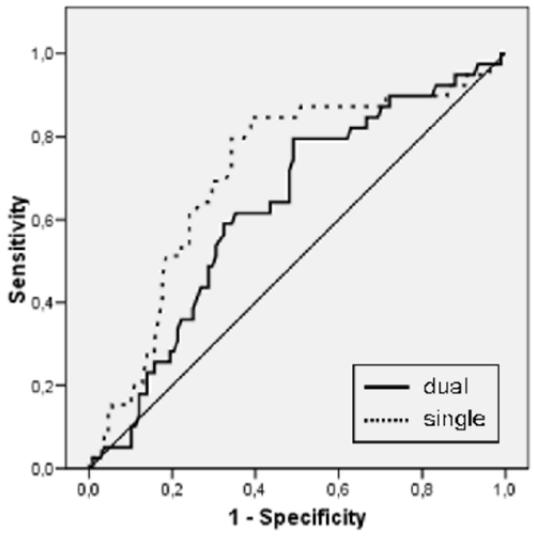

Figure 4. ROC curves of single and dual bolus minimal myocardial perfusion reserve for detection of significant coronary artery disease at vessel based analysis. There was no significant difference between area under the curve of single bolus and dual bolus technique, 0.71 ±0.05 (95% CI: 0.62-0.81) and 0.63±0.05 (95% CI: 0.53-0.73), respectively.

DISCUSSION

The present study compared diagnostic accuracy of dual to single contrast bolus MR-MPI for detection of significant CAD. The dual bolus technique showed lower mean perfusion values in patients with no or mild CAD. Furthermore, it had no incremental diagnostic value over the single bolus technique for the detection of significant CAD.

Dual bolus myocardial perfusion values in patients with no or only mild CAD in the present study were in line with values reported in previous studies. Kostler et al. (7) found rest perfusion values ranging from 0.67 ± 0.10 to 0.72 ± 0.13 ml/g/min in 6 healthy volunteers using a dual bolus technique. Ritter et al. (8) reported mean rest perfusion values of 0.52 ± 0.11 ml/g/min, mean stress perfusion values of 1.8 ± 0.5 ml/g/min and mean MPR of 3.6 ± 1.3 in 12 healthy volunteers. Hsu et al. (10) performed dual bolus MR-MPI in 10 healthy humans and reported mean rest and mean stress perfusion values of 1.0 ± 0.2 and 3.4 ± 0.6 ml/g/min, respectively.

The decreased mean perfusion value of the dual bolus approach compared to the single bolus technique is induced by the reduction of signal saturation in the arterial input function. The difference between AUC of signal intensity time curves of the AIF-db and the AIF-sb suggests that strong saturation is present in the single bolus technique. This is in line with earlier work by Kostler et al. (7), who compared dual to single bolus technique in

healthy volunteers. They also reported lower rest perfusion values by using the dual bolus technique (0.67-0.72 ml/g/min) compared to the single bolus technique (1.1-1.2 ml/g/min), although this difference was not tested for significance.

Previous ^{13}N-ammonia PET studies have presented myocardial perfusion values in healthy volunteers at rest ranging from 0.6 ± 0.1 ml/g/min (17) to 0.8 ± 0.2 ml/g/min (12). Recently, Fritz-Hansen et al. (18) reported rest and stress PET perfusion values in healthy subjects of 0.7 ± 0.2 ml/g/min and 2.0 ± 0.7 ml/g/min, respectively. Thus, the dual bolus technique provided perfusion values in patients without or only mild CAD that were more in line with ^{13}N-ammonia PET values than single bolus values. However, the standard of reference for in-vivo perfusion imaging is ^{15}O-water PET. Chareonthaitawee et al. (19) performed ^{15}O-water PET in a large group of normal volunteers and reported rest and stress perfusion values of 1.0 ± 0.2 and 3.5 ± 1.0 ml/g/min, respectively. This suggests an underestimation of perfusion by the dual bolus technique. It may be explained by saturation effects at peak concentration within the myocardium with the contrast dose applied in the present study. Although the arterial bolus of contrast is dispersed during transit through the coronary tree, a contrast dosage of 0.1 mmol/kg may still cause considerable signal saturation. Utz et al. (20) have shown that the myocardial response curve is not linear at contrast concentrations above 0.05 mmol/kg bodyweight. In a recent study (9), they compared the single and dual bolus technique at a contrast dosage of 0.05 mmol/kg in subjects without CAD, but reported only MPR values. They found only a small difference (10%) in MPR between the single bolus and dual bolus technique. In contrast, we observed a larger effect on MPR. This may be explained by the overall reduction of signal saturation at 0.05 mmol/kg in comparison to 0.1 mmol/kg, thereby decreasing the difference between single and dual bolus MPR. However, the effect of the dual bolus technique at this smaller (0.05 mmol/kg) main bolus on stress and rest perfusion values remains unclear.

In the present study the dual bolus technique had no incremental diagnostic value over single bolus technique for detection of significant CAD. This might be explained by the introduction of extra noise from the separate pre-bolus analysis. Although there was no significant increase in the inter-individual relative variance of perfusion, there was a trend towards a larger variance of dual bolus stress perfusion values. Kostler et al. (7) reported a lower standard deviation in perfusion values obtained from the dual bolus technique compared to data from the single bolus technique. However, this lower standard deviation was found in comparison to a single bolus technique using a small bolus (3 ml). When comparing dual bolus technique to a single bolus technique in a similar set-up as the present study (1-12 ml versus 12 ml), Kostler et al. did not observe any significant change in relative variance between the single and dual bolus technique either. Utz et al (9) reported a difference in intra-individual relative standard deviation of perfusion over the myocardial segments between the single and dual bolus technique (27% versus 19%). In our study no significant difference between the intra-individual relative standard deviation of the single

and the dual bolus technique was found (33% versus 26% respectively). Using an F-test, these differences are not significant in both studies.

The present study confirms the high diagnostic accuracy of MR-MPI for detection of significant CAD that is in line with previously published data (14). In the present study the AUC of the minimal perfusion value was significantly higher than the AUC of the myocadial perfusion reserve. This may be explained by the extra noise introduced by the rest perfusion value that has a large physiologic variance (19).

There were some limitations in the present study. First, single and dual bolus techniques were performed during one single scanning session. The pre-bolus may have had a slight saturation effect on the AIF-sb and the single bolus myocardial response and thus influenced absolute perfusion values of the single bolus technique. However, the pre-bolus is minimally 10 times as small as the large bolus, therefore this effect is expected to be small. In contrast to other studies investigating the dual bolus technique, in the present study the pre-bolus contrast volume was not diluted to the same contrast volume of the main bolus. Although this made the injection protocol more practical, it might have influenced the results slightly. We recognize that the diagnostic accuracy may be subject to referral bias, as some patients were referred for ICA on basis of MR-MPI results. Still, this did not influence the comparison between single and dual bolus technique. For comparison of MR perfusion values to PET values from the literature, the present study investigated patients instead of healthy volunteers. Although in these patients significant CAD was excluded by ICA, perfusion values might be lower when compared to healthy volunteers. The interval between MR-MPI and ICA was relatively large, however, no patients had any clinical sign of progression of CAD between MR-MPI and ICA and thus their CAD was assessed as stable.

In conclusion, in this study the dual contrast bolus technique did not have incremental diagnostic value over single contrast bolus MR-MPI for detection of significant CAD with the used contrast concentrations.

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