

CORONARY ANGIOGRAPHY

Detection of Coronary Stenoses with Contrast Enhanced, Three-Dimensional Free Breathing Coronary MR Angiography Using the Gadolinium-Based Intravascular Contrast Agent Gadocoletic Acid (B-22956)

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ABSTRACT

Purpose: To determine the diagnostic value of the intravascular contrast agent gadocoletic acid (B-22956) in three-dimensional, free breathing coronary magnetic resonance angiography (MRA) for stenosis detection in patients with suspected or known coronary artery disease. **Methods:** Eighteen patients underwent three-dimensional, free breathing coronary MRA of the left and right coronary system before and after intravenous application of a single dose of gadocoletic acid (B-22956) using three different dose regimens (group A 0.050 mmol/kg; group B 0.075 mmol/kg; group C 0.100 mmol/kg). Precontrast scanning followed a coronary MRA standard non-contrast T2 preparation/turbo-gradient echo sequence (T2Prep); for postcontrast scanning an inversion-recovery gradient echo sequence was used (real-time navigator correction for both scans). In pre- and postcontrast scans quantitative analysis of coronary MRA data was performed to determine the number of visible side branches, vessel length and vessel sharpness of each of the three coronary arteries (LAD, LCX, RCA). The number of assessable coronary artery segments was determined to calculate sensitivity and specificity for detection of stenosis $\geq 50\%$ on a segment-to-segment basis (16-segment-model) in pre- and postcontrast scans with x-ray coronary angiography as the standard of reference. **Results:** Dose group B

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(0.075 mmol/kg) was preferable with regard to improvement of MR angiographic parameters: in postcontrast scans all MR angiographic parameters increased significantly except for the number of visible side branches of the left circumflex artery. In addition, assessability of coronary artery segments significantly improved postcontrast in this dose group (67 versus 88%, $p < 0.01$). Diagnostic performance (sensitivity, specificity, accuracy) was 83, 77 and 78% for precontrast and 86, 95 and 94% for postcontrast scans. **Conclusions:** The use of gadocoletic acid (B-22956) results in an improvement of MR angiographic parameters, assessability of coronary segments and detection of coronary stenoses $\geq 50\%$.

INTRODUCTION

Coronary magnetic resonance angiography (MRA) is proposed as a non-invasive means to detect coronary artery disease (CAD) and has been shown to be valuable for the detection of significant left main coronary artery or three-vessel disease (1). Commonly, a T2 suppression prepulse in combination with a fat suppression prepulse and prospective navigator correction is used to achieve a maximum contrast between blood and surrounding tissue. However, this approach is prone to saturation effects frequently resulting in misinterpretation of the true coronary luminal diameter, thereby causing false positive and false negative results.

As we have previously shown, coronary MRA with intravascular contrast enhancement using gadocoletic acid (B-22956) was found to be superior to the conventional T2 preparation pulse coronary imaging approach (2, 3) regarding contrast and MR angiographic parameters in volunteers.

The aim of the present study was to determine the diagnostic value of the intravascular contrast agent gadocoletic acid (B-22956) in three-dimensional, free breathing coronary MRA for stenosis detection in patients with suspected or known coronary artery disease.

METHODS

Study population

The study was conducted in accordance with the standards of the Charité and Virchow-Klinikum Ethics Committee and conducted in accordance with the recommendations of the World Medical Association (Declaration of Helsinki, 1964, last amendment in Edinburgh, Scotland, October 2000). Between October 2002 and August 2003, 18 patients (8 female, age ranging from 49 to 86 years) with chest pain referred to the German Heart Institute for cardiac catheterization were prospectively enrolled after written informed consent was obtained. Patients were eligible if they had suspected or known coronary artery disease but no prior coronary stent implantation. Patients were not considered for study inclusion if they had typical contraindications for MR imaging.

Prior to MR imaging the patients were randomized to receive one of the three following contrast agent dosages (Fig. 1): group A, 0.050 mmol/kg; group B, 0.075 mmol/kg; group C, 0.100 mmol/kg. Postcontrast imaging began five minutes after

intravenous administration of the respective B-22956 dose (a 0.25 M solution in saline, infusion rate of 0.3 mL/second).

Magnetic resonance study

CMR was performed with the patient in the supine position using a 1.5 Tesla MR scanner (Philips Intera CV, Best, The Netherlands) equipped with a PowerTrak6000 gradient system (23 mT/m; 219 μ sec rise time), a 5-element phased array coil and software package release 9. Cardiac synchronization was performed using four electrodes placed on the left anterior hemithorax (Vector-ECG, Philips Medical Systems, Best, Netherlands).

Magnetic resonances imaging technique

The imaging technique has already been described in detail elsewhere (2, 3). Briefly, for precontrast scanning a three dimensional segmented k-space gradient echo sequence with a T2 preparation prepulse was used (4). The postcontrast scan comprised a three dimensional segmented k-space gradient echo sequence with an inversion recovery (IR) prepulse (2). A spectrally selective fat suppression prepulse was employed for both the precontrast and the postcontrast scan. For all coronary scans respiratory motion compensation was done using a real-time prospective navigator (gating window: 5 mm) which was positioned on the dome of the right hemidiaphragm.

Before each postcontrast coronary MRA scan an inversion prepared, segmented k-space echo-planar imaging Look-Locker sequence was run to determine the optimal inversion recovery prepulse delay, i.e., the delay at which myocardial signal was completely nullified (IR delay usually between 140 to 220ms depending on dose group and time point of imaging). The individually determined IR prepulse delay was then set in the subsequently performed three dimensional postcontrast coronary MRA scan.

Scan procedure

The left and right coronary artery systems were imaged in two separate single volume scans using the three-point plan-scan tool for planning of the optimal imaging planes (identical geometry for pre- and postcontrast imaging) (3). Typical in-plane spatial resolution was 0.7×1.0 mm, with an acquired slice thickness of 3.0 mm interpolated by zero-filling to 1.5 mm during reconstruction.

Data acquisition was always performed during the individually determined rest period of the left or right coronary artery as

Table 1. Comparison of precontrast and postcontrast MR angiographic parameters in the three different dose groups (n = 6 patients per group)

	Group A (0.050 mmol/kg)		Group B (0.075 mmol/kg)		Group C (0.100 mmol/kg)	
	Precontrast		Precontrast		Precontrast	
LAD						
No. of branches	1.5 ± 0.5	1.3 ± 0.5	1.7 ± 0.5	2.5 ± 0.5*	1.7 ± 0.8	2.5 ± 0.8**
Length (mm)	71 ± 20	76 ± 10	90 ± 17	98 ± 16**	68 ± 14	93 ± 8**
Sharpness (%)	44 ± 3	52 ± 6*	43 ± 6	52 ± 5*	44 ± 4	56 ± 6**
LCX						
No. of branches	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	1.7 ± 0.5	1.2 ± 0.4	1.5 ± 0.5
Length (mm)	61 ± 11	63 ± 14	58 ± 7	81 ± 6**	57 ± 10	65 ± 9*
Sharpness (%)	40 ± 4	52 ± 5**	39 ± 5	49 ± 5*	37 ± 6	44 ± 6*
RCA						
No. of branches	2.5 ± 0.5	2.0 ± 0.6	2.0 ± 0.9	3.5 ± 0.8**	1.8 ± 0.8	3.3 ± 1.4**
Length (mm)	112 ± 23	115 ± 12	111 ± 15	126 ± 11*	120 ± 9	137 ± 14*
Sharpness (%)	48 ± 5	50 ± 7	40 ± 5	48 ± 6*	39 ± 4	50 ± 7*

Values are expressed as mean ± SD.

LAD indicates left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

*p < 0.05 and **p < 0.01 for the comparison of precontrast versus postcontrast values in the respective dose group.

visually evaluated from a cine scan (steady state free precession sequence, 40 phases/cardiac cycle, repetition time 2.7 ms, echo time 1.4 ms, flip angle 60°) (5).

Prior to MR imaging the order of the single volume coronary MRA scans for the right or left coronary artery system was randomized in each patient and applied to pre- and postcontrast scanning.

Quantitative MR image analysis

Quantitative evaluations were performed using a previously published dedicated coronary MRA analysis tool (“soap-bubble” visualization) (6). In all patients the following parameters were determined in pre- and postcontrast scans for each of the three main coronary arteries (LAD, LCX, RCA): the number of visible side branches, overall vessel length and vessel sharpness (7).

Diagnostic performance

For the assessment of coronary artery stenoses the unprocessed raw data were used. A 16-segment model according to the 29-segment model of the AHA/ACC guidelines (8) was ap-

plied considering the following segments of the coronary arteries for evaluation: (1) left main segment, (2) proximal segment of LAD, (3) mid segment of LAD, (4) distal segment of LAD, (5) first diagonal branch, (6) second diagonal branch, (7) proximal segment of LCX, (8) mid segment of LCX, (9) distal segment of LCX, (10) first marginal branch, (11) second marginal branch, (12) proximal segment of RCA, (13) mid segment of RCA, (14) distal segment of RCA, (15) right posterolateral segment (RPL), and (16) posterolateral descending artery segment (PDA).

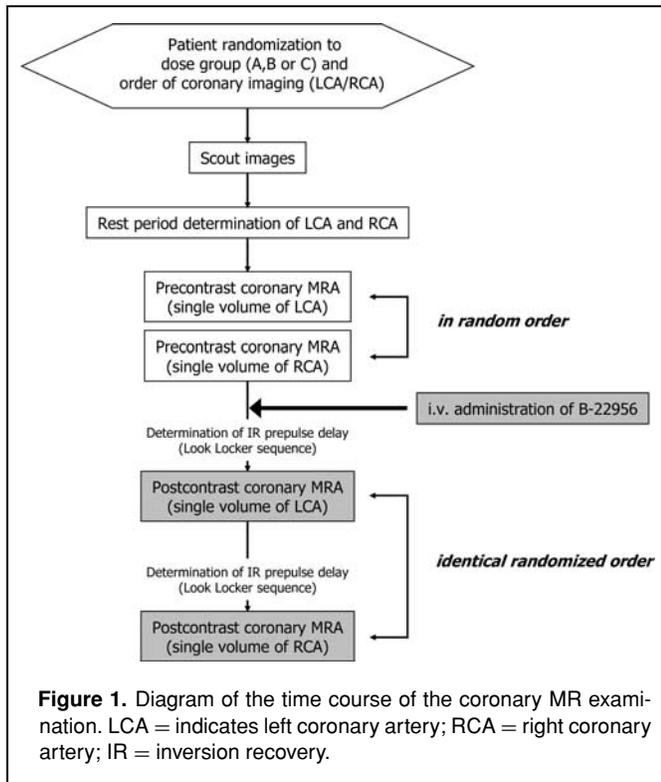
The coronary artery segments were classified as evaluable or impossible to evaluate with the latter referring to non-visibility of the respective coronary segment; these segments were not considered for diagnosis. Visual assessment of stenosis detection was done in the remaining coronary artery segments; these were classified as having significant stenosis (i.e., ≥50% diameter reduction) or showing the absence of a significant stenosis. Two observers being fully blinded to the results of invasive coronary angiography independently performed the analysis of the coronary MR angiograms; cases of disagreement were settled in a consensus reading. For determination of interobserver variability the independent evaluations of both readers were used.

Table 2. Assessability of coronary segments and diagnostic performance of postcontrast coronary MRA in the three dose groups (n = 6 patients per group)

	Group A (0.050 mmol/kg)		Group B (0.075 mmol/kg)		Group C (0.100 mmol/kg)	
	Precontrast		Precontrast		Precontrast	
Assessable segments (%)	62 (59/96)	82 (79/96)	67 (64/96)	88 (85/96)**	67 (64/96)	86 (83/96)
Sensitivity (%)	85 (11/13)	85 (11/13)	83 (5/6)	86 (6/7)	74 (17/23)	88 (21/24)
Specificity (%)	76 (35/46)	86 (57/66)	77 (45/58)	95 (74/78)*	56 (23/41)	90 (53/59)
Diagnostic accuracy (%)	78 (46/59)	86 (68/79)	78 (50/64)	94 (80/85)*	63 (40/64)	89 (74/83)

Data in parenthesis are those used to calculate the percentages.

*p < 0.05 and **p < 0.01 for the comparison of precontrast versus postcontrast values of dose group B.



Invasive x-ray coronary angiography

All coronary x-ray angiographies were performed within two weeks after coronary MRA using the transfemoral Judkins approach with selective catheterization of the left and right coronary artery system in multiple projections. Three experienced interventionalists unaware of the results of MR imaging evaluated the x-ray angiograms visually; cases of disagreement were settled in a consensus reading. Significant coronary stenosis was defined as $\geq 50\%$ luminal diameter narrowing in vessels with ≥ 2 mm diameter.

Statistical analysis

For all continuous parameters mean \pm standard deviation are given. The paired Student's t-test or one-way ANOVA was used to assess statistical significance of continuous variables. Group differences for categorical variables were tested with the χ^2 - or Fisher's exact test. All tests were two tailed; $p < 0.05$ was considered to be statistically significant.

Sensitivity, specificity and accuracy were calculated according to standard definitions and compared between groups (χ^2 or Fisher's exact test).

Cohen's kappa was applied to measure agreement between the two readers evaluating the coronary MR angiograms.

Data analysis was performed using SPSS for Windows 12.0.1 (SPSS Inc., Chicago, IL, USA)

RESULTS

MR angiographic parameters

Table 1 provides the MR angiographic parameters of the three major epicardial coronary arteries (LAD, LCX and RCA) for precontrast T2 preparation and postcontrast (B-22956 enhanced) imaging of the three dose groups A, B and C (for imaging examples see Fig. 2).

All MR angiographic parameters significantly improved in postcontrast scans of group B except for the number of visible side branches of the LCX. In this dose group, the effect of B-22956 on vessel sharpness was a 21, 26 and 20% increase for the LAD, LCX and RCA, respectively, compared to the corresponding precontrast scans.

With regard to the number of visible side branches and vessel length, group B reached the highest values (except for the RCA vessel length). As to the influence of the dose group on the number of visible side branches of the LCX, there was no statistically significant difference between the groups.

Diagnostic performance

Table 2 compares the number of assessable segments and the standard statistical values of diagnostic performance between precontrast and postcontrast scans for the three different dose groups of B-22956. Representative imaging examples are given in Figs. 3 and 4.

The highest overall diagnostic accuracy could be achieved in group B (0.075 mmol/kg of B-22956). Assessability and specificity were significantly higher for postcontrast imaging in group B; though sensitivity was slightly higher postcontrast, this effect did not reach the level of statistical significance.

Interobserver variability

The kappa coefficient of agreement regarding the presence or absence of a significant stenosis on coronary MRA in the three dose groups A, B and C was 0.70, 0.79 and 0.75 (precontrast scans) and 0.69, 0.89 and 0.89 (postcontrast scans), respectively.

DISCUSSION

Coronary MRA is technically highly demanding: a high spatial resolution of a three dimensional dataset is required to adequately depict the relatively small coronary vessels. With current three dimensional MR imaging, this can usually only be achieved at the expense of a decreased signal and contrast to noise ratio and particularly affects the signal received from the coronary arterial lumen.

In addition, image quality of coronary MRA is substantially influenced by respiratory and cardiac motion. It could be shown that respiratory motion compensation using the free breathing navigator technique results in a higher percentage of correctly diagnosed coronary segments (13%) when compared to the breath-hold technique (9), and, thus may be considered more favorable. Cardiac motion compensation is preferably done by triggering data acquisition to the relative standstill (i.e., the rest period) of

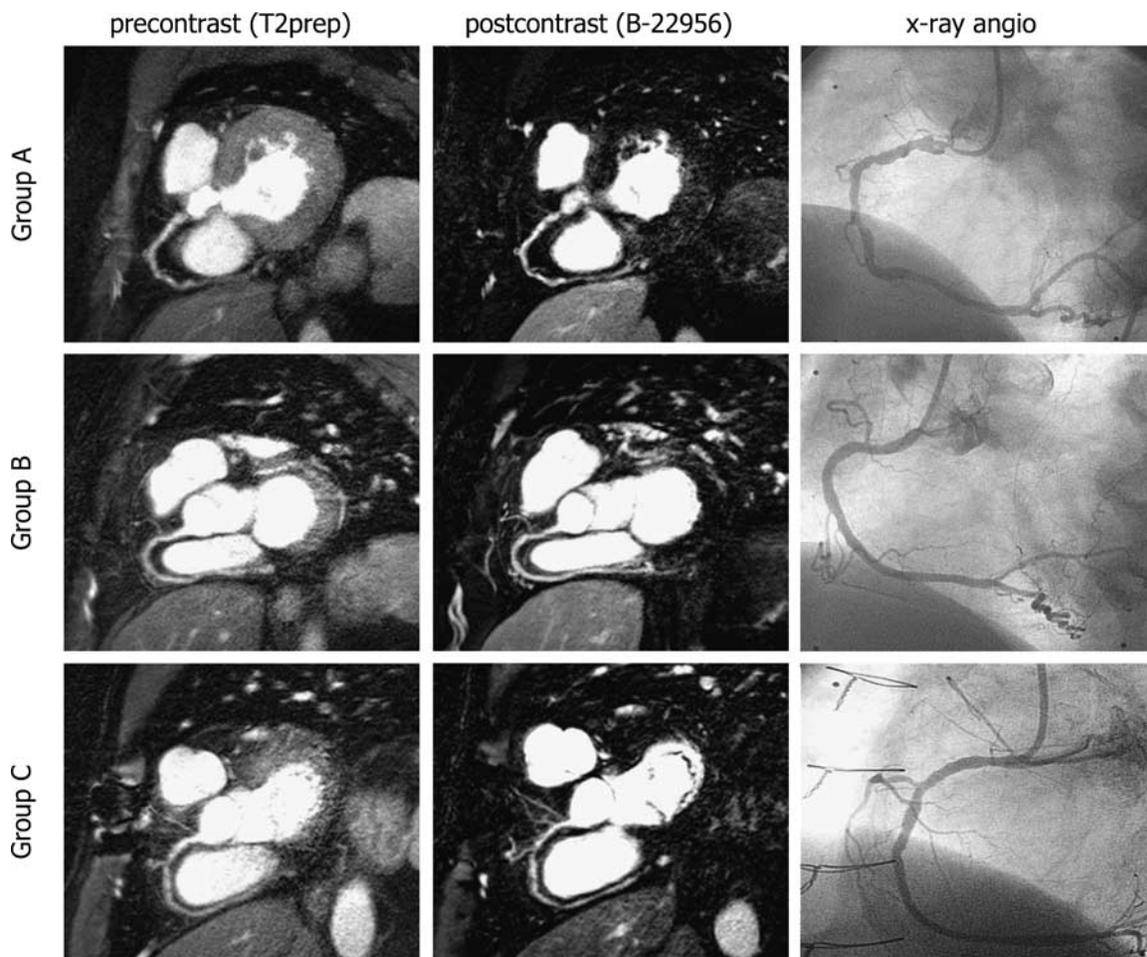


Figure 2. Representative examples of the right coronary artery of three patients (group A: 0.050 mmol/kg; group B: 0.075 mmol/kg; group C: 0.100 mmol/kg). Multiplanar reformatted MR coronary angiograms of the precontrast T2 preparation scan, the postcontrast B-22956 enhanced inversion recovery scan and the corresponding x-ray coronary angiography are provided. For all three dose groups, the overall improvement in visible vessel length and vessel sharpness as well as the increased visibility of coronary side branches can be appreciated.

the coronary arteries during the cardiac cycle: cine sequences with a high temporal resolution are used for visual detection of coronary arterial rest periods or an automatic approach is employed (5). In order to achieve a complete freezing of cardiac motion related coronary artery movement, these measurements need to be performed for each patient individually (10).

While techniques and imaging approaches have been established to sufficiently compensate for respiratory and cardiac motion, the issue of receiving a consistently high signal from coronary blood is yet to be resolved. Of note, the commonly used T2 preparation/turbo-gradient echo coronary MRA approach is basically a flow dependent imaging technique: the signal from the coronary artery lumen is determined by the inflow of fresh, unsaturated spins and thus, it is prone to saturation effects.

Thus, contrast enhanced coronary MRA strategies have been suggested using extra- and intravascular contrast agents. With extracellular contrast agents, however, there was a trade off between the concomitant signal enhancement of blood and myocardium, which occurred rapidly after contrast agent applica-

tion and rendered vessel border delineation problematic (11). Iron oxide-based intravascular contrast agents (ultrasmall iron-containing particles, USPIOs), though increasing contrast-to-noise, showed increased susceptibility artifacts related to dosage and echo time used thereby leading to difficulties in stenosis detection (12).

Previously, we have reported the development of a coronary MRA imaging approach making use of the gadolinium-containing, intravascular contrast agent gadocoletic acid (B-22956) (2) and initial results of coronary MRA in volunteers were highly encouraging with regard to the beneficial effects of the intravascular contrast agent on signal and contrast characteristics of blood and myocardium (3).

Our present data shows that the use of intravascular contrast enhancement for coronary MRA in patients significantly improves MR angiographic parameters and detection of coronary stenoses with $\geq 50\%$ diameter reduction. To optimally achieve this, the intermediate dosage of B-22956 at 0.075 mmol/kg given as a single intravenous bolus administration appears preferable,

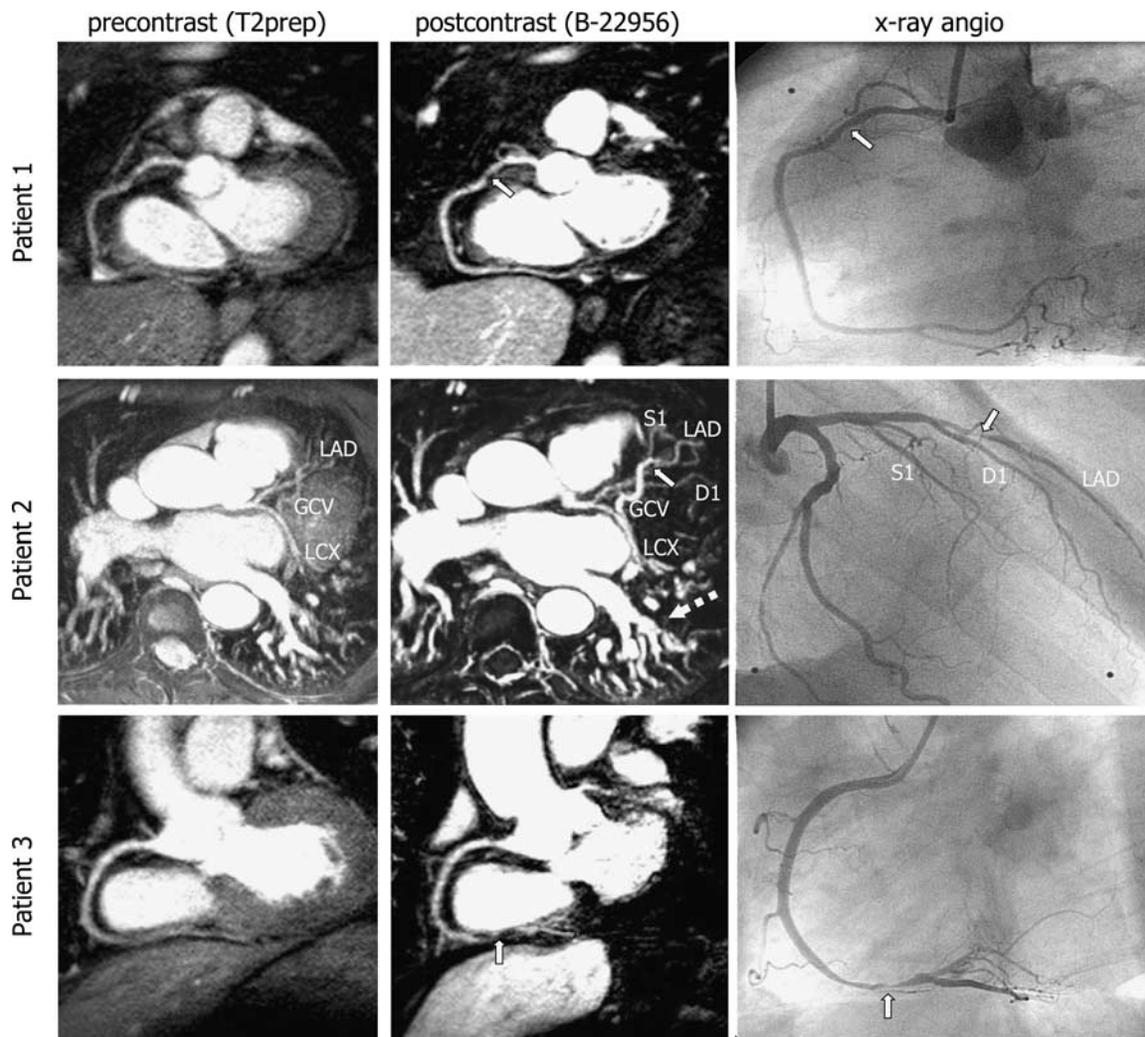


Figure 3. Detection of coronary stenoses. Patient 1: In the precontrast T2prep scan, there are signal irregularities within the coronary artery lumen and the visibility of the distal RCA is limited. The postcontrast scan allows the diagnosis of a coronary stenosis in the proximal RCA and depicts the vessel course beyond the crux. Patient 2: In the precontrast T2prep scan, the decrease in signal intensity in the mid-portion of the LAD is suggestive of a coronary stenosis, though reader confidence might be low. The postcontrast scan with its improved depiction of the distal LAD allows the definite diagnosis of a focal and high grade mid LAD stenosis. Patient 3: In the precontrast T2prep scan, the distal RCA lumen appears blurred. The postcontrast scan with its flow-independent and thus, clear depiction of the distal RCA lumen provides the diagnosis of a long distance stenosis before the crux. White arrows show coronary stenosis.

mainly due to the favorable effects on MR angiographic measurements and assessability of coronary segments. Both effects can be attributed to the high intravascularity of the contrast agent (half-life of around 4 hours), thereby leading to clear depiction of the coronary arterial lumen including coronary side branches.

The main diagnostic benefit of contrast enhanced coronary MRA with B-22956 was a significantly increased specificity resulting in an increased overall diagnostic accuracy for stenosis detection. Again, this is most likely related to the high intravascular containment of the contrast agent and the resultant stable signal from the coronary artery lumen. Thus, the problem of mistaking signal irregularities as coronary stenoses (as frequently done with the non-contrast enhanced T2 prep approach) could be overcome.

As with other intravascular contrast agents, B-22956 enhances all vascular structures, i.e., there is a concomitant enhancement of coronary arteries and the cardiac veins or the coronary sinus respectively. Depending on the patients' individual coronary anatomy, an overlap of arterial and venous signal can occur (especially in the LCX territory), which might render detection of coronary arterial side branches and LCX stenoses problematic. The reader needs to address this by carefully evaluating the original data of the coronary MRA scan, reformatting the dataset from different radial angles or performing segmentation of arterial and venous signal. However, this arterial-venous signal overlap is most likely the reason why in our patient population we could not demonstrate a statistically significant increase in visibility of side branches of the LCX territory.

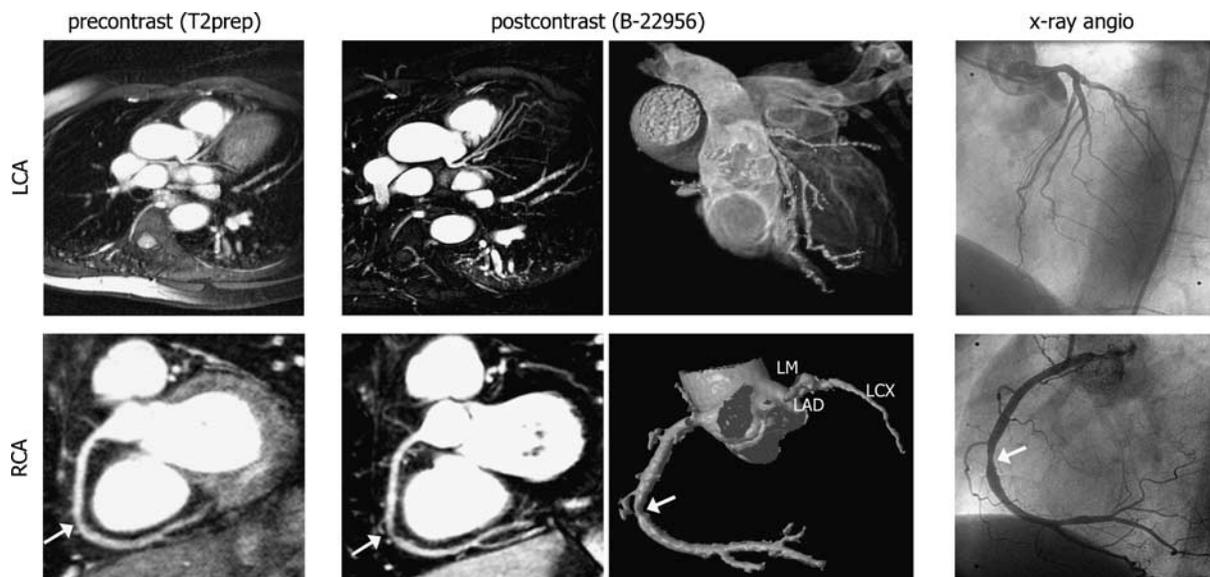


Figure 4. Imaging of the right and left coronary artery system of a patient (group B, 0.075 mmol/kg). The multiplanar reformatted precontrast T2 prep scan, the postcontrast B-22956 enhanced scan (left: multiplanar reformatted image; right: surface rendered image) and corresponding x-ray angiography are shown. Upper row: The precontrast scan does not visualize the distal LAD and side branches. The postcontrast scan shows a normal left coronary artery system. Bottom row: On the precontrast scan, the lumen of the mid RCA appears normal while the postcontrast scan gives clear evidence of obstructive coronary disease in this segment.

Study limitations

The choice of the optimal dosage of B-22956 can be judged from the viewpoint of improved MR angiographic parameters, assessability of coronary segments or the achieved diagnostic performance with regard to stenosis detection. Despite randomization of the patients to the three different dose groups, those patients receiving the intermediate dosage of 0.075 mmol/kg showed only 7 stenotic segments on x-ray coronary angiography. Thus, a statistical comparison among the dosage groups regarding a diagnostically superior dose regimen cannot reasonably be done. However, the statistically significant improvement of MR angiographic parameters and the better assessability of coronary segments favors the 0.075 mmol/kg dosage of B-22956. In addition, the number of patients in the present study was limited: more studies are needed to verify the superiority of B-22956 contrast enhanced coronary MRA in larger patient populations and in comparison to other non-contrast enhanced coronary MRA imaging techniques (e.g., steady-state free precession sequence). With the use of flow-independent steady state free precession imaging sequences for coronary MRA becoming more widespread, future studies are needed to ultimately define the role of intravascular contrast enhancement in comparison to or applied to steady state free precession coronary MRA.

At the time the present study was conducted, a sophisticated and stable running 'whole heart' coronary imaging approach utilizing the steady-state free precession sequence (i.e., a rather flow independent, non-contrast-enhanced imaging sequence) was not available at our institution but has since been established and published recently (13, 14). The T2 preparation

approach with single volume imaging of the left and right coronary system, however, still represents a widely used coronary MRA technique and, thus, was chosen for comparison with the contrast enhanced approach.

None of the patients participating in this study had prior myocardial infarction; thus, we cannot fully rule out a possible accumulation of B-22956 in infarcted tissue. However, as reported previously (3), the high intravascularity of B-22956 as assessed up to 45 min post injection suggests that such a 'delayed enhancement phenomenon' is unlikely to occur within the time frame needed for B-22956 enhanced coronary MRA.

CONCLUSION

The use of gadocoletic acid (B-22956) in patients with suspected or known coronary artery disease resulted in an improvement of MR angiographic parameters, assessability of coronary segments and detection of coronary stenoses $\geq 50\%$ in comparison to the standard T2 preparation coronary MRA.

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