

Comparison of the quality of lower limb magnetic resonance angiographies performed with different paramagnetic contrast agents in relation to body mass index and ejection fraction

Lukas Hrdina^a, Martin Kocher^a, Miroslav Herman^a, Marie Cerna^a, Jiri Kozak^a, Zbynek Tudos^a, Shankari Mahathmakanthi^a, Katerina Langova^{b,c}

Aim. To compare the quality of magnetic resonance angiographies (MRAs) performed with different contrast agents and to evaluate the effect of body mass index (BMI) and ejection fraction (EF) on the quality of these MRAs.

Materials and Methods. 120 patients between the age of 43 and 86 years were subjected to MRAs with different contrast agents (Gadobutrolum, Dimeglumini gadobenas, Gadofosveset trisodium). Each patient's BMI was calculated, and EF was established using MR examination of the heart. Objective evaluations of the quality of the MRAs were done using abdominal fat-to-aorta enhancement ratio (FAR) comparisons. This ratio was then correlated with the patient's BMI and EF. Subjective evaluations of the quality of the MRAs were done by 5 blinded evaluators. Correlation analysis and analysis of variance were used for statistical assesement.

Results. There was no statistically significant difference in FAR for any of the contrast agent groups. There was a meso-scale correlation between a patient's BMI and FAR. However, no correlation was found between the EF and FAR for any of the contrast agent groups. The results of the subjective evaluation showed that there was no statistical difference in the quality of MRAs regardless of the contrast agent used.

Conclusion. Subjectively there was no statistically significant difference in the quality of the MRAs. Irrespective of the type of contrast used or the patient's EF, the lower the BMI of a patient the higher the signal enhancement and hence the better the quality of the MRA produced in that patient.

Key words: ischemic disease of lower leg arteries, MR angiography, paramagnetic contrast agent

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^aDepartment of Radiology, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

^bDepartment of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc

^cInstitute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc

Corresponding author: Lukas Hrdina, e-mail: Lukas.hrdina@post.cz

INTRODUCTION

Peripheral arterial disease (PAD) is one of the world's most frequent diseases. The prevalence of this disease is 7-21%, depending on age, sex and evaluative criteria¹. A major etiologic factor is the level of atherosclerosis in the lower extremity arteries.

Intermittent claudications - pain of the extremity during common physical stress, when blood supply for working muscles cannot be increased due to narrowing of a main artery - are typical clinical complaints of affected patients. Resting pain and ischemic ulcers can appear in later stages of the disease. All these symptoms of PAD are very frustrating for patients to deal with and their life quality is evidently reduced. The only solutions to these problems are surgery or endovascular revascularisation.

Clear imaging of the lower extremity arteries is important for making optimal decisions on therapy. The length, severity, localization and number of lesions determine whether the patient requires surgical or endovascular treatment.

There are several modalities for arterial system imaging each with its own advantages and disadvantages. The most accessible method of examination is doppler ultrasound. It is non-invasive and cost-efficient, but on the other hand very subjective and the accuracy is low. Results greatly depend on the examiner's experience. Doppler ultrasonography can find the artery involved and also determine the stage of its impairment, but it does not give exact morphological information regarding the extent and the nature of the stenosis, which is critical for therapeutical decisions. A clear indication for the use of doppler ultrasounds is patients being monitored after revascularisation procedures².

Digital subtraction angiography (DSA) has the best spatial resolution of angiographic methods, but it is not used for routine diagnostic examinations. This is because of the risks and disadvantages that accompany DSAs such as X-ray exposure, allergic reactions to the iodine contrast agent, catheterisation and its complications and the need for hospitalisation in some cases. Regardless of the disadvantages it is still regarded as the golden standard for im-

aging quality. This once diagnostic method has now been replaced by computed tomography angiography (CTA) and magnetic resonance angiography (MRA). The choice between CTA and MRA differs in each hospital depending on the knowledge and experience of the clinicians³. The majority of radiology departments, including ours, prefer MRAs, however, CTAs are still being used on patients with contraindications for MRA (ref.⁴).

CTA uses X-rays and iodine as the contrast agent just like DSA. However, there is no need to catheterise patients as the contrast agent is administered intravenously.

MRAs can be performed with or without the use of a contrast agent. Some examples of non-contrast enhanced MRA methods are time-of-flight (TOF) and phase-contrast (PC) angiographies. The inflow effect of non-saturated spins flowing through stationary tissues saturated by radiofrequency pulses is used to obtain sufficient contrast between vessels and surrounding tissues in TOF MRAs. PC MRAs utilise the phase drift created between moving spins in the gradient magnetic field and non-moving spins of the surrounding tissues⁵. Non-contrast MRA is now only used for depiction of certain arteries such as the arteries of the brain and that of the calves. Contrast-enhanced MRA (CEMRA) is used to visualise all other arteries of the body.

The fundamental basis of CEMRA is the intravenous administration of a contrast agent, which reduces the T1 relaxation time of arterial blood below to that of surrounding tissues. The time is reduced to about 270 ms, which is the T1 relaxation time of fat⁶. Contrast agents also increase the signal-to-noise ratio, shorten the time of the procedure and eliminate the presence of artifacts⁵. CEMRA gives detailed angiographic images which enable an accurate evaluation of arteries.

Advantages of CEMRA in comparison to non-contrast techniques are a better contrast between arteries and surrounding tissues, shorter examination time and that they are not influenced by blood flow characteristics. The only significant disadvantage of CEMRA is its cost.

Contrast agents for CEMRA can be classified as extravascular and intravascular. Extravascular contrast agents such as half-molar Dimeglumini gadobenas (Multihance, Bracco Imaging, Konstanz, Germany) and molar Gadobutrolum (Gadovist, Bayer Schering Pharma, Berlin, Germany) spread into the extravascular space. This distribution causes a reduction in the contrast between arteries and their surrounding tissues within a short period of time. In addition to this, extravascular contrast agents are quickly eliminated by kidneys. This is why we can only use these contrast agents for first pass examinations. Molar contrast agents contain double the dose of gadolinium in the same volume as half-molar contrast agents.

Intravascular contrast agents are a recent development and the most readily used agent is Gadofosveset trisodium (Vasovist, Bayer Schering Pharma, Berlin, Germany).

Gadofosveset trisodium reversibly binds to blood albumin and that is why it does not spread into the extravascular space and its concentration within blood remains high for a longer time. Gadofosveset trisodium is not eliminated quickly by the kidneys. This is why we can use

it for first pass examinations and also for steady state examinations. Getting data from steady state examinations can be a long process, but they give detailed images of the peripheral arterial system with a better spatial resolution, which makes it worthwhile.

CEMRA has two main advantages in comparison to DSA and CTA, one being the absence of X-rays and the other being the use of paramagnetic contrast agents, which have a very low risk of allergic reactions. The disadvantages are reduced spatial resolution and a higher requirement for examination performance.

The aim of this study was to compare the quality of images produced by first pass MRAs performed with the following paramagnetic contrast agents - Gadobutrolum, Dimeglumini gadobenas and Gadofosveset trisodium.

This work is a continuation of a pilot project that was published in a Czech Radiology Journal last year. However, we carried out a larger number of examinations than the pilot project and the quality of our MRAs were correlated with our patients' Body Mass Indexes (BMI) and ejection fractions (EF).

MATERIALS AND METHODS

In this project, we compared 120 first pass MRAs, which were performed with three different paramagnetic contrast agents. Patients were separated into four groups. In two of these groups Gadobutrolum was used as contrast agent. One group was injected with 8 mL of Gadobutrolum and the other with 10 mL. In the third group 10 mL of Dimeglumini gadobenas was used and in the fourth 10 mL of Gadofosveset trisodium. For each group there were 30 examinations.

The examinations were chosen at random and the age of the patients ranged from 43 to 86 years, mean age 65 years. The BMIs of all patients were calculated. Written informed consent was obtained from all patients before the examinations.

1.5 T MR machine (Siemens Magnetom Avanto, Erlangen, Germany) was used for the examinations with gradients Q-ENGINE (33 mT/m) and matrix phased-array surface coils. First pass MRAs were standardly performed at three levels - abdominal aorta and pelvic arteries (1.7 x 1.3 x 1.5 mm; 11 s), thighs (1.6 x 1.3 x 1.6 mm; 13 s) and calves (1.6 x 1.0 x 1.5 mm; 23 s). MIP reconstructions of subtracted images were produced. The above mentioned amounts of respective contrast agents were administered by an automatic injector (Medrad Spectris, Indianola, USA) into the antecubital vein, at a flow rate of 1.3 mL/s followed by a 25 mL saline flush. MR fluoroscopy (CARE BOLUS) was used to determine the contrast bolus timing. Before the use of MRAs, cinematic examination of the heart in the short axis was performed for EF measurements.

The evaluation of the examinations was divided into two parts - objective and subjective.

Objective evaluation consisted of comparing the fat-to-aorta ratio (FAR) of all examinations. FAR represented the objective quality of a CEMRA. FAR compared the

Table 1. Comparison of the FAR of all examinations - results for the analysis of variance were only significant if below 0.05. The calculated significance was higher than this limit value and hence there is no statistically significant difference in the FAR in any of the examinations.

	Sum of Squares	Degrees of freedom	Mean Square	F test value	Significance
Between Groups	0.047	3	0.016	1.872	0.138
Within Groups	0.961	116	0.008		
Total	1.008	119			

enhancement of the abdominal aorta to the signal intensity of subcutaneous abdominal fat, which was regarded as the standard. The regions of interest (ROI) of the abdominal aorta for signal intensity measurements were localised as being at the level of the renal arteries, in the middle of the subrenal aorta and near the aortic bifurcation. ROI for fat signal intensity measurements were in the subcutaneous abdominal fat bilaterally at the level of the renal arteries and that of the aortic bifurcation (Fig.1). FAR of the mean values was calculated according to the following equation: FAR = subcutaneous fat signal intensity/postcontrast aorta signal intensity. The data were analysed using ANOVA.

The second part of the objective evaluation was the analysis of FAR in relation to BMIs and EFs.

Subjective evaluation of the quality of MRAs was carried out by five blinded evaluators, who concentrated on the following five criteria:

1. Contrast enhancement distributional area
2. Sufficiency of contrast enhancement

Table 2. The results for the analysis of the correlation between the patient's FAR and BMI and EF. Results were only significantly positive if below 0.01. Resulting significance for the correlation between FAR and BMI is lower than this limit value and hence there is a positive correlation. Pearson's coefficient shows a mesoscale correlation. Resulting significance for the correlation between FAR and EF, however, is higher than this limit value, which means that there is no correlation between a patient's FAR and EF.

	FAR
BMI Pearson Correlation	0.400
Significance (2-tailed)	0.000
N	120
EF Pearson Correlation	-0.131
Significance (2-tailed)	0.162
N	115

Table 3. Results for the subjective comparison of the quality of MRAs from one evaluator and one evaluated level (thighs). The analysis of variance was performed and was only significant below the value of 0.05. The value of significance for all evaluated criteria are higher than this limit value and this means that there is no statistically significant difference between the MRAs in the all evaluated criteria. Comparable results are seen with all the evaluators and all 3 evaluated levels of MRAs.

	Sum of Squares	Degrees of freedom	Mean Square	F test value	Significance
Thighs Between Groups	0.588	3			
Contrast enhancement Within Groups	73.567	116	0.186	0.293	0.830
distributional area Total	74.121	119	0.634		
Thighs Between Groups	1.400	3			
Sufficiency Within Groups	66.067	116	0.467	0.819	0.486
of contrast enhancement Total	67.467	119	0.570		
Thighs Between Groups	1.900	3			
Depiction Within Groups	105.267	116	0.633	0.698	0.555
of the details Total	107.167	119	0.907		
Thighs Between Groups	0.758	3			
Artery outlines Within Groups	34.367	116	0.253	0.853	0.468
Total	35.125	119	0.296		
Thighs Between Groups	1.800	3			
Overall impression Within Groups	82.867	116	0.600	0.840	0.475
Total	84.667	119	0.714		

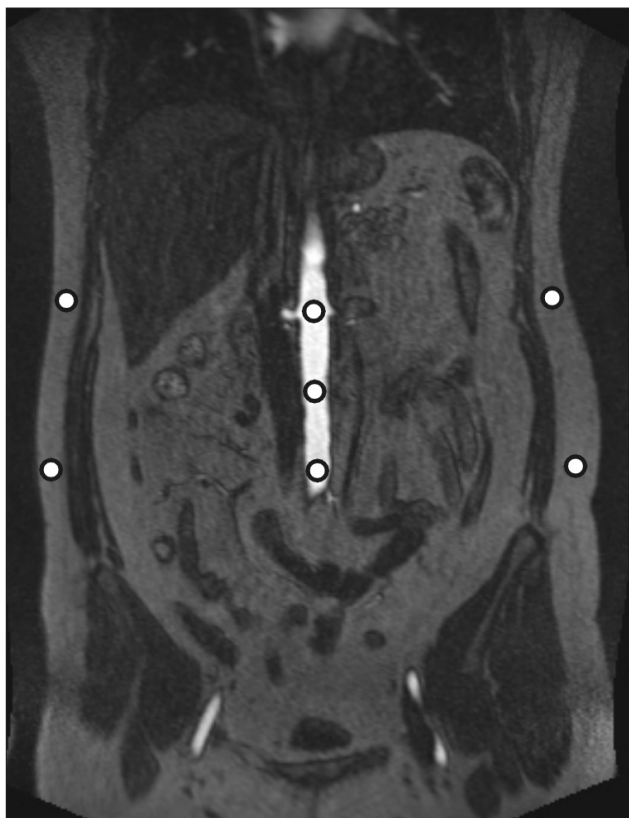


Fig. 1. Positions of the ROI of the abdominal aorta and subcutaneous fat for signal intensity measurements.

3. Depiction of the details
4. Artery outlines
5. Overall impression

A scale from 1 to 10 was used, 1 being the best and 10 being the worst. All areas of each MRA were assessed. The data were analysed using ANOVA.

RESULTS

Objective quality of CEMRA was expressed in terms of FAR, where the lower the FAR the better the contrast between the aorta and its surrounding tissues. The fat-to-aorta ratio was 0.346 for group I (Gadobutrolum 10 mL), 0.304 for group II (Gadobutrolum 8 mL), 0.356 for group III (Dimeglumini gadobenas 10 mL) and 0.323 for group IV (Gadofosveset trisodium 10 mL). The differences found in the fat-to-aorta ratios between the groups had no statistical significance (Table 1).

The correlation between FARs and BMIs of the patients showed that the lower the BMI the lower the FAR, giving a better contrast. The quality of the CEMRA was found to be independent of the patient's EF, since there was no correlation between the FAR and the EF (Table 2, Fig. 2).

Analysing the variance of the subjective data we obtained showed that the scores given for the quality of the CEMRAs are not dependent on what contrast was used, and this was true for all the evaluators (Table 3).

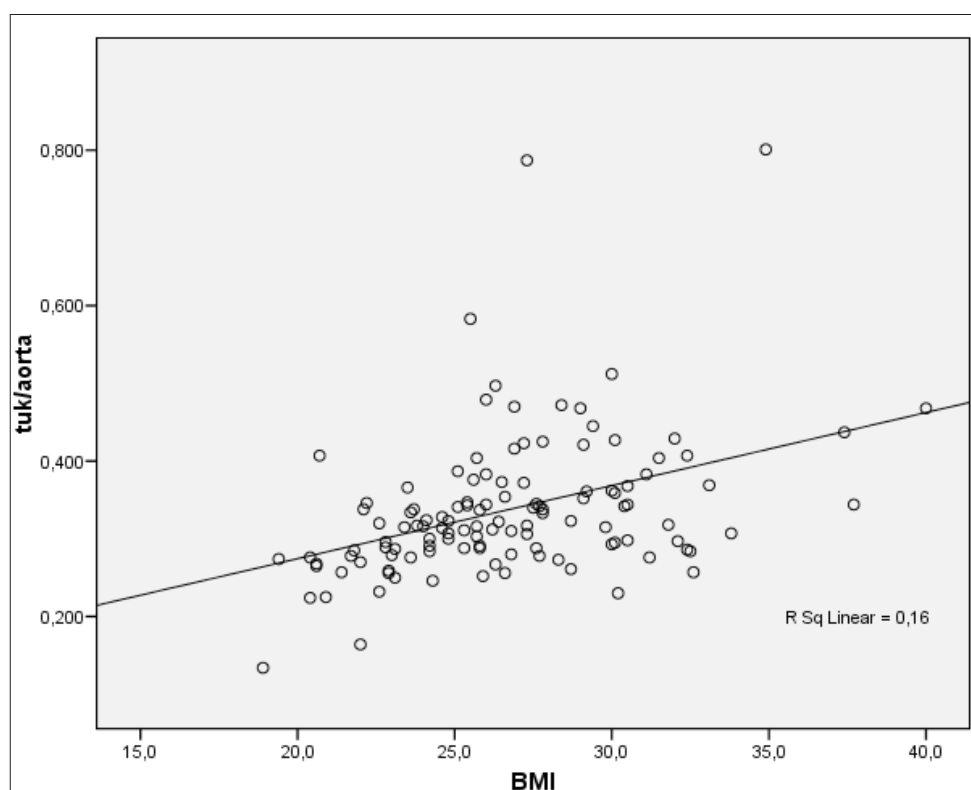


Fig. 2. Graphic illustration of mesoscale correlation between patients' FAR and BMI.



Fig. 3a,b,c. MRA of aorta abdominalis and lower leg arteries, MIP reconstruction. Subjectively one of the best evaluated MRA, enhanced with 10 mL of Dimeglumini gadobenas.

DISCUSSION

In this project we wanted to evaluate what effect the type and volume of paramagnetic contrast agent we used would have on the quality of the CEMRAs produced. Each of the paramagnetic contrast agents have different features, some of which were mentioned above, but the differences in price is also significant. This is why we also aimed to find out if it is necessary to use the most expensive contrast agent to obtain a respectable quality CEMRA or if a cheaper alternative contrast agent is adequate to obtain a sufficient quality. Our pilot project showed that subjectively there was no statistically significant difference in the quality of the CEMRAs produced when different paramagnetic contrast agents were used. However, objectively Gadobutrolum seems to be the best⁷. After several remarks on our pilot study we decided to extend the number of evaluated examinations and correlate the quality of CEMRAs with both body mass index and the ejection fraction of the patients.

The results of our current study, reveal that there is no statistically significant difference in the quality of CEMRAs produced with the tested contrast agents, which means that we can use all of these contrast agents to obtain adequate diagnostic information. In our department, we routinely use Gadobutrolum and Dimeglumini gadobenas to perform CEMRAs. We do not use Gadofosveset trisodium due to its higher cost. The differences noticed in the quality of CEMRAs in the pilot study could have



Fig. 4a,b,c. MRA of aorta abdominalis and lower leg arteries, MIP reconstruction. Subjectively one of the worst evaluated MRA, enhanced with 8 mL of Gadobutrolum.

been caused by the small number of evaluated examinations in the pilot study.

The comparable results obtained for Dimeglumini gadobenas even though it only contains half the amount of gadolinium as Gadobutrolum, can be explained by its almost twice the relaxivity at all field strengths, which is caused by a weak and transient affinity of Dimeglumini gadobenas for serum albumin^{8,9} (Fig. 3,4).

Creating an adequate contrast between artery and its surrounding tissues particularly depends on the level of gadolinium (Gd) within the examined artery. It is necessary to reach a certain level of Gd, which decreases the T1 relaxation time below 270 ms. The best contrast is achieved when the T1 relaxation time is reduced to around 150 ms.

The level of gadolinium in blood is influenced by two parameters: contrast agent injection rate (IR) and cardiac output (CO) according to the following equation $[Gd] = IR/CO$ (ref.⁶). This results in a higher concentration of gadolinium with a higher injection rate, lower cardiac output or both. In the case of a lower cardiac output little contrast agent is required as its not distributed in the cardiovascular system very fast during its first pass. This makes it easier to reach a higher concentration of Gd in the examined area at the time of the scan. In patients with decreased cardiac outputs it takes longer to reach a sufficient concentration of gadolinium in the examined area. The time between the administration of the contrast agent and the scanning is extended. To simplify the measurements we correlated the quality of CEMRAs with the

patients' EFs and in our cases the quality was independent of the EF. In our group of patients, the lowest measured EF was around 20. We had no patients with extremely low EFs but in such patients performing a CEMRA can be very complicated.

Another question is if the same volume of contrast agent should be administered to patients with different BMIs. According to our findings there is a mesoscale correlation between the BMI and the quality of the CEMRA. Patients with a higher BMI have a larger volume within which the contrast agent can be distributed and this is why the contrast agent is more diluted and its resulting concentration within the arteries is lower. It should be noted that this effect has a minimal impact on first pass examinations. In patients with a higher BMI, a decrease in signal-to-noise ratio is found and this is thought to be the reason for the worsened contrast between arteries and their surrounding tissues. In these patients a better quality of CEMRAs are achieved by administering higher doses of gadolinium. We recommend higher doses of gadolinium in patients with a BMI higher than 27.

Results for Gadofosveset trisodium correspond to those claimed by the manufacturer. It has comparable features to extravascular contrast agents in first pass examinations. Moreover it has one major advantage over extravascular contrast agents, which is the possibility of carrying out steady state examinations with a higher spatial resolution. This feature of Gadofosveset trisodium was however not evaluated in this study.

CONCLUSION

High-quality imaging of the arterial system is a very important part of the planning process of for possible therapies in patients with PAD. CEMRAs have become a method of choice in the majority of institutions. Our results after comparing four groups of CEMRAs performed with different contrast agents, or different volume of the same contrast agent in one case, showed that all groups provide sufficient diagnostic information and there is statistically significant difference between them. Correlation analysis shows the relation of CEMRA quality to patient's body mass index and independence of patient ejection fraction.

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