Optimization and clinical utility of peripheral MR angiography

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Haec ego non multis scribo, sed tibi: satis enim magnum alter alteri theatrum sumus.

I write this not to the many, but to you only, for you and I are surely enough of an audience for each other.

(Epicurus)

VOOR MIJN VADER

Contents

Introduction

Atherosclerotic peripheral arterial occlusive disease (PAOD) is an important healthcare problem in Western society with an estimated prevalence in the general population of 2.5% in the age group over 50 years of age. In the age group over 70 years old, the prevalence is estimated at about 7%.(1) Patients who have complaints of PAOD usually present with a history of intermittent claudication; this term is derived from the Latin 'claudicatio' which means 'to limp'. Intermittent claudication is caused when blood flow to exercising leg and calf muscles is insufficient compared to the metabolic demands because of obstructions in arteries supplying the lower limbs and leads to cramping and pain in buttocks, thighs and lower legs. Upon cessation of exercise, these complaints typically disappear rapidly. A minority of patients with intermittent claudication subsequently progresses to critical ischemia; that is, the oxygen and nutrient supply of the distal lower extremity falls below the level for maintenance of normal cellular processes in resting conditions. Clinically, this is manifested by rest pain and tissue loss (i.e. non

*Table 1 Clinical categories of chronic limb ischemia**

Grade	Category	Clinical Description	Objective Criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise and ankle pressure after >50 mmHg but ≥ 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise and ankle pressure after exercise <50 mmHg
II	4	Ischemic rest pain	Resting ankle pressure <40 mmHg; flat or barely pulsatile ankle or metatarsal pulse volume recording; toe pressure <30 mmHg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure <60 mmHg; ankle or metatarsal pulse volume recording flat or barely pulsatile; toe pressure <40 mmHg
	6	Major tissue loss – extending above tarsometatarsal level, functional foot no longer salvageable	Same as category 5

* according to Rutherford (7); grades II and III, categories 4, 5 and 6 are embraced by the term chronic critical ischemia

healing ulcers and gangrene). In table 1, the classification system for the severity of PAOD is listed.

The diagnosis of PAOD is made on the basis of the typical history, physical examination (palpation of arterial pulsations) and measurement of the ankle-brachial index.(1,2) When a patient presents to the general practitioner or the vascular surgeon with complaints of PAOD, the first line treatment consists of modification of obvious cardiovascular riskfactors such as smoking, hypertension, hypercholesterolemia and the institution of exercise training.(3-5) Only when the patient's complaints become too limiting to pursue regular activities the vascular surgeon will consider an invasive intervention. For patients with intermittent claudication, the decision to intervene is largely dependent on relative criteria (patient and surgeon preference) but for patients with chronic critical ischemia the need to intervene is more urgent since tissue perfusion does not meet basic metabolic demands, even at rest. Of 100 patients presenting with PAOD, 5 eventually undergo percutaneous or surgical treatment.(1) Although this is only a small minority of patients with PAOD, the estimated annual number of percutaneous and surgical procedures performed for PAOD in the U.S alone was over 100,000 in 1986, with sharp increases expected(6), illustrating the large scope of the problem and impact on the lives of the nation's citizens.

Imaging of peripheral arterial occlusive disease

Because the diagnosis of PAOD is usually made from the typical history, physical examination and ankle-brachial index, the need for imaging of the peripheral arterial arteries only arises when a percutaneous or surgical intervention is considered. Imaging is needed to explore the extent of the disease process (the number, location and severity of atherosclerotic lesions) and to plan the correct approach for therapy.(8)

Traditionally, the standard of reference for imaging PAOD has been acquisition of X-ray images during intra-arterial injection of iodinated contrast media. Until about 20 years ago, translumbar placement of a needle in the abdominal aorta was a routine procedure to accomplish this.(9) In 1953, the transfemoral approach was developed by Seldinger in which arterial access is gained through the superficial or common femoral artery.(10) Having been refined and technically optimized, this is the procedure most widely used in state-of-the-art angiography today and is considered the standard of reference. When combined with digital subtraction techniques, high resolution projection arteriograms of the peripheral arterial circulation can be obtained in a routine fashion. However, substantial rates of local and systemic procedure related complications are still associated with intra-arterial angiography. Although the number and severity of complications have declined since the translumbar approach era, intra-arterial angiography is still not without risk. Waugh et al report an overall adverse event rate for intra-arterial digital subtraction angiography of 9.5%, with a small but definite risk of developing acute renal failure in 0.2% of the patients.(11) In selected patients such as those with diabetic nephropathy, the prevalence of renal failure can amount to over 30%.(12) Other complications that are routinely encountered are post-interventional groin hematoma, arterial wall dissection, and pseudoaneurysm.(13) In addition to the complications associated with the invasive nature of IA-DSA there is the omnipresent concern for patient and hospital personnel of radiation exposure.(14) Although most patients undergoing preinterventional evaluation for PAOD are beyond their reproductive years and have little hematopoetic marrow within their pelvis and long bones, X-ray exposure should be avoided when possible. Furthermore, next to the risk for adverse events and radiation issues the invasive nature of intra-arterial catheterisation demands a short hospital stay that makes the procedure expensive.

Magnetic resonance angiography

Only in 1973 did Paul Lauterbur first succeed in generating a two-dimensional image of water in capilliary tubes using magnetic field gradients. He proposed to name the method zeugmatography from the Greek ζευγμα "that which is used for joining". In his publication Lauterbur realizes the potential of the new technique for medical imaging and speculates that: "a possible application of considerable interest at this time would be to the in vivo study of malignant tumors, which have been shown to give proton nuclear magnetic resonance signals with much longer water spin-lattice relaxation times than those in corresponding normal tissues."(15) In 1985, Wedeen et al first described the possibility to use magnetic resonance to image arteries noninvasively. The essence of the technique, that: "background structures become in effect transparent, enabling the three-dimensional vascular tree to be imaged by projection to a two-dimensional image plane"(16) is exactly the reason why MR angiography has become such a valuable and widely used diagnostic tool in the last few years.

Different methods of MR angiography

Nowadays, several different MR angiographic techniques are used to image the lumen of arteries. The most used techniques are: 1) phase-contrast, 2) inflow (time-of-flight), 3) black-blood and 4) contrast-enhanced MR angiography.(17-20) Although all these different techniques are routinely used in clinical practice, contrast-enhanced MR angiography (CE-MRA) is the most promising method because it can avoid artefacts inherent to the other methods and allows for data acquisition within seconds to minutes.(21-23) Intracranial, carotid, thoracic, abdominal and peripheral arteries have all been imaged succesfully and with high diagnostic accuracy using CE-MRA.(24-45)

The main difference between contrast-enhanced MR angiography (CE-MRA) and other MRA techniques is the intravenous administration of (super)para–magnetic contrast media. Generally, these contrast media shorten blood's T1, which leads to bright intravascular signal when a strong T1-weighted pulse sequence is used. In a strict sense, injection of contrast medium makes CE-MRA minimally invasive instead of non-invasive. However, adverse event rates after intravenous injection of gadolinium chelates, the only MR contrast agents approved for clinical use, are extremely low.(46,47) In a recent review of 28340 administrations of gadolinium chelates only 19 mild to moderate and 1 severe adverse event (0.06%) had occurred.(48)

Magnetic resonance angiography in current clinical practice

In current clinical practice, CE-MRA enjoys widespread enthousiasm in the radiological community. Since it's inception in 1996, CE-MRA for detection and grading of PAOD has rapidly evolved into a procedure that is being performed in many hospitals with a variety of different MR scanners. However, CE-MRA should still considered to be in the 'proof of concept' phase because to date, many questions remain about the most optimal protocols, the suitability of the technique for certain patient populations and most importantly, if CE-MRA of the peripheral arteries offers sufficient added value over existing techniques that it warrants a separate status. This is an especially pertinent consideration in an ever more cost-conscious and evidence based environment that demands proven added value for every euro spent on health care.

The current thesis

This thesis addresses several problems related to the diagnosis of peripheral arterial disease with magnetic resonance angiography.

The objectives of this thesis are:

1. To summarize the overall diagnostic performance of MR angiography and to identify the most important sources of variation in diagnostic accuracy between studies.
2. To optimize current contrast-enhanced MR angiographic protocols.
3. To study the safety and efficacy of a new contrast medium for peripheral MR angiography.

4. To assess the utility of contrast-enhanced MR angiography in patients with chronic critical ischemia and tissue loss.
5. To investigate the comparative accuracy of contrast-enhanced MR angiography and duplex ultrasonography for the diagnosis of peripheral arterial disease.
6. To investigate the comparative utilities of contrast-enhanced MR angiography and duplex ultrasonography for preinterventional treatment planning.

Outline of the thesis

- In chapter 2, the diagnostic performance of MR angiography techniques for the detection and exclusion of hemodynamically significant stenoses is summarized in a meta-analysis using summary receiver operator characteristic analysis.
- In chapter 3, a technique based on differential, optimized high resolution imaging for aortoiliac, upper and lower leg arteries is presented for optimization of contrast-enhanced peripheral MR angiography.
- In chapter 4, the necessity for background suppression in contrast-enhanced MR angiography is investigated and fat-saturation and subtraction are explored as suppression strategies.
- In chapter 5, a new, three-station (129 cm) dedicated receiver coil for peripheral MR angiography is tested and used for optimization of scanning protocols. The specific aim of the study was to improve quality of the distal, lower leg station.
- In chapter 6, the safety and efficacy of a new contrast material for peripheral MR angiography is tested in a prospective, multicenter trial, using X-ray angiography as the standard of reference.
- In chapter 7, it is investigated if contrast-enhanced MR angiography is a valid and accurate tool for detection and grading of peripheral arterial disease in patients with chronic critical ischemia and tissue loss.
- In chapter 8, the comparative accuracy of contrast-enhanced MR angiography and color duplex ultrasonography are investigated in a prospective study, using X-ray angiography as the standard of reference.
- In chapter 9, the effect of substituting contrast-enhanced MR angiography for color duplex ultrasonography on treatment planning in the diagnostic workup of patients with suspected or known peripheral arterial occlusive disease is investigated.
- In chapter 10, the findings of this thesis concerning the diagnosis of peripheral arterial disease are placed in perspective and current state-of-the-art MR angiography is discussed. An outlook is provided for future developments in the diagnosis of peripheral arterial disease.

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Peripheral arterial disease: meta-analysis of the diagnostic performance of MR angiography

Radiology 2000; 217: 105-114

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Abstract

Purpose

To summarize the overall diagnostic performance of magnetic resonance (MR) angiography in the evaluation of peripheral arteriosclerotic occlusive disease and to identify the most important sources of variation in diagnostic accuracy between studies.

Materials and methods

A search strategy in MEDLINE and citation tracking were used to identify relevant English-language articles published since 1991. Each article was critically appraised for examination, patient, and study design characteristics. The accuracy data from different studies were analyzed by constructing summary receiver operating characteristic curves; multiple linear regression was used to examine the variation between study results.

Results

Twenty-three studies were included. There was much heterogeneity in the study results, which could not be explained as differences in the threshold for a positive result. About half of the variation was due to the type of MR angiographic examination and the extent of image evaluation. The relative diagnostic odds ratio (DOR) for three-dimensional (3D) gadolinium-enhanced MR angiography compared with two-dimensional (2D) time-of-flight MR angiography was 7.46 (95% CI: 2.48, 22.20). The relative DOR for review of transverse source images or multiplanar reformations in addition to maximum intensity projections (MIPs) compared with the use of only MIPs for image evaluation was 4.53 (95% CI: 1.46, 13.87).

Conclusion

The diagnostic accuracy of 3D gadolinium-enhanced MR angiography is superior to that of 2D time-of-flight MR angiography. Also, the review of transverse source images or use of additional postprocessing techniques, such as multiplanar reformation, results in significantly better diagnostic performance.

Introduction

In patients with peripheral arteriosclerotic occlusive disease, the planning of revascularization procedures requires precise anatomic mapping of disease site and severity. Until now, conventional angiography has been the standard of reference for the investigation of peripheral vascular disease. However, the use of this invasive technique is not without risk, especially in patients with renal insufficiency or contrast material allergy. For this reason, noninvasive examinations such as duplex ultrasonography and magnetic resonance (MR) angiography are increasingly used in the diagnostic work-up in patients with peripheral arterial disease.

Over the years, multiple reports have been published that validate MR angiography against conventional angiography as the standard. As is often the case in the evaluation of diagnostic examinations, the various studies yielded a broad spectrum of values for sensitivity and specificity. Meta-analysis has become popular as a method for summarizing results from independent studies and for exploring the potential sources of variation between study results. The meta-analysis of diagnostic accuracy is a relatively new area of investigation, but several methods have been proposed. It was common practice in medical review articles to present means of the sensitivity and specificity estimates weighted by the sample size of the studies. However, such pooling relies on a single threshold or cutoff point for classifying an examination result as positive. Often, this assumption is not justified. Even when studies use the same explicit threshold, their implicit threshold may differ, especially if interpretation of the images requires judgment. The use of implicit thresholds is common in the interpretation of radiologic imaging techniques. Radiologists may agree to use the same words to describe imaging examination results but still differ in what they regard as the boundary between "abnormal" and "probably normal".(1) This problem may be less pertinent to MR angiography, because the degree of stenosis is measured semiquantitatively. However, in some situations, for example, in stenoses between 45% and 55%, the ultimate decision of whether the stenosis is smaller or larger than 50% may still require some judgment.

A change in the threshold for a positive examination result that increases the sensitivity leads to a decrease in the specificity and vice versa. This trade-off between sensitivity and specificity makes it imperative that they be considered jointly. In meta-analysis, this is possible with construction of a summary receiver operating characteristic (ROC) curve.(2,3) The present meta-analysis has the purposes of (a) summarizing the overall diagnostic performance of MR angiography in the detection or exclusion of stenoses of 50%–99% or occlusions in the peripheral vascular tree and (b) identifying the most important sources of variation in diagnostic accuracy between studies. Study results are summarized with summary ROC curves.

Materials and methods

Selection of studies on the diagnostic accuracy of MRA

A MEDLINE search was performed to retrieve all English-language articles published from January 1991 through June 1999 that report on the diagnostic accuracy of MR angiography in the evaluation of peripheral arterial disease. The search terms used were: peripheral vascular disease; peripheral arterial disease; arterial occlusive disease; intermittent claudication; arterial insufficiency; lower limb ischemia; lower extremity ischemia; peripheral; lower extremity combined with magnetic resonance angiography, MR angiography, or MRA. Additional articles were obtained with citation tracking of review articles and original articles. Only original studies were included. The other inclusion criteria were (a) conventional angiography was used as the standard of reference; (b) a hemodynamically significant lesion was defined as either a stenosis of 50%–99% or an occlusion; (c) the absolute numbers of true-positive (TP), false-negative (FN), true-negative (TN), and false-positive (FP) observations were available or derivable from the data presented.

Data Extraction

A standard form was used to extract relevant data from the included studies. Recorded were the examination, patient, and study design characteristics and the examination results.

examination characteristics

A distinction was made between studies in which the diagnostic accuracy of two-dimensional (2D) time-of-flight MR angiography was evaluated and those in which the diagnostic accuracy of three-dimensional (3D) gadolinium-enhanced MR angiography was evaluated. The year of publication was considered to be an indicator of advances in MR angiographic technology and learning experience associated with the generation and interpretation of MR angiographic images. Also documented were the extent of image evaluation, that is, only maximum intensity projection (MIP) versus MIP supplemented by review of transverse source images or additional postprocessing techniques, and whether cardiac synchronization was used for 2D time-of-flight MR angiography.

patient characteristics

For each study population, the mean age; percentage of male patients; percentage of patients with clinical indications such as claudication, critical ischemia, or other indications; and anatomic sites studied were recorded. Also documented was the percentage of aortoiliac segments included in the evaluated trajectory. With 2D time-of-flight MR angiography, the aortoiliac segments are more difficult to image, because the tortuous course of these vessels can cause (partial) in-plane saturation and diminish signal intensity. This loss of signal intensity sometimes mimics stenosis, which results in FP results.

study design characteristics

Characteristics of the study design considered important were blinding of the readers of MR angiographic images to the results of conventional angiography and vice versa (yes vs no), sample size, and a low potential for verification bias (yes vs no). Verification bias may exist if the decision to perform the standard examination depends on the results of the examination under investigation, that is, if verification with conventional angiography occurred more often in patients with positive MR angiographic results than in patients with negative MR angiographic results.(4)

examination results

In many articles, the numbers of TP, FN, TN, and FP observations were directly available. If not, the numbers were derived from the marginal totals and the reported sensitivity and specificity. Where possible, site-specific results were also listed. For studies in which more than one anatomic level was evaluated, the data were pooled into three anatomic areas: the aortoiliac arteries, the femoropopliteal arteries, and the below-knee arteries. If results were reported for more than one observer, the results from the first observer were used.

Data Analysis

summary ROC curves

For fitting a summary ROC curve, Littenberg and Moses (2) and Moses et al (3) proposed a data-analytic approach in which linear regression on the logit scale was used. This method includes three steps. In ROC analysis, sensitivity, or the TP rate (TPR), is plotted on the vertical axis against the corresponding FP rate (FPR, 1-specificity) on the horizontal axis. The first step is to transform the vertical and horizontal scales in a way that allows for fitting of a straight-line regression, because linear regression models can be fit within statistical packages that are widely available. For this purpose, the sensitivity and the FPR of each study are transformed to the logit scale. The logit of a probability p is the natural logarithm of the odds of p, that is, logit $p = \ln [p / (1-p)]$. Following this logit transformation, two new variables D and S are constructed, where D is the difference between and S is the sum of the logit transforms: D = logit(sensitivity)

- logit(1 - specificity), and S = logit(sensitivity) + logit(1 - specificity). The dependent variable D is equal to the natural logarithm of the diagnostic odds ratio (DOR): ln (DOR). The DOR is a measure of the discriminatory power of an examination and represents the odds of a positive examination result among diseased persons relative to the odds of a positive examination result among non-diseased persons (see the Appendix for a more detailed explanation). S is a measure of the threshold for classifying an examination result as positive; as the threshold becomes more lenient (less stringent), both sensitivity and FPR become larger, so S increases. The second step involves plotting the D values from each study on the vertical axis against the corresponding S values on the horizontal axis. In this plot, a linear regression line $D = A + BS$ is fitted. The y intercept A of the model is the estimated ln DOR when S is 0, and the regression coefficient B provides an estimate of the extent to which the ln DOR is dependent on the threshold.(5)

In the third step, the transformation is reversed to find the summary ROC curve. Once the slope and the intercept A of the transformed line are known, a summary ROC curve can be constructed by means of back transformation with the equation:

$$TPR = 1/\langle\{1 + exp[-A/(1 - B)]\} \times [(1 - FPR)/FPR]^{(1-B)/(1+B)}\rangle$$

Remaining sources of between-study variation.

The described method is useful for evaluating whether the variation between study results can be explained as differences in the threshold for a positive examination result. Furthermore, this data-analytic approach by using linear regression permits the identification of other important sources of variation in diagnostic accuracy between studies. The model $D = A + BS$ can easily be expanded to a multiple linear regression model by adding one or more covariates, such as examination (X_1), patient (X_2), and study design (X_3) characteristics: $D = A + BS + B_1X_1 + B_2X_2 + B_3X_3$. The regression coefficients (B_1, B_2, B_3) are indicators of the independent effects of the corresponding covariates (X_1, X_2, X_3) on the dependent variable, that is, ln DOR. The magnitude of the regression coefficient of a variable represents the difference in ln DOR between studies with different levels of that variable, with all other variables held constant. A large regression coefficient indicates that the corresponding covariate has a large influence on diagnostic accuracy. After anti-logarithmic transformation, the regression coefficient can be interpreted as a relative DOR.

The basic regression model $D = A + BS$ was first expanded by adding one covariate. Separate analyses were performed for nine potentially relevant study design characteristics, which were entered as dichotomous variables with values of 1 or 0: MR angiographic examination type (3D gadolinium enhanced versus 2D time of flight), use of cardiac synchronization (yes vs no), year of publication (after 1995 vs 1995 or before), postprocessing technique (MIP in combination with review of transverse source images or multiplanar reformation vs only MIP), mean age (≥65 years vs <65 years), percentage of male patients (≥75% vs <75%), the prevalence of stenosed segments (>25% vs ≤25%), the presence of aortoiliac segments in the evaluated trajectory (yes vs no), and sample size (>30 vs ≤30). Studies with missing values for one or more of the variables were excluded from the relevant analyses.

The relative importance of these nine study design characteristics was assessed according to the magnitude of the corresponding relative DOR. The examination, patient, and study design characteristics with the largest relative DORs were evaluated simultaneously in one multiple variable model to evaluate the independent effects on the ln DOR. The goodness of fit of the regression line $D = A + BS$ is evaluated by using R^2, which is the square of the correlation coefficient for the relationship between the observed values of D and the predicted values of D, and provides a quantitative measure of how predictive of the dependent variable the combination of independent variables in the model is. If all the observed values fall on the fitted regression line, R^2 is 1. If there is no linear relationship between the observed and predicted values, R^2 is 0. (5) The linear regression models were fitted by using unweighted least squares analysis, that is, by giving equal weight to each study. Weighted analysis –weighting by the inverse of the variance of each study– is inappropriate, because it gives more weight to studies that appear to show poorer accuracy.(6)

Results

Of the 51 articles retrieved, 21 articles reporting on 23 studies were included: 11 (7–17) in which only 2D time-of-flight MR angiography was evaluated, eight (18–25) in which only 3D gadolinium-enhanced MR angiography was evaluated, and two (26,27) in which both 2D time-of-flight and 3D gadolinium-enhanced MR angiography were evaluated. Several studies (28–32) were excluded from the meta-analysis but are included in the discussion in this article. We assumed that there was no data overlap between articles from the same group, with one exception: an article by Snidow et al (33) was excluded, because it was an update of a study published in 1995 and partly duplicated the same study population. The study from 1995 was preferred for inclusion, because it presented results from the evaluation of the total leg.

A list of studies that were excluded from meta-analysis and the reasons for exclusion is available on request. The most important reasons for exclusion were that conventional angiography was not used as the standard, another cutoff point was used, a measure of agreement between MR angiographic and conventional angiographic findings other than sensitivity and specificity was used, and/or the absolute numbers of TP, FN, TN, and FP observations could not be derived. Also excluded were articles in which 2D gadolinium-enhanced or phase-contrast MR angiography was evaluated, because the number of articles on these specific MR angiographic examinations was too small to enable a meta-analytic comparison with articles on 2D time-of-flight MR angiography or 3D gadolinium-enhanced MR angiography.

Table 1 gives an overview of the examination and patient characteristics in the included studies. In total, 344 patients were evaluated in 13 studies on 2D time-of-flight MR angiography and 253 patients were evaluated in 10 studies on 3D gadolinium-enhanced MR angiography.

Table 2 gives an overview of the anatomic sites studied and the absolute numbers of TP, FN, TN, and FP observations. For 2D time-of-flight MR angiography, the sensitivity ranged from 64% to 100% and the specificity varied between 68% and 96%; for 3D gadolinium-enhanced MR angiography, the sensitivity ranged from 92% to 100%, and the specificity ranged from 91% to 99%. In studies in which 2D time-of-flight MR angiography was evaluated, the prevalence of stenosed segments ranged from 13% to 73%, whereas in studies in which 3D gadolinium-enhanced MR angiography was evaluated, the range of prevalences was much smaller, varying from 13% to 36%.

Table 3 gives an overview of site-specific results. Classification of the studied anatomic sites into mutually exclusive anatomic levels, such as aortoiliac versus femoropopliteal versus below-knee arteries, was possible for only 13 of 23 studies.

First, separate summary ROC curves were constructed for studies reporting on 2D time-of-flight MR angiography and for studies reporting on 3D gadolinium-enhanced MR angiography. Figure 1a plots the observed values of the variables D and S. Each data point represents one of the included studies. Linear regression lines $D = A + BS$ were fitted to the observed data points, which resulted in an intercept A of 4.13 and a slope B of 0.41 for 2D time-of-flight MR angiography and an intercept A of 5.93 and a slope B of 20.37 for 3D gadolinium-enhanced MR angiography. Both slopes B were not significantly different from 0 ($P = .39$ and $P = .43$ for 2D time-of-flight MR angiography and 3D gadolinium-enhanced MR angiography, respectively), and R^2 was close to 0 ($R^2 = 0.07$ for 2D time-of-flight MR angiography and $R^2 = 0.08$ for 3D gadolinium-enhanced MR angiography).

For graphic purposes, the regression lines were converted back to summary ROC curves. Figure 1b shows the separate summary ROC curves for 2D time-of-flight MR angiography and 3D gadolinium-enhanced MR angiography. Especially for studies on 2D time-of-flight MR angiography, there are considerable discrepancies between the summary ROC curve and the observed data points. These findings indicate that differences in the threshold for a positive examination result explain only a small part of the variation between study results and point to the need to explore other sources of variation by adding other variables to the linear regression model.

Table 1 Examination and Patient Characteristics

Author	Year of Publication	MR Angiography	Postprocessing Technique	No. of Patients
Cortell et al (7)	1996	2D time of flight	MIP and transverse source images	31
Currie et al (8)	1995	2D time of flight	NI	40
Davis et al (9)	1997	2D time of flight	MIP and transverse source images	14
Eklöf et al (10)	1998	2D time of flight	MIP and transverse source images	24
Glickerman et al (11)	1996	2D time of flight with cardiac synchronization	MIP and transverse source images	23
Ho et al (12)	1997	2D time of flight with cardiac synchronization	MIP	28§
Ho et al (26)	1998	2D time of flight with cardiac synchronization	MIP	24
Hoch et al (13)	1996	2D time of flight	MIP	45
McDermott et al (14)	1995	2D time of flight	MIP	21‖
Mulligan et al (15)	1991	2D time of flight	MIP	12
Poon et al (27)	1997	2D time of flight with cardiac synchronization	MIP and transverse source images	15
Snidow et al (16)	1995	2D time of flight	MIP	42**
Yucel et al (17)	1993	2D time of flight	MIP and transverse source images	25
Hany et al (18)	1997	3D gadolinium-enhanced	MIP and multiplanar reformation	39
Hany et al (19)	1998	3D gadolinium-enhanced	MIP	20
Ho et al (26)	1998	3D gadolinium-enhanced	MIP	28
Ho et al (20)	1998	3D gadolinium-enhanced	MIP	43††
Meaney et al (21)	1999	3D gadolinium-enhanced	MIP	20
Poon et al (27)	1997	3D gadolinium-enhanced	MIP and coronal source images	15
Rofsky et al (22)	1997	3D gadolinium-enhanced	MIP	15
Snidow et al (23)	1996	3D gadolinium-enhanced	MIP and multiplanar reformation	30‡‡
Sueyoshi et al (24)	1999	3D gadolinium-enhanced	MIP	23
Yamashita et al (25)	1998	3D gadolinium-enhanced	MIP	20

* Data are percentages of patients. NI = no information. † Data are percentages of aortoiliac segments.
‡ C = consecutive series, N = nonconsecutive series, R = random series.
§ Of 31 patients examined with MR angiography, 29 patients underwent conventional angiography of the same region and 28 patients had comparable MR angiograms.
‖ Conventional angiography was used as the standard in 21 of 31 patients; in the other 10 patients (not

Mean Age (y)	Male (%)*	Female (%)*	clinical indications* Claudication (%)	Critical Ischemia (%)	Other (%)	Aortoiliac Segments Included in Trajectory (%)'	Series of Patients ‡
69	65	35	45	55	0	0	NI
64	74	26	97	3	0	100	C
74	43	57	71	29	0	0	NI
72 (median)	50	50	4	96	0	0	NI
67	100	0	65	30	4	19	C
64	58	42	100	0	0	50	C
63	75	25	100	0	0	47	C
65	76	24	18	82	0	0	NI
50–87#	48	52	13	84	3	0	C
62	100	0	NI	NI	NI	NI	N
58	80	20	NI	NI	NI	NI	NI
NI	95	5	69	25	6	18	N
68	60	40	84	16	0	23	NI
62	72	28	NI	NI	NI	100	R
62	55	45	NI	NI	NI	100	N
63	75	25	100	0	0	47	C
50	72	28	65	0	35	24	NI
65	60	40	100	0	0	23	C
58	80	20	NI	NI	NI	NI	NI
66	60	40	NI	NI	NI	NI	C
63	98	2	36	38	26	100	C
68	87	13	83	17	0	NI	NI
65	90	10	NI	NI	NI	NI	NI

included in the analysis), MR angiography was compared with intraoperative angiography.# Only the age range was given. Ten of 42 MR angiographic examinations were incomplete, but the evaluated segments were included in the analysis.†† Fifteen of the 43 subjects were healthy volunteers.‡‡ The final MR angiographic protocol was tested in 32 of 50 patients; 30 of these 32 patients underwent conventional angiography.**

Table 2 Anatomic sites studied and MR angiographic results

Author	Year of Publication	Anatomic Sites Studied
Cortell et al (7)	1996	Infrapopliteal through plantar arch
Currie et al (8)	1995	Infrarenal part of the aorta through common femoral artery
Davis et al (9)	1997	Popliteal artery through peroneal artery
Eklöf et al (10)	1998	Popliteal artery through peroneal artery
Glickerman et al (11)	1996	Distal abdominal aorta through peroneal artery
Ho et al (12)*	1997	Aorta through superficial femoral artery
Ho et al (26)†	1998	Iliac arteries through upper femoral
Hoch et al (13)	1996	Common femoral artery through dorsal pedal artery
McDermott et al (14)	1995	Anterior tibial arteries through plantar arch
McDermott et al (14)	1995	Tibial anterior arteries through plantar arch
Poon et al (27)‡	1997	Common iliac artery through femoral artery
Snidow et al (16)	1995	Iliac through peroneal artery
Yucel et al (17)	1993	Distal abdominal aorta through infrapopliteal
Hany et al (18)	1997	Suprarenal part of the aorta through internal iliac artery
Hany et al (19)§	1998	Abdominal aorta through common iliac artery
Ho et al (26)†	1998	Iliac through upper femoral
Ho et al (20)‖	1998	Aorta through peroneal artery
Meaney et al (21)	1999	Distal aorta through peroneal artery
Poon et al (27)‡	1997	Common iliac artery through femoral artery
Rofsky et al (22)	1997	Variable: aorta through midcalf and/or ankle
Snidow et al (23)	1996	Abdominal aorta through ankle
Sueyoshi et al (24)	1999	Common iliac artery through trifurcation
Yamashita et al (25)	1998	Variable: abdominal aorta through popliteal artery

* Comparison of four inflow techniques. The results in the table are based on interpretation of systolic synchronized fast field-echo images.

† Comparison of systolic synchronized 2D time-of-flight MR angiography versus 3D gadolinium-enhanced MR angiography without subtraction versus 3D gadolinium-enhanced MR angiography with subtraction. The results in the table are based on interpretation of 2D time-of-flight MR angiograms and subtracted 3D gadolinium-enhanced MRA

Table 4 shows the regression coefficients and relative DORs for nine potentially relevant study design characteristics. The three characteristics with the largest relative DORs were MR angiographic examination type, year of publication, and extent of image evaluation. These covariates and the variable S were entered simultaneously into one multivariate model. We kept the variable S in the model, because capturing its effect on D is essential to the data-analytic approach used in this meta-analysis. The definition of a large relative DOR (2) is arbitrary, but it was decided to add no more than three covariates to the basic model $D = A + BS$ because of the limited number of studies included in the meta-analysis (n = 23). The extent of image evaluation (postprocessing technique) was associated with a relative DOR exceeding 2, and although this relative DOR was not statisti-

No. of TP Observations	No. of FN Observations	No. of TN Observations	No. of FP Observations	Sensitivity (%)	Specificity (%)
172	3	208	10	98	95
48	10	15	7	83	68
100	6	45	3	94	94
59	14	31	2	81	94
210	31	605	24	87	96
20	8	122	19	71	87
27	10	187	18	73	91
172	12	155	13	93	92
124	15	70	7	89	91
124	15	70	7	89	91
12	0	70	8	100	90
80	7	215	76	92	74
65	6	119	16	92	88
62	2	163	7	97	96
54	2	118	11	96	91
34	3	191	14	92	93
90	7	243	4	93	98
108	25	443	44	81	91
12	0	77	1	100	99
37	1	108	4	97	96
27	0	117	6	100	95
67	2	351	3	97	99
48	2	75	15	96	83

‡ Comparison of 2D time-of-flight MR angiography with 3D gadolinium-enhanced MR angiography. The results for both tests were used.
§ Comparison of four postprocessing techniques. || The results in the table are based on the interpretation of MIP images. The results of two observers were averaged.

cally significant (95% CI: 0.70, 12.43), the a priori hypothesis that review of transverse source images or use of additional postprocessing techniques increases diagnostic performance was considered strong enough to include this covariate in the multivariate model.

The goodness of fit of the model, including the three covariates and *S*, was R^2 = 0.55. After multivariate adjustment for the effect of MR angiographic examination type and the extent of image evaluation, the regression coefficient for the publication year decreased from 2.41 to 0.88. Leaving out the variable "publication year" resulted in a more parsimonious model with a comparable goodness of fit of R^2 = 0.52. About half of the between-study variation was due to four factors: (a) the intercept *A*; (b) the variable *S*, which is a measure of the leniency of the threshold for a positive examination result; (c) the MR angiographic examination type; and (d) the extent of image evaluation. The adjusted relative DORs and corresponding 95% CIs for the MR angiographic examination type and the extent of image evaluation that result from the final model are presented in Table 4. The relative DOR for 3D gadolinium-enhanced MR angiography (compared with 2D time-of-flight MR angiography) was 7.46 (95% CI: 2.48, 22.20); the relative DOR for use of only MIP compared with MIP plus review of transverse source images or additional postprocessing techniques was 4.53 (95% CI: 1.46, 13.87).

Other factors, such as the inclusion of aortoiliac segments in the evaluated trajectory, the prevalence of stenosed segments, a high percentage of male patients, a high mean age of the study population, the use of cardiac synchronization, and a large sample size were associated with only small relative DORs (Table 4). The results indicate that these study design characteristics are poor predictors of diagnostic performance. Clinical indications could not be included in the regression model, because in seven of the 23 studies this information was lacking.

Figure 2a plots the regression lines (predicted D vs S) for four groups of studies chosen to be the available combinations of the two covariates *MR angiographic*

Table 3
Site-specific results

	Aortoiliac Segments						Femoropopliteal Segments	
Author	No. of TP Observations	No. of FN Observations	No. of TN Observations	No. of FP Observations	Sensitivity (%)	Specificity (%)	No. of TP Observations	No. of FN Observations
Cortell et al (7)	ND	ND	ND	ND	ND	ND	ND	ND
Currie et al (8)	48	10	15	7	83	68	ND	ND
Davis et al (9)	ND	ND	ND	ND	ND	ND	ND	ND
Glickerman et al (11)	16	2	140	3	89	98	62	7
McDermott et al (14)	ND	ND	ND	ND	ND	ND	ND	ND
Poon et al (27)	12	0	70	8	100	90	ND	ND
Snidow et al (16)	20	0	11	37	100	23	38	5
Yucel et al (17)	25	2	55	11	93	83	36	3
Hany et al (18)	62	2	163	7	97	96	ND	ND
Hany et al (19)	54	2	118	11	96	91	ND	ND
Ho et al (20)*	16.5	1.5	65	1*	92	98	41.5	2.5
Snidow et al (23)	27	0	117	6	100	95	ND	ND
Sueyoshi et al (24)†	23	0	69	2	100	97	12	0

ND = no data. * The results of two observers were averaged.
† Sensitivity and specificity were evaluated separately for the (a) iliac segments, (b) femoral segments,

examination type and *extent of image evaluation*. Group 1 comprises studies on 2D time-of-flight MR angiography with only MIP as a postprocessing technique (12–16,26), group 2 comprises studies on 2D time-of-flight MR angiography with MIP plus review of transverse source images or multiplanar reformations as a postprocessing technique (7,9 –11,17,27), group 3 comprises studies on 3D gadolinium-enhanced MR angiography with only MIP as a postprocessing technique (19–22,24–26), and group 4 comprises studies on 3D gadolinium-enhanced MR angiography with MIP plus review of transverse source images or multiplanar reformations as a postprocessing technique.(18,23,27)

The vertical distances between the regression lines provide measures of the difference in mean ln DOR between the study groups. The regression lines were converted back to the summary ROC curves shown in Figure 2b. The summary ROC curves for studies on 3D gadolinium-enhanced MR angiography with review of transverse source images or additional postprocessing techniques are most proximal to the upper left-hand corner, which indicates that these studies on average yielded the best accuracy results.

				Below-Knee Segments					
No. of TN Obser-vations	No. of FP Obser-vations	Sensi-tivity (%)	Speci-ficity (%)	No. of TP Obser-vations	No. of FN Obser-vations	No. of TN Obser-vations	No. of FP Obser-vations	Sensi-tivity (%)	Speci-ficity (%)
ND	ND	ND	ND	172	3	208	10	98	95
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	100	6	45	3	94	94
251	5	90	98	132	22	214	16	86	93
ND	ND	ND	ND	124	15	70	7	89	91
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
146	33	88	82	22	2	58	6	92	91
40	3	92	93	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
109	3	94	97	32	3	69	0	91	100
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
80	1	100	99	30	2	200	0	94	100

and (c) segments of the calf (popliteal, tibioperoneal, anterior tibial, peroneal, and posterior tibial segments).

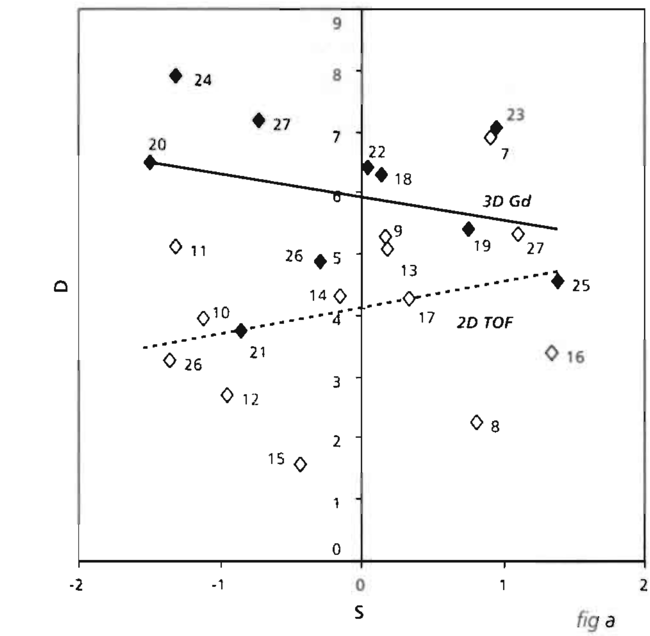

fig a

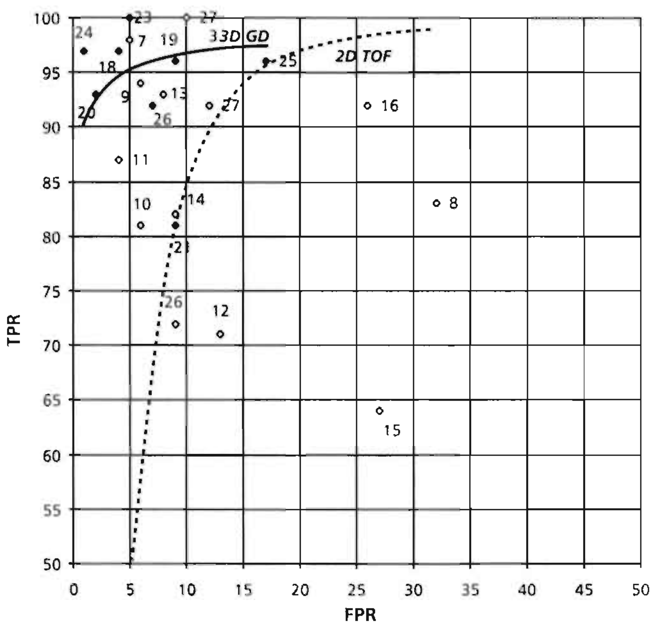

fig b

Figure 1 (a) Graph of observed values of D plotted against the observed values of S. The large scatter of the observed values of D around the regression lines for 2D time-of-flight (TOF) MR angiography (dotted line) and for 3D gadolinium-enhanced (Gd) MR angiography (solid line) indicates that the variable S, which is a measure of the leniency of the threshold for a positive examination result, does not explain the heterogeneity of the study results: $R^2 = 0.07$ for 2D time-of-flight MR angiography, and $R^2 = 0.08$ for 3D gadolinium-enhanced MR angiography. (b) Summary ROC curves for 2D time-of-flight (TOF) MR angiography (dotted line) versus 3D gadolinium-enhanced (Gd) MR angiography (solid line). The horizontal scale represents the FPR (1 - specificity), and the vertical scale represents the TPR (sensitivity). The large discrepancies between the summary ROC curves and the observed data point to the need to explore other sources of heterogeneity. (The scales of both axes are restricted to a range of 50 percentage points to magnify the differences.) In a and b, ◇ = observed data points from 2D time-of-flight MR angiography studies, ◆ = observed data points from 3D gadolinium-enhanced MR angiography studies. The numbers are the reference numbers for the individual studies.

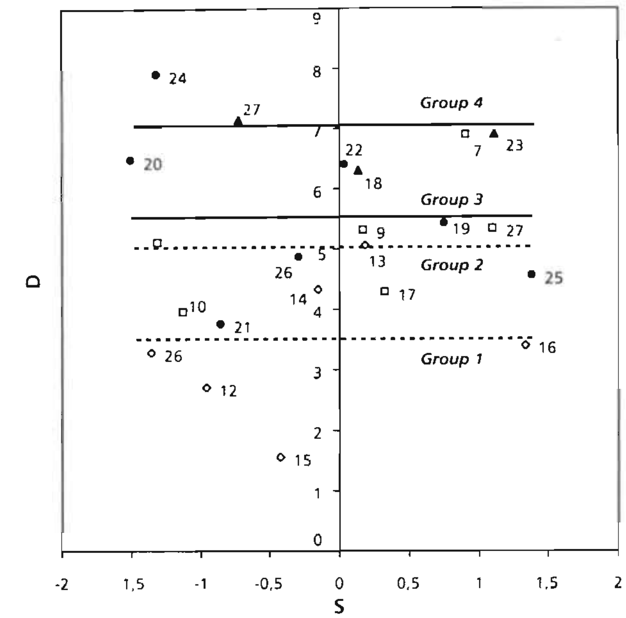

fig a

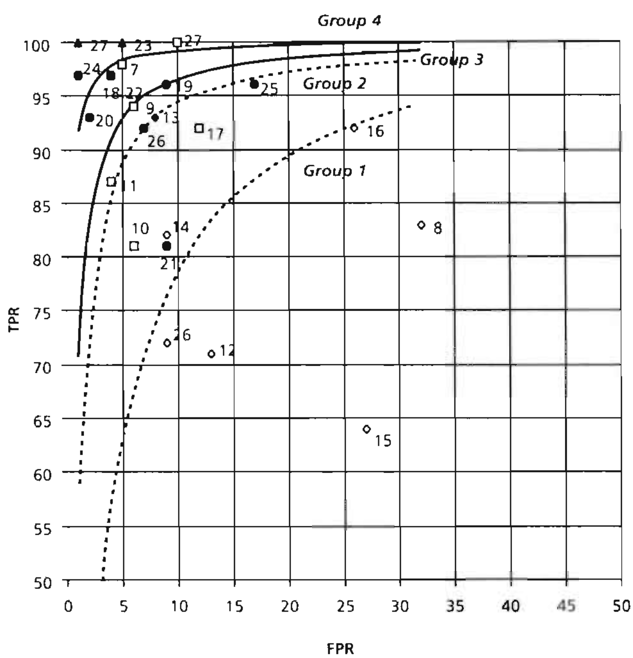

fig b

Figure 2 (a) Graph shows the regression lines (predicted D vs S; solid lines = regression lines for 2D time-of-flight MR angiography, dotted lines = regression lines for 3D gadolinium-enhanced angiography) for four groups of studies chosen to be the available combinations of the two covariates MR angiographic examination type and extent of image evaluation. The predicted D (ln [DOR]) at S = 0 increases with increasing group number: D for group 1 is 3.52, D for group 2 is 5.03 (3.52 + 1.51), D for group 3 is 5.53 (3.52 + 2.01), and D for group 4 is 7.04 (3.52 + 1.51 + 2.01). (b) Summary ROC curves (solid line = 3D gadolinium-enhanced MR angiography, dotted line = 2D time-of-flight MR angiography) for the four subgroups of studies. The best summary ROC curve is found for studies from group 4: High TPRs are reached at low FPRs. (The scale of both axes is restricted to a range of 50 percentage points to magnify the differences). In a and b, the numbers are the reference numbers of the individual studies. ◇ = observed data points from studies in group 1 (i.e. studies on 2D time-of-flight MR angiography and image evaluation with only MIP), □ = observed data points from studies in group 2 (i.e. studies on 2D time-of-flight MR angiography and image evaluation with MIP plus review of transverse source images or multiplanar reformations), ● = observed data points from studies in group 3 (i.e. studies on 3D gadolinium-enhanced MR angiography and image evaluation with only MIP), ▲ = observed data points from studies in group 4 (i.e. studies on 3D gadolinium-enhanced MR angiography and image evaluation with MIP plus review of transverse source images or multiplanar reformations).

Discussion

The findings of this meta-analysis partly answer the question why the various studies included in the review reported a wide range of sensitivities and specificities. Differences in the threshold for a positive examination result did not explain the between-study variation in diagnostic accuracy. Independent contributors to diagnostic accuracy were the MR angiographic examination type and the extent of image evaluation. The DOR was significantly higher for 3D gadolinium-enhanced MR angiography studies compared with 2D time-of-flight MR angiography studies. This finding indicates that 3D gadolinium-enhanced MR angiography is superior to 2D time-of-flight MR angiography for the detection and grading of peripheral arterial disease. Moreover, additional evaluation of transverse source images or multiplanar reformations provides diagnostic gain as compared with interpretation based only on MIPs, which is in conformity with the results reported by Hany et al.(19)

It was not possible to give an adequate summary of all study results with one common underlying summary ROC curve for each MR angiographic examination. On the basis of the results of linear regression analysis, separate summary ROC curves were constructed for four subgroups. Within these subgroups, the summary ROC curves provided a more adequate description of the study results.

It should be kept in mind that a summary ROC curve differs from traditional ROC analysis. A traditional ROC curve represents a single population and describes how the sensitivity and the TPR vary as the threshold for a positive examination result varies, all else being held constant. A summary ROC curve results from fitting a smooth line near data points that represent pairs of sensitivity and FPR from multiple studies, which shows differences with respect to factors affecting sensitivity and specificity estimates.

The presentation of the summary ROC curve should be restricted to the range of sensitivities and FPRs reported in the included studies. Therefore, the area under the curve, which is a global measure of diagnostic accuracy in traditional ROC analysis, is not available for the summary ROC curve. (3) An important advantage of a summary ROC curve as a summary of diagnostic accuracy across studies is that it provides a description of all pairs of sensitivity and FPR. In clinical decision-making and cost-effectiveness analyses, the summary ROC curve can provide data for modeling the effect of examination on patient treatment and clinical outcomes at different operating points.

It has been hypothesized that the accuracy of MR angiography may vary with the anatomic level, with a higher accuracy of 2D time-of-flight MR angiography at lower anatomic levels (below-knee > femoropopliteal > aortoiliac).(30) With 3D gadolinium-enhanced MR angiography, the situation may be the other way around. Distal vessels are more difficult to study, because the concentration of contrast material is reduced or the arrival of the bolus may be delayed, particularly if proximal vessels are diseased.(22) Also, veins filled with contrast material can cause diminished image interpretability because of overprojection.

Unfortunately, a meta-analysis of site-specific results was infeasible, because for 10 of 23 studies it was not possible to classify the studied anatomic sites into mutually exclusive anatomic levels, such as aortoiliac versus femoropopliteal versus below-knee arteries (table 3). Site-specific results for more than one anatomic level could be derived from three 2D time-of-flight MR angiography studies (11,16,17) and from two 3D gadolinium-enhanced MR angiography studies (20,24). These studies showed no clear trend in diagnostic accuracy with varying anatomic level (table 3).

In many respects, the method in the included studies was adequate. Most studies provided a detailed description of the MR angiographic technique and

Table 4
Regression coefficients (B) and relative DORs for nine potentially relevant study design characteristics

Study Design Characteristic	B	Relative DOR*	R^2
Basic model (intercept plus S) plus one covariate			
S[†]	0.055	1.06 (0.45, 2.23)	0.00
Year of publication (>1995 vs ≤1995)	2.41	11.13 (2.41, 51.42)	0.35
MR angiographic examination (3D gadolinium enhanced vs 2D time of flight)	1.88	6.55 (1.57, 27.39)	0.33
Cardiac synchronization (yes vs no)[‡]	0.04	1.04 (0.15, 7.32)	-
Postprocessing technique (MIP+ vs only MIP)[§]	1.09	2.97 (0.70, 12.43)	0.12
Age ≥ 65 y vs <65 y)	0.57	1.77 (0.35, 8.85)	0.04
Prevalence of stenosed segments (>25% vs ≤ 25%)	0.42	1.52 (0.33, 7.03)	0.02
Male sex (≥75% vs <75%)	0.17	1.19 (0.26, 5.42)	0.003
Study size (≤ 30 vs >30)	0.13	1.14 (0.22, 5.87)	0.001
Inclusion of aortoiliac segments in trajectory (yes vs no)	-0.23	0.79 (0.13, 4.95)	0.004
Final multivariate model[‖]			
S	0.015	1.02 (0.57, 1.82)	-
MR angiographic examination (3D gadolinium enhanced vs 2D time of flight)	2.01	7.46 (2.48, 22.20)	-
Postprocessing technique (MIP+ vs only MIP)[§]	1.51	4.53 (1.46, 13.87)	-

* The 95% CI is in parentheses.
[†] The displayed relative DOR is associated with an increase in S by one unit.
[‡] The variable "cardiac synchronization," which pertains only to 2D time-of-flight MR angiographic studies, was not considered separately but was considered only in combination with the variable "MR angiographic examination."
[§] MIP+ = MIP in combination with transverse source images or multiplanar reformation.
[‖] Intercept, A, is 3.52.

the method of conventional angiography. In almost all studies, the readers of MR angiographic and conventional angiographic images were blinded to the results of the other imaging technique. However, information on clinical indication was lacking in seven of 23 studies. Such information is important, because it describes the distribution of severity of disease in the patients selected for study and the sensitivity and specificity may be higher in more severely affected patients. Therefore, part of the unexplained variation between studies may be due to differences in patient selection.

Many studies also did not provide the information needed to exclude the potential for verification bias. This bias usually results in overestimation of sensitivity and underestimation of specificity. The best way to avoid verification bias is to perform a prospective study with consecutive patients in which all patients receive definite verification of disease status or to examine a random sample of consecutive patients.(4)

Nonconsecutive patients were included in three studies (15,16,19), and as many as 10 studies lacked information on this item (Table 1). Only two studies gave a detailed description of the number of eligible patients, the number of excluded patients, and the reasons for exclusion.(11,23) Therefore, it was not possible to study the effect of verification bias on diagnostic accuracy. The effects of verification bias are worse as the diagnostic examination under study becomes more accurate, because physicians begin to rely on the examination more as a way to screen for those who need the verification examination.

In this meta-analysis, we used conventional angiography as the standard of reference and focused on the ability of MR angiography to depict hemodynamically significant stenoses. However, for selection of the optimal surgical treatment and distal runoff vessels, the ability to detect patent vessels is also important. For this purpose, the use of conventional angiography as the standard of reference has been discussed. Several reports documented better visualization of patent vessel segments at MR angiography; therefore, conventional angiography was not considered suitable as a standard. These reports came from a single group, and the ability of 2D time-of-flight MR angiography to show patent runoff vessels not revealed at conventional angiography varied between 13% and 23%.(14,29,31,32)

Two studies (28,30) compared both MR angiography and conventional angiography with intraoperative angiography as the standard of reference. Both studies were excluded from this meta-analysis for two reasons. First, it was preferred to restrict the meta-analysis to studies with the same standard of reference. Inclusion of studies with another examination standard would add another potential source of heterogeneity to the study results. Second, intraoperative angiography can be used only in selected study populations, such as patients who are candidates for bypass surgery. Moreover, the excluded studies by Baum et al (28) and Huber et al (30) focused on the use of MR angiography to detect patent vessels rather than stenosed vessels.

A possible limitation of this meta-analysis is that multiple regression analysis was used with many (nine) covariates to analyze 23 studies. Several multiple regression models that included different covariates were explored, and eventually the most parsimonious model with a good fit to the observed data was selected. Multiple examinations could have resulted in overestimation of the statistical significance. On the other hand, due to the relatively small number of studies, the relative DORs for most study design characteristics had wide 95% CIs.

Another important problem in the performance of meta-analyses is the possibility of publication bias. Studies that eventually get published are likely to be a biased set, probably with overestimation of examination accuracy(6). In particular, small studies that show overly optimistic results may be published more easily than small studies with less favorable results. However, evaluation of the effect of sample size on the DOR showed that small studies (<30 patients) did not show a better diagnostic performance D than larger studies. It is concluded that one of the objectives of this meta-analysis, to summarize the results of all studies with one summary ROC curve, could not be achieved because of heterogeneity in the studies. Half of the variation between study results was explained by differences in the evaluated MR angiographic examination and differences in the extent of image evaluation. The other part of the variation remained unexplained, probably because of method problems that could not be captured by the evaluated examination, patient, and study design characteristics. The higher overall diagnostic accuracy of studies in which 3D gadolinium-enhanced MR angiography was evaluated compared with studies in which 2D time-of-flight MR angiography was evaluated supports the use of 3D gadolinium-enhanced MR angiography in the evaluation of peripheral vascular disease. Also, review of transverse source images or supplementation of MIP with additional postprocessing techniques results in better diagnostic performance.

Appendix

A standard way of describing the performance of a diagnostic examination is the two-by-two table (Table A1), which gives the numbers of patients with positive or negative examination results and the numbers of patients with or without disease. In Table A1, n_1 is the number of persons with disease, and n_2 is the number of persons without disease; a is the number of TP observations, b is the number of FN observations, c is the number of FP observations, and d is the number of TN observations.

$TPR = TP/n_1 = a/n_1.$
$1 - TPR = FN/n_1 = b/n_1.$
$FPR = FP/n_2 = c/n_2.$
$1 - FPR = TN/n_2 = d/n_2.$

$$
\begin{aligned}
D &= logit(TPR) - logit(FPR) \\
&= ln[TPR/(1 - TPR)] - ln[FPR/(1 - FPR)] \\
&= ln[(TP/n_1)/(FN/n_1)] - ln[(FP/n_2)/(TN/n_2)] \\
&= ln[(a/n_1)/(b/n_1)] - ln[(c/n_2)/(d/n_2)] \\
&= ln(a/b) - ln(c/d) \\
&= ln(ad/bc) \\
&= ln(odds\ ratio),
\end{aligned}
$$

and

$$S = logit(TPR) + logit(FPR).$$

If either the TPR is 1 or the FPR is 0, then the above equations are undefined. This is avoided by adding 0.5 to the absolute numbers of the TP, FN, TN, and FP observations.

Table A1 Performance of diagnostic examination: two-by-two table

Examination Result	Patients with Disease (n_1)	Patients without Disease (n_2)
Positive	TP (a)	FP (c)
Negative	FN (b)	TN (d)

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Three-dimensional contrast-enhanced moving-bed infusion-tracking (mobi-track) peripheral MR angiography with flexible choice of imaging parameters for each field of view

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Abstract

Purpose

To optimize moving-bed single-bolus three-dimensional gradient-recalled echo magnetic resonance angiography by imaging peripheral arteries with flexible choice of scan parameters for pelvic, upper and lower leg arteries.

Subjects and methods

Five healthy volunteers underwent peripheral MR angiography with fixed and, in a different session, with flexible scan parameters for each field-of-view. To compare image quality of both imaging methods signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were determined in predefined arterial segments of the lower limb as well as venous enhancement and subjective interpretability (both on 3-point scales). Additionally, six patients were imaged to test the feasibility of the new method in a clinical setting.

Results

The volunteer study yielded higher SNR and CNR for the flexible parameter technique in the iliac and lower leg stations (all P values $< .001$); less venous enhancement ($P = .002$) and better subjective interpretability for each station ($P < .001$) compared with imaging with fixed parameters. All patients were imaged succesfully with the flexible imaging technique except for a single vessel segment in one patient where a volume was misplanned.

Conclusions

Imaging peripheral arteries with the new technique in volunteers yielded better image quality and is feasible for patients.

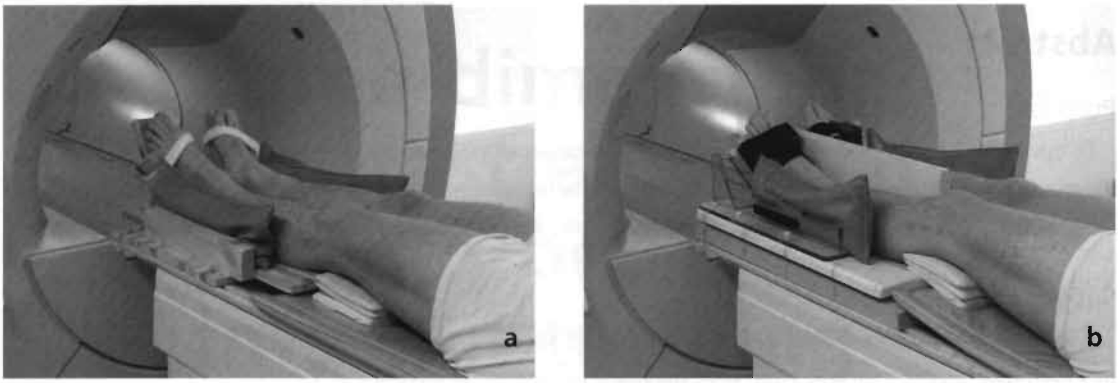


Figure 1a,b Custom-made wooden footboard used for subject positioning in the technique with fixed parameters for each field of view. Sandbags are placed lateral to the lower legs to prevent side motion. Feet are strapped to footholders, which allow them to be placed in slight exorotation for optimum subject comfort. b: The prototype quadrature phased array lower extremity reception coil with integrated footboard design. Note that positioning is essentially the same as in a except that additional reception elements are placed between the lower legs. Also note wider straps over feet, which allow for better fixation of feet and prevention of subtraction misregistration artifacts.

Introduction

Several approaches to contrast-enhanced magnetic resonance angiography (MRA) have recently been described to depict the peripheral arterial vasculature by sequentially imaging multiple stations in order to obtain a total peripheral arteriogram from the aorta to the arteries at the level of the ankles. Different authors have used different approaches to accomplish this (1–9). Imaging multiple stations necessitates interscan table movement and depending on how fast this can be accomplished either one or multiple injections of contrast medium.

One of the concepts employed is a "moving-bed" technique in which the table with the patient is dynamically translated to different positions while a single bolus of contrast material is injected and a number of overlapping stations are imaged by repeating a scanning sequence with the exact same parameters a number of times. A contrast-enhanced three-dimensional (3D) peripheral MR arteriogram with a total coverage of about 1200 mm can be obtained in this way in 4 minutes.(1) Some advantages of this particular approach to peripheral MRA are that a 3D dataset can be obtained, it is very fast, it is possible on conventional MR systems not equipped with state-of-the-art gradients, and arteries are imaged before venous and surrounding tissue enhancement occurs (first-pass imaging). Imaging all peripheral arteries during first-pass of contrast medium prevents significant enhancement of background tissue and reduction of vessel-to-background contrast. However, there are also disadvantages associated with this approach. First, because a single injection is used, the total imaging time for all stations is limited to the time in which the contrast material is mainly present in the arterial space (arterial window). A second important disadvantage is that because of this time constraint it is not feasible to define new scans for each separate station and, more important, to perform preparation phases prior to execution for those sequences within a single arterial window. These limitations have led to the use of identical overlapping 3D scanning volumes when imaging the peripheral arteries, ie, pelvic, upper and lower leg arteries are imaged with the exact same scanning parameters. A drawback of this approach is that arterial segments with varying diameters are imaged using the exact same imaging parameters. This potentially reduces image quality, for instance, because of insufficient spatial resolution to resolve arteries reliably in the lower leg.

To overcome the drawbacks described above, we have developed an improved way to perform single-injection moving-bed peripheral MRA. The principle of our technique is to prescribe individually tailored 3D scanning sequences for the pelvic, upper and lower leg arteries and to perform these scans twice, first without

Table 1
Scan parameters for Fixed and flexible peripheral MR angiographic techniques

	technique			
parameter	**fixed parameter**	**flexible parameter**		
Station	**All**	**Pelvic**	**Upper leg**	**Lower leg**
TR (msec)	**7.6**	**7.6**	**5.3**	**5.8**
TE (msec)	1.9	1.9	1.5	1.6
Flip angle (degrees)	30	25	30	30
Field of view (FOV; mm)	530 x 443	530 x 292	512 x 325	512 x 282
Matrix	512 x 131	512 x 149	512 x 197	512 x 282
Slice thickness (mm)	2.5	2.5	2.1	2.0
No. of slices	34	26–28	20–22	19-23
Voxel volume (mm^3)	6.8	5.1	3.5	2.0
Duration (sec)	34*	29–32	21–23	31–38
K-Space profile ordering	Linear	Linear	Centric	Centric
Reception coil used	Body	Body	Body	Lower leg

Imaging parameters tabulated for the five volunteers scanned with the fixed and all subjects scanned with the flexible parameter techniquesas described in the text. For the fixed parameter technique, all sequence parameters were identical for each volume scanned.
* Because three separate stations are acquired, the total scan time for the MRA technique with the fixed parameters for each station is actually 3 x 34 seconds, which is 102 seconds. Note that time for table movement (4 seconds) between two consecutive FOV is not included here.

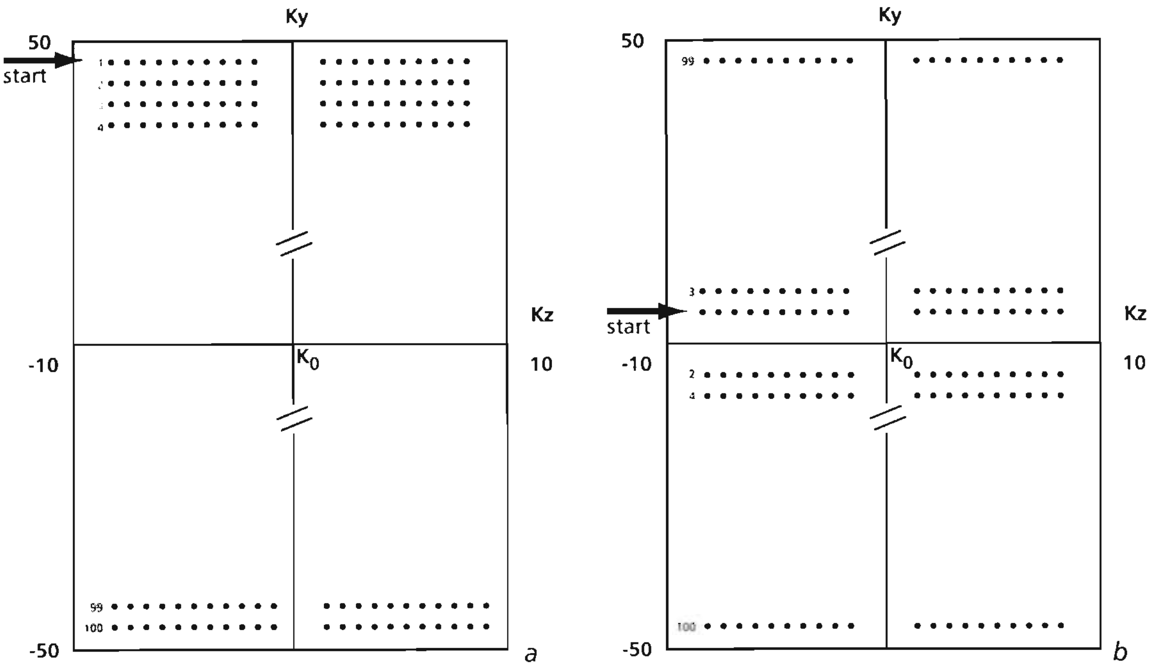


Figure 2 a,b K_y-K_z K-space grids schematically showing "linear" and "centric" K-space orderings. a: "Linear" K-space filling is illustrated for a 3D acquisition with 100 phase encoding steps (K_y) and 20 slices (K_z). Each dot represents a single echo and before moving on to the next line all points are sampled on the horizontal lines. Lines are measured in the order denoted by the number directly to the left of each line. b: Centric ("low-high", per Philips terminology) K-space ordering is illustrated for the same number of phase encoding steps and slices.

and then with contrast material. The crucial advantage over already described techniques is that it is possible to define different, nonrelated scans in which all parameters can be chosen freely. We hypothesize that this new approach can improve image quality and interpretability for multiple-station peripheral MRA. In this paper we report our findings using this novel approach to image peripheral arteries in five healthy volunteers and six patients.

Materials and methods

Imaging Technique

For all acquisitions we used a commercially available 1.5 T MR scanner (PowerTrak 6000, release 6.1; Philips Medical Systems, Best, The Netherlands) with a gradient strength of 21 mT/m and a slew rate of 105 mT/m/msec. Five healthy volunteers underwent two MRA examinations, one using the approach with fixed parameters for all stations and one using the new method with the possibility of flexibly programming sequence parameters for each station. All six patients underwent only the new MRA technique.

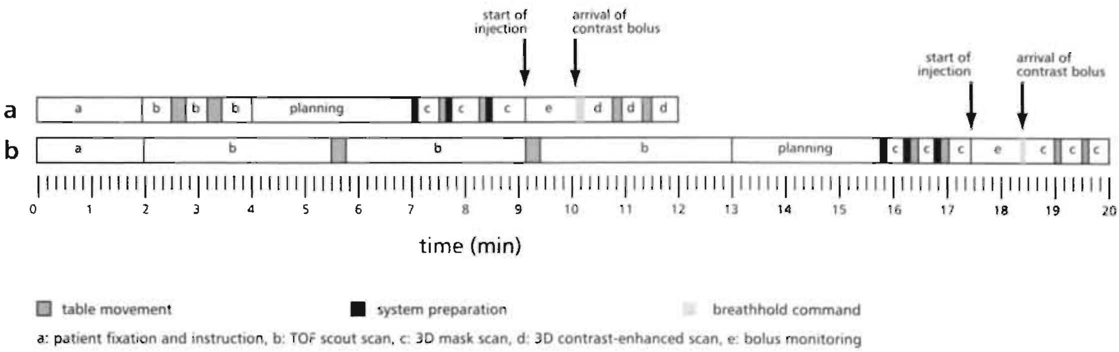
Imaging With Fixed Parameters

To obtain MR arteriograms of the entire peripheral arterial tree, a commercially available software package was used (MobiTrak, Philips Medical Systems, Best, The Netherlands), which allowed fast scanner-controlled interscan table movement. Imaging of subjects consisted of the following steps: a) subject positioning, b) obtaining time-of-flight (TOF) MRA "localizer" scans to plan the 3D mask and contrast-enhanced volumes, c) acquisition of moving-bed 3D mask volumes, and d) acquisition of moving-bed 3D volumes during injection of a single bolus of contrast material.

To obtain adequate results using this peripheral MRA approach, correct subject positioning is necessary. Subjects were placed in the supine position with their lower legs and feet immobilized in a specially designed footboard to prevent potential subtraction misregistration artifacts due to patient movement between acquisition of mask scans and contrast-enhanced scans. Legs were immobilized using Velcro straps (Philips Medical Systems) and sandbags. The feet were placed in slight exorotation to ensure optimal subject comfort (figure 1a). Before scanning was started, venous access was established by inserting an 18-gauge intravenous cannula (Venflon, Ohmeda, Helsingborg, Sweden) in an antecubital vein. Subjects were instructed to hold their arms on their abdomen to minimize wraparound artifacts in the phase-encoding (left-right) direction.

After patients were correctly positioned, TOF scans were obtained for pelvic and upper and lower leg arteries to identify their position coarsely. We used a gradient-recalled echo [GRE; turbo field echo (TFE)] pulse sequence with flip angle sweep and a 180° inversion prepulse for optimal background tissue suppression. Parameters for the TOF sequence were as follows: TR(msec)/TE(msec)15/6.9

Figure 3 Graphic display of the mean time required for the imaging procedure with fixed parameters. Patient fixation includes the time to establish venous acces by one of the investigators. The MR technician secures the subjects' legs in this period. b: mean time required for the flexible parameter imaging protocol. Time-of-flight scout scans take 11 vs. 2 minutes for the new method, which accounts for most of the time difference between the two different techniques. Note that acquisition of the 3D volumes (mask and contrast-enhanced data) is shorter with the flexible parameter technique.



msec, flip angle 50°, field of view (FOV) 512x282 mm, matrix 256x100, 20 axial slices with 2.5 mm slice thickness and 20 mm interslice gap, and an inferior concatenated saturation band. For signal transmission and reception in the three TOF scans, the standard quadrature body coil was used. Total scan time for each FOV with this sequence was 30 seconds. Sagittal maximum intensity projection (MIP) images were used to prescribe following 3D mask and contrast-enhanced volumes.

To increase vessel-to-background contrast, non-contrast-enhanced 3D mask scans were obtained for each FOV, which were later subtracted from identical scans obtained during injection of contrast material. The MobiTrak software package stores the preparation phases of the three separate mask scans and makes this information available when the same sequence is executed again (i.e., during the injection of contrast material). Thus, preparation phases can be skipped during the injection of contrast material and a delay of only 4 seconds is needed to start the acquisition of the next volume, during which table translation can be

Table 2 Clinical cindings for the six patients who underwent flexible parameter MR angiography

Patient no.	Age (yr)	Sex	Smoker	Fontaine	ABI	Duplex findings	Correlation with MRA
1	33	F	No	II	ND	Bilateral stenosis ≥ 50% in internal iliac arteries	Both stenoses ≥ 50% confirmed with MRA
2	59	F	Yes	II	ND	≥ 50% stenosis right iliac artery	≥ 50% stenosis confirmed on MRA
3	57	F	Yes	II	ND	<50% stenosis in aorta	<50% stenosis in aorta on MRA
4	61	M	Yes	IV	NR	Stenosis <50% left common femoral Occlusion left distal superficial femoral	<50% stenosis confirmed on MRA Occlusion confirmed on MRA
5	63	F	Yes	III	Right: 69/50 Left: 96/68	Bilateral common iliac artery stenosis ≥ 50%	≥ 50% stenosis in right common iliac artery with saccular aneurysm
6	70	M	Yes	II	ND	Abdominal aortic aneurysm	Aneurysm confirmed on MRA and later on CTA

Fontaine refers to the severity of intermittent claudication as defined by Fontaine (I = lesion but no symptoms, II = intermittent claudication, III = rest pain, IV = tissue loss) (17). CTA = CT angiography, ND = not done, NR = not reliable.

performed. Imaging parameters used with the 3D fixed parameter technique are tabulated in table 1; they were the same for pelvic and upper and lower leg volumes and were empirically chosen.

K-Space filling was set to "linear," meaning that central profiles were acquired at around half the total scan time per FOV (figure 2a). We used a 3D GRE [fast field echo (FFE)] pulse sequence with partial echo sampling. Volumes could be angulated with respect to a left-right axis through the patient and with respect to each other. Overlap between stations was set to 25 mm. Volumes were planned so that all arteries as seen on the sagittal MIP images obtained with the TOF scans were included. For imaging the pelvic arteries, subjects were instructed to hold their breath from the start of the acquisition as long as they were able to. For signal transmission and reception, the standard quadrature body coil was used.

After acquiring the three mask scans, injection of contrast medium was started [35 mL gadolinium-diethylene triamine pentaacetic acid (DTPA; Magnevist®, Schering, Berlin, Germany and Omniscan®, Nycomed Amersham, Oslo, Norway)] followed by injection of 20 mL of saline using an MR-compatible remote-controlled power injector (Medrad Spectris, Medrad, Indianola, PA). The injection rate was set to 0.3–0.4 mL/sec. To time arrival of contrast medium before starting the contrast-enhanced scans, a real-time bolus monitoring software package (BolusTrak, Philips Medical Systems) was used. The bolus monitoring software uses a coronal 2D thick-slice GRE acquisition in combination with real-time complex subtraction to visualize the arrival of contrast material in the vascular territory of interest. The coronal slab was placed over the abdominal aorta and pelvic arteries, and a new image was acquired every 1.0 seconds. This sequence was started together with injection of contrast medium. After the first image with clearly visible aorta and iliac arteries, the 2D sequence was aborted, and the 3D sequences were started with a delay time of approximately 4 seconds, which was used to give subjects a breath-hold command. All 3D scans were set to "delayed reconstruction,", permitting reconstruction of images at a later time point, thus not taking any time when acquiring the sequential 3D volumes. A graphic display of the examination is shown in figure 3a.

Imaging With Flexible Parameters

The MRA examination with use of flexible imaging parameters per station consisted essentially of the same steps as described above: a) subject positioning, b) obtaining TOF MRA "localizer" scans to plan the 3D mask and contrast-enhanced volumes, c) acquisition of moving-bed 3D mask volumes, and d) acquisition of moving-bed 3D volumes during injection of a single bolus of contrast material.

Since defining and executing different (nonrelated) scans on our system is not compatible with fast scanner-controlled table translation, the table was released from the mechanical positioning system. This allowed for fast manual table translation in between acquisition of 3D volumes. Patients were positioned, and venous access was achieved in the same way as described above except for the use of a prototype quadrature phased-array lower leg reception coil (Philips Medical Systems) integrated into a footboard with which a subject's lower legs and feet could comfortably be immobilized (figure 1b). After subjects were positioned, TOF localizer scans were acquired in the same way as for the fixed parameter technique, except that a larger number of slices was acquired at a higher matrix (75 slices; matrix 256x185). Total scan time was 209 seconds. After a station was scanned, the patient was manually repositioned to the next using a repositioning device as described by Ho et al (1), and the TOF scan was repeated. Overlap between separate stations was set to 35 mm. For signal transmission and reception of the three TOF scans, the standard quadrature body coil was used. After TOF scans were completed, sagittal MIP images were generated in order to determine the maximum anteroposterior distance (and thus the most economical volume) of the arterial tree in the vascular territory of interest. Acquisition of mask scans was identical to the method with fixed parameters. For imaging parameters used for the three 3D scans with flexible parameters per volume, see Table 1. K-Space filling was set to "linear" for the pelvic station and to "low-high" (centric) for the upper and lower leg stations (figure 2b). The preparation phase for each scan acquired before acquisition of the mask scans was stored and retained for availability when starting acquisition of the contrast-enhanced scans. After acquiring the three mask scans, injection of contrast medium was started also using 35 mL of gadolinium-DTPA and a 20 mL saline flush. The injection rate was set to 0.7 mL/sec in order to increase the concentration of contrast medium in the arteries.(10) We chose to do this because scan times were shorter and voxel volumes smaller for the flexible parameter scans. With the use of the real-time bolus detection software, the arrival of contrast medium was determined and after switching to the 3D sequences, the exact same scanning sequence as performed for the mask scans was started using the previously acquired preparation phases. The 3D contrast-enhanced volumes were then acquired with quick manual interscan table repositioning. All 3D scans were set to "delayed reconstruction" so that raw data could be reconstructed at a later time point. A graphic display of the time course of the examination is shown in figure 3b.

Subjects Studied

Before starting patient studies, five healthy volunteers underwent the fixed and, in a different session, the flexible parameter technique. Subsequently six patients [two men and four women; mean age 57 years (range 33–70 years), five (former) smokers, all with moderate to severe intermittent claudication] were scanned using only the flexible parameter imaging method. Consecutive patients referred for MRA by the vascular surgeons in our hospital were asked to participate in the study; they underwent contrast-enhanced peripheral MRA with the new flexible parameter method only. No additional X-ray angiography was carried out in these patients. Patients underwent flexible parameter MRA as the diagnostic modality of choice, and management was determined on the basis of the results of this exam. The study protocol was approved by the medical ethics committee in our hospital, and informed consent was obtained from each subject before inclusion in the study. Patient characteristics and findings from hemodynamic investigations are listed in table 2.

Image Analysis

After acquisition, magnitude images of corresponding 3D volumes were subtracted on a section by section basis. For image analysis purposes the arterial tree was divided into the following segments: infrarenal aorta and left- and right-sided common iliac, external iliac, common femoral, superficial femoral (three segments per side), popliteal (above and below knee), anterior tibial (three segments), posterior tibial (two segments), and peroneal (two segments) arteries.

For each vessel segment, signal-to-noise ratios (SNRs) and contrast-to-noise ratios (CNRs) were determined, and a subjective interpretability score (SIS) was given based on review of separate partitions of the contrast-enhanced 3D volumes and coronal and sagittal whole-volume MIP images. In addition, targeted subvolume rotational MIP images around a craniocaudal axis in increments of 30° were created so that the arterial segments of interest were optimally displayed. Vessel segments on the edges of the FOV were evaluated in the imaging volume where they exhibited best SNR and CNR, least venous enhancement, and best subjective interpretability, as judged by the observer. SNR was determined by drawing a region of interest (ROI) within the vessel segment and dividing the mean signal value by the standard deviation of noise measured outside of the subject. CNR was determined by subtracting the signal intensity as measured within a ROI next to the vessel segment from intravascular values and dividing by the standard deviation of noise measured outside the subject. (11) SIS ranged from 0 = good interpretability to 1 = suboptimal interpretability to 2 = poor interpretability. In addition, a venous enhancement score (VES) was given ranging

Table 3 Mean differences in SNR, CNR, SIS, and VES with P values between fixed and flexible parameter peripheral MR angiographic techniques

	technique			
	fixed parameter	flexible parameter	difference (95% CI)	P value
Mean SNR				
Overall	65.9	118	52.1 (37.0–67.7)	<.001
Pelvic	32.3	47.3	15.0 (10.6–19.5)	<.001
Upper leg	58.9	53.8	-5.1 (21.23–11.5)	.111
Lower leg	83.6	185	101 (74.3–128)	<.001
Mean CNR				
Overall	54.1	108	53.9 (39.1–67.7)	<.001
Pelvic	21.5	36.4	14.9 (10.6–19.1)	<.001
Upper leg	51.3	47.3	-4.0 (22.0–10.1)	.184
Lower leg	69.0	172	103 (78.5–127)	<.001
Mean SIS	0.19	0.00	0.19 (0.13–0.25)	<.001
Mean VES	0.16	0.04	0.12 (0.05–0.20)	.002

SNR = signal-to-noise ratio, CNR = contrast-to-noise ratio, SIS = subjective interpretability score, VES = venous enhancement score.

from 0 = no veins visible to 1 = some veins visible to 2 = lots of visible veins.

Images obtained with both scanning methods were evaluated in two separate sessions, 4 weeks apart, on an off-line workstation (Sun UltraSparc 30, Sun Microsystems, Mountain View, CA) using commercially available image processing software (EasyVision release 4.0, Philips Medical Systems).

Statistical Analysis

SNRs, CNRs, SIS, and VES were compared for both techniques in volunteers with the paired sample t-test using a commercially available software package (SPSS 7.5, Chicago, IL). Mean differences between the fixed and flexible parameter techniques were considered statistically significant when *P* values were <0.05. Comparisons were made on a vessel segment basis. After overall comparison for all vessel segments together, comparisons between both methodswere made for the vessel segments in each separate station.

Results

All subjects tolerated the MRA examinations without side effects.

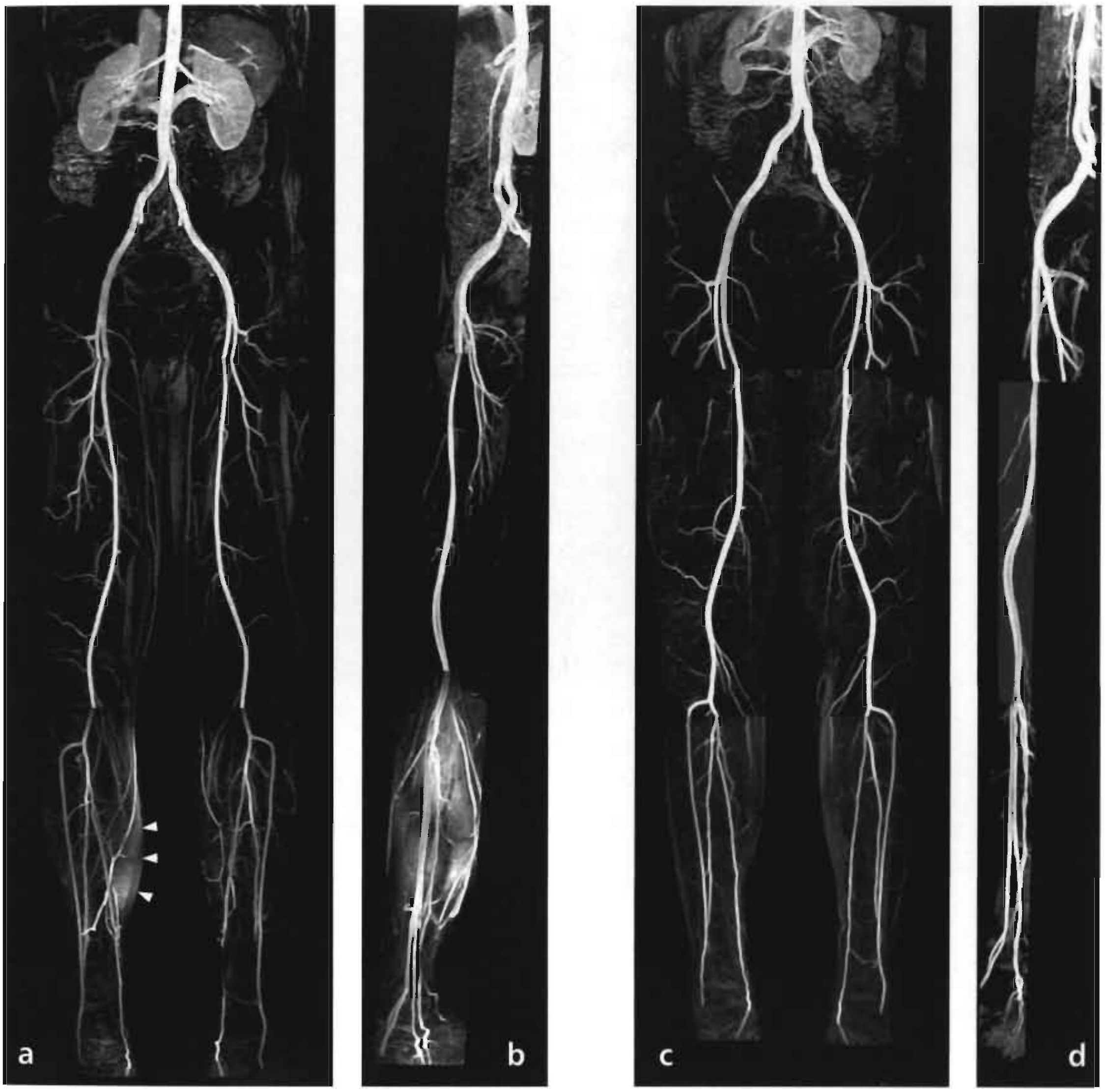


Figure 4 a,b,c,d Coronal (a, c) and sagittal (b, d) maximum intensity projection images of 3D moving-bed infusion-tracking peripheral MR angiograms in a 26-year-old healthy male volunteer. The left dataset (a, b) was obtained with the fixed parameter technique, and the right dataset (c, d) was obtained using the flexible parameter technique. In the coronal image obtained with the fixed parameter technique, a slight subtraction misregistration artifact can be seen (a). Note the absence of venous enhancement in the depiction of upper and lower legs and better depiction of the vessel segments on the edge between upper and lower leg volumes with use of the flexible parameter technique. On sagittal images (b, d), note that volumes for the pelvis and upper and lower legs (containing a different number of partitions) are of different thicknesses.

Volunteers

Volunteer imaging with the fixed parameter method could be completed in about 12 minutes. Reconstruction, postprocessing (including ROI measurements), and evaluation of the acquired datasets took on average about 1 hour and 15 minutes. No vessel segments were excluded from analysis. In one volunteer a slight subtraction misregistration artifact was encountered. However, this artifact was not severe enough to render images uninterpretable (figure 4). Results for SNR, CNR, VES, and SIS measurements are tabulated in table 3.

Imaging with the flexible parameter technique took on average 20 minutes. No subtraction misregistration artifacts were encountered with the use of the flexible parameter scan method. Results of SNR, CNR, VES, and SIS values are also tabulated in table 3. For all vessel segments in the three stations taken together, SNR and CNR values obtained with the flexible imaging method were significantly higher ($P < .001$) compared with the fixed parameter technique. However, when comparing on a station basis, the new technique led to significantly higher SNR and CNR values for the pelvic (both $P < .001$) and lower leg stations (both $P < .001$); for the upper leg, SNR and CNR values were not significantly different ($P = .111$ and $P = .184$). A representative example of a volunteer scanned with both MR angiographic techniques is shown in figure 4.

For both the fixed and flexible scanning methods, no vessel segments at the craniocaudal edges of the FOV were uninterpretable because of lack of overlap between consecutive FOV or distortion of the magnetic field at the edges of the FOV. A finding that we consistently encountered for the method with the flexible scan parameters was that the transition between the FOVs in which upper and lower legs were imaged was more easily evaluable due to the higher SNR in the lower leg images (see also figure 4).

Patients

All patients were imaged succesfully with the flexible parameter imaging technique except for one patient for whom the iliac 3D mask and contrast-enhanced volume were misplanned. A representative patient exam is shown in figure 5. All images were considered of excellent quality by the radiologist and referring vascular surgeon and were used for further treatment planning. In patients, no subtraction misregistration artifacts were encountered and venous enhancement never degraded image interpretability. In patient 6, with tortuous iliac arteries, which were not visible on the sagittal TOF MIP image due to in-plane saturation in the original 2D slice, the iliac volume was misplanned so that a transversely and posteriorly deflected part of the left external iliac artery was excluded from the mask and contrast-enhanced volumes (figure 6). This patient later underwent abdominal CT scanning, which was in concordance with the results found with MRA. In another patient, the distal anastomosis of an arterial bypass graft was considered to be of poor interpretability due to susceptibility artifact because of a ferromagnetic clip used to ligate a side branch of the bypass graft. Correlations between findings at MRA and hemodynamic investigations are also tabulated in table 2.

Figure 5 a,b Coronal (a) and sagittal (b) maximum intensity projection images of 3D moving-bed infusion-tracking peripheral MR angiogram obtained in a 59-year-old female patient with complaints of intermittent claudication. The dataset was obtained using the flexible parameter technique and shows a severe stenosis in the left internal iliac artery, a mild stenosis in the right external iliac artery, and a fusiform aneurysm originating from the right common iliac artery. These findings were confirmed at stent placement 2 months later.

Discussion

In this study we have shown that it is feasible to image peripheral arteries using a single-injection, multiple FOV imaging protocol with flexible choice of imaging parameters for pelvic and upper and lower leg arteries with improvements in SNR, CNR, and subjective interpretability and decrease in venous enhancement. This technical improvement can be of further benefit to an area in which MRA has already proved to be relatively successful. The development of the moving-bed concept has brought clinical acceptance of peripheral MRA as the preferred imaging modality for diagnostic evaluation of peripheral arterial obstructive disease near.(12) Busch et al (13) even found that moving table MRA can provide images of equal quality in 75%–79% of patients and of better quality in 16%–18% when compared with intraarterial digital subtraction angiography. Artifacts, as encountered with more flow-dependent MRA techniques, can be avoided, and imaging times have decreased dramatically.

Our new approach as described in this paper combines the advantages of tailoring imaging volumes to the specific anatomical and physiological conditions in the arterial territory of interest with the advantages of using a single injection to image the entire peripheral vascular tree. Although separate preparation phases for each station could be obtained in the fixed parameter method, it was not possible to define different scan parameters for these stations.

Due to limitations on the maximum obtainable FOV (usually <50 cm in current commercially available MR scanners) and lack of ultrafast gradient systems, the earliest of the multiple-station methods were dependent on a separate injection of contrast material for each FOV.(4,5) Multiple injections were needed because the arteries in the patient outside the FOV had to be repositioned to the isocenter of the magnet for imaging and because multiple high-resolution 3D datasets could not be acquired within a single "arterial window."

The advantage of this method over more recently described single-injection protocols is freedom of choice of imaging parameters for each FOV. However, multiple injections of extracellular paramagnetic contrast medium can potentially degrade image quality because of the presence of contrast material in the vascular space and the surrounding tissues when imaging a second or third FOV; thus they can reduce vessel-to-background contrast and enhance the venous circulation. Furthermore, when using peripheral MRA imaging protocols based on multiple injections, one should also be aware that the T1 of blood changes between subsequent acquisitions and that optimum values for TR, TE, and flip angle may change.(14) An improvement of the flexible parameter method in general is that because of the shorter acquisition times, contrast medium can be injected at almost double the speed of what we were used to (0.7 mL/sec vs. 0.3–0.4 mL/sec). This increase in injection speed leads to a higher concentration of gadolinium in the arteries during scanning and thus to more signal returned from

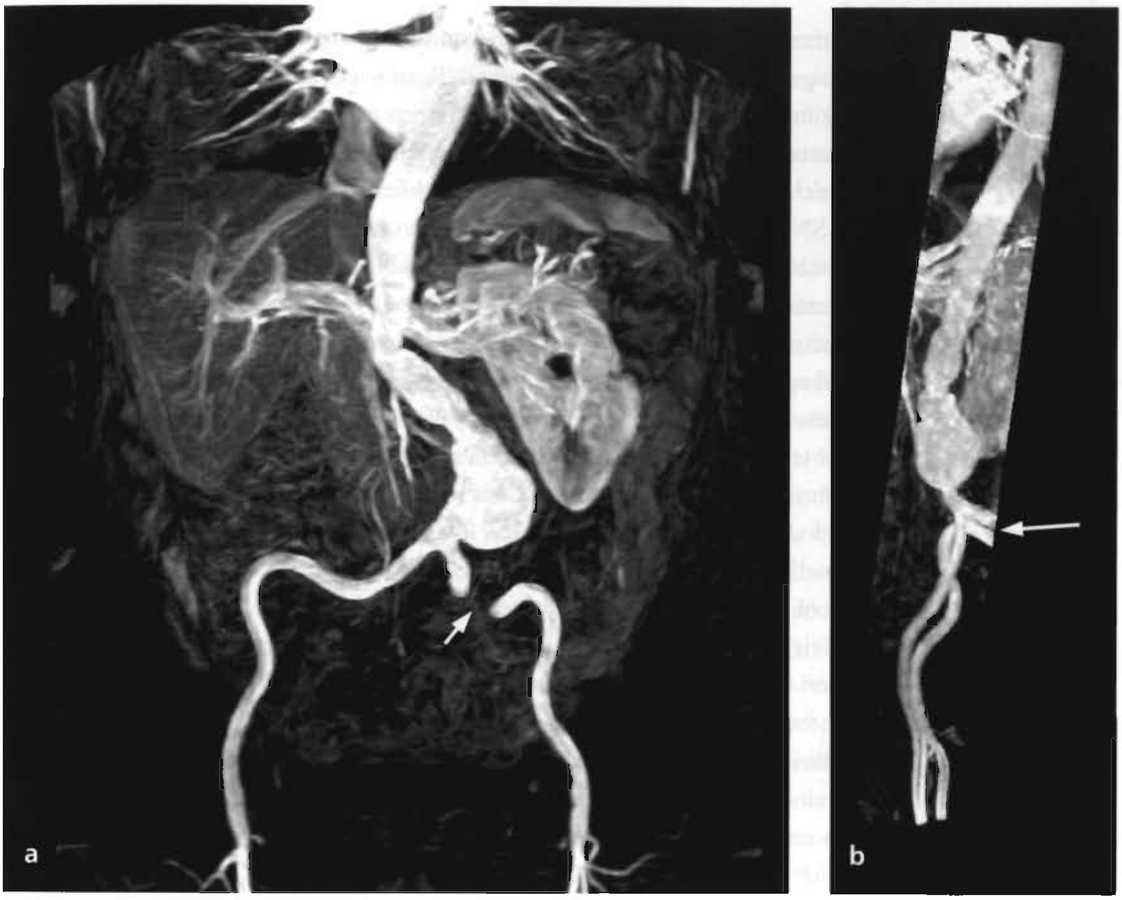


Figure 6 a,b Coronal (a) and sagittal (b) maximum intensity projection images of the pelvic station of a three-station MoBI-Track acquisition with the flexible parameter method. On the coronal image, an occlusion in the left common iliac artery cannot be ruled out (short arrow). However, review of the sagittal image shows exclusion of part of the left common iliac artery from the imaging volume (long arrow). This part of the iliac arteries suffered from in-plane saturation in the time-of-flight scan and was not depicted on the sagittal TOF MIP, which led to erroneous planning of the subsequent 3D acquisition.

the volume.(15) This increased signal in turn leads to the possibility of choosing a smaller voxel size, as we have done, without significant loss of SNR and CNR. An alternative option is to decrease the amount of gadolinium injected (and the cost of the exam) while using the same resolution as in the fixed parameter technique.

For the pelvic station, the possibility of choosing a shorter acquisition time means that a better compromise can be made between a subject's ability to sustain a breath-hold and the time required to obtain a high-resolution 3D dataset. In our study we have chosen to decrease voxel volume in the volunteers using approximately the same scan time as before (29-32 vs 34 seconds), a choice that also proved feasible in patients. A potential advantage may be that with the use of smaller voxel volumes, more reliable differentiation between high-grade stenoses and occlusions becomes possible.

For the femoral arteries, we have shown that although our new approach does not yield significantly different SNR and CNR, subjective image interpretability is better for the technique with flexible parameters and venous enhancement is less compared with the fixed parameter technique in the volunteers. Thus with the new technique, resolution was increased, while at the same time preserving sufficient SNR and CNR through faster injection of contrast material. Complementary to this, an interesting avenue of exploration will be to test whether the use of a dedicated extremity coil can increase SNR and CNR to values high enough to obviate mask scans.

Until now, achieving diagnostic MRA image quality, especially of the lower leg arteries, could be problematic for single-injection, multiple-station approaches. Lower leg arteries are different from more proximal arteries in that they are much smaller in diameter. In the presence of severe atherosclerotic occlusive disease and a fixed, relatively large voxel size, less accurate depiction of stenoses and obstructions and enhancement of background tissue can thus occur.

One of the improvements instituted in our new technique is the use of a dedicated rigid quadrature phased-array lower extremity reception coil. The design of this coil integrates gain in SNR with a design that allows for comfortable fixation of the lower legs. In combination with our new imaging technique, the use of this coil allowed us to increase spatial resolution (decrease in voxel volume) with a simultaneous gain in SNR and CNR. The gain in SNR and CNR for the lower legs is especially notable at the cranial edge of the lower leg station, an example of which is shown in figure 4. We think that the increase in SNR and CNR can be explained not only by the use of the dedicated coil but also by the use of smaller voxels, which decrease partial volume effects. Theoretically this may improve diagnostic confidence because in vessels with a smaller diameter the use of higher resolution allows more reliable assessment of atherosclerotic arterial obstructive disease.

Another improvement in our new technique for imaging the lower legs involves shorter acquisition times, first due to omission of as many slices as possible not containing arteries, and second by decreasing the rectangular FOV. This allows for scanning at higher resolutions in about the same scan time (31-38 vs 34 sec). Another advantage of our new technique is the reduction in the amount of data acquired (on average, 33% less), which facilitates faster review of the material and easier storage. An element that improves image quality, common to both the upper and the lower leg arteries, is acquiring the contrast-determining central K-space profiles from the start of the acquisition ("centric" acquisition).(16) Using such a K-space filling order diminishes sensitivity of a sequence for venous enhancement because by the time veins opacify, information on image resolution is acquired instead of contrast information. In case of venous depiction, especially when relatively large voxel volumes are used, differentiation between arteries and veins in the lower legs can be very cumbersome. As we have shown in this paper, use of centric K-space filling together with a reduction in scan time per station leads to diminished venous enhancement scores. We believe that this new technique can be of benefit in patients with inflammation due for instance to an infected arteriosclerotic ulcer of the lower leg because it is our experience that in these patients venous return occurs much earlier than in other patients.

Overall, image quality has improved using the new imaging technique. However, the new technique also has some drawbacks. To prescribe the imaging volumes adequately for the flexible parameter 3D acquisitions, a relatively long localizer sequence has to be used, thus prolonging examination time. In our new approach, this sequence took 209 vs 30 seconds in the old approach. A potential drawback of using a relatively thin 3D volume is that arteries of interest may be excluded from the imaged volume. In patients, one exam was technically inadequate for the iliac arteries because the prescribed volume was too thin and subsequently did not contain a transversely and posteriorly deflected part of the iliac arteries. To avoid this artifact in future patients, we now also review original TOF slices in addition to orthogonal MIPs when planning the 3D scans. Another potential drawback of the technique is that it is subtraction based. Although we did not see disturbing subtraction misregistration artifacts in the relatively small sample of volunteers and patients we report on in this paper, this can be a source of suboptimal image interpretability. However, when patient fixation and instruction are carefully carried out, especially for the lower legs, as shown in Fig. 1, it is our experience subtraction misregistration artifacts can be prevented in almost all subjects.

To limit the possibility of artifacts due to this problem, it has to be investigated whether the use of faster scanning protocols, which allow faster injection speeds without significant venous enhancement, are suitable to evaluate arteries in the extremities without subtracting unenhanced mask scans. It should also always be common practice when reviewing any MRA exam to review the contrast-enhanced original partitions, in order to avoid erroneous conclusions due, for instance, to subtraction misregistration artifacts, based on the sole review of subtracted datasets or MIP images.

As far as overlap between the different stations is concerned, we had no interpretation problems. Overlapping vessel segments were adequately depicted on both FOVs for both scanning methods. However, care should be taken to avoid overlap that is too small. We recommend an overlap of at least 25 mm between adjacent FOVs. With regard to the selected imaging parameters per station in the new technique, we must comment that they were chosen on empirical grounds. In future studies it must be shown whether other choices of imaging parameters are able to improve image quality further.

Conclusions

We have presented an MRA technique with which imaging parameters can be chosen flexibly and differently for each FOV to image peripheral arteries in a multiple-station, single-bolus injection scheme. For volunteers, this new technique yields significantly higher SNR, CNR, and better subjective image interpretability and significantly less venous enhancement. For patients we have shown that it is feasible to obtain a peripheral MR angiogram with flexible choice of parameters for each station when imaging volumes are carefully planned.

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The need for background suppression in contrast-enhanced peripheral magnetic resonance angiography

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Abstract

Purpose

To determine if background suppression is beneficial for peripheral magnetic resonance angiography (pMRA), non-subtracted, subtracted and fat-saturated contrast-enhanced peripheral magnetic resonance angiography were compared in 10 patients with peripheral arterial disease.

Subjects and methods

Signal- and contrast-to-noise ratios as well as venous enhancement and subjective interpretability were determined in a station-by-station fashion for each technique. In three patients X-ray angiography was available as standard of reference. Two observers judged subjective image quality and venous enhancement (three point scales).

Results

Signal- and contrast-to-noise ratios were significantly higher for fat-saturated peripheral MR angiography versus the other two techniques (P = .005). Subjective interpretability was best for subtracted datasets in the lower leg station. In the pelvic station fat-saturated datasets were considered to have lower interpretability than subtracted datasets. Venous enhancement occurred significantly more often in the lower leg station with the fat-saturated technique (observer 1: P = .007; observer 2: P = .012).

Conclusions

The value of subtraction depends on the hardware one has available and is a usefull tool if dedicated surface coils are used. Background suppression by means of magnitude subtraction leads to the best lower leg image interpretability. Care must be taken to avoid venous enhancement in the lower leg station when using fat-saturation.

Introduction

Several magnetic resonance angiography (MR angiography) methods have been described to image peripheral arteries. Time-of-flight (TOF) techniques, phase-contrast (PC) techniques and contrast-enhanced (CE) techniques have all been investigated for detection and grading of peripheral arterial disease, with varying degrees of success and each with its own advantages and drawbacks. The most promising technique to image peripheral arteries to date has been CE MR angiography with excellent results reported by a number of groups. Reported sensitivities and specificities for detection and grading of stenoses > 50% range from 90-100% with X-ray angiography as the gold standard.(1-5) CE MR angiography of the peripheral arteries seems able to avoid classic artifacts inherent to non-CE MR angiographic techniques while at same time being a faster examination method. Because of the necessity to image multiple fields of view and the availability of different hardware (scanners, coils), the reported results were obtained by using a host of different scanning and contrast injection protocols. In order to present the MR angiographic data in a readily accesible format usually the maximum intensity projection algorithm is used, which necessitates adequate background suppression. If background tissue is not adequately suppressed, small vessel branches and subtle stenoses might be obscured, especially when dedicated surface coils are used which enhance signal from fat overlying arteries. For peripheral MR angiography the most commonly used method to suppress background tissue is subtraction. With this technique unenhanced mask scans are subtracted from contrast-enhanced scans. Another possible way to suppress background tissue is to selectively eliminate tissues with the shortest T1 that are not of interest. For MR angiography which utelizes strongly T1 weighted sequences this would mean eliminating signal from fat by using spectral presaturation or selective inversion prepulses which effectively null the signal from fatty tissue.(6)

With the advent of ultrafast scanners and fast gradient switching background suppression can also be achieved by using a very short TR, thereby effectively saturating background tissue including signal from fat. Because it is not clear if background suppression is needed when imaging the peripheral vasculature we compared three techniques.

The purpose of this study was to compare non-subtracted, subtracted and fat-saturated contrast enhanced peripheral MR angiography and to evaluate objective and subjective image quality. In a subsample of patients we also compared the ability of both techniques to adequately detect and grade peripheral arterial disease in comparison to intra arterial digital subtraction angiography (IA-DSA), which was used as the standard of reference.

Subjects and Methods

Subjects studied

Consecutive patients with complaints of moderate to severe intermittent claudication undergoing duplex ultrasound evaluation at the surgical outpatient clinic were invited to participate in the study. Of a total of 21 patients screened, 10 participated (7 males, 3 females, average age 63 years). The medical ethics committee in our hospital approved all protocols and all patients were required to give consent before participating in the study. All patients underwent two MR angiographic examinations. First multistation CE peripheral MR angiography with and without subtraction of unenhanced partitions was done and in a separate, second session (within one week) non-subtracted fat-saturated CE peripheral MR angiography. In addition to the MR angiographic examinations, 3 patients were referred for IA-DSA. A complete runoff IA-DSA was obtained in these patients before any lesions were treated. The results of the IA-DSA were compared with the results of the MR angiographic techniques.

Imaging technique

For all acquisitions we used a commercially available 1.5 T MR scanner (PowerTrak 6000, release 6.1; Philips Medical Systems, Best, The Netherlands) with a gradient strength of 21 mT/m and a slew rate of 105 mT/m/msec and standard available pulse sequences. During all examinations patients were placed on the scanning table in the supine position with their lower legs fixated in a dedicated quadrature phased array lower leg receiver coil (Philips Medical Systems, Best, The Netherlands). To prevent patient movement between mask and contrast-enhanced scans for the subtracted technique, patients were instructed to lie very still and sandbags were placed lateral to the upper and lower legs. Feet and arms were fixated with velcro straps and the arms were placed over the abdomen. For all acquisitions we used manual table movement and with the subtracted technique we used a repositioning device as described by Ho et al to ensure proper realignment of the table between mask and contrast-enhanced scans.(1) Prior to all 3D acquisitions of the pelvic station patients were instructed to hold their breath as long as possible in end inspiration.

Multistation (non-)subtracted CE peripheral MRA

Non-subtracted and subtracted imaging consisted of 4 steps: 1) patient positioning and establishing venous access in an antecubital vein, 2) acquisition of two-dimensional (2D) TOF localizer scans, 3) acquisition of non-contrast-enhanced three-dimensional (3D) mask scans and 4) acquisition of contrast-enhanced 3D scans during infusion of 35 mL of contrast medium (Magnevist®, Schering, Berlin, Germany). Contrast material was injected at 0.7 mL/s for the first 15 mL and at 0.6 mL/s for the last 20 mL, followed by a saline flush of 20 mL at 0.6 mL/s with a remote controlled MR compatible power injector (Spectris, Medrad, Indianola, PA, USA). We chose this dual phase injection rate because during routine clinical use at our institution it had shown to reliably visualize arteries with minimal venous enhancement. To ensure adequate timing of the start of the 3D contrast-enhanced scans a real-time bolus monitoring software package was used (BolusTrak, Philips Medical Systems, Best, The Netherlands). The imaging procedure we used has been described previously. For each station (pelvic, upper and lower leg) a customized 3D imaging volume was prescribed, tailored to the patients' specific vascular anatomy.(7) Imaging parameters used for the TOF localizer scans were: TR/TE (msec): 7.8 / 3.2, flip angle: 50°, matrix 256 x 93. For each station 60 axial slices of 4.0 mm thickness, spaced 3 mm were acquired. For the 3D mask and 3D contrast-enhanced scans identical scanparameters were used so that they could be subtracted after acquisition was completed. Scanparameters for the 3D scans are tabulated in table 1.

Table 1
Scanparameters for the (non-) subtracted multistation and fat-saturated techniques

	Pelvic		Upper leg		Lower leg	
Parameter	**(no-)sub**	**fatsat**	**(no-)sub**	**fatsat**	**(no-)sub**	**fatsat**
TR (msec)	7.6	7.6	5.3	5.3	5.8	5.8
TE (msec)	1.9	1.9	1.5	1.5	1.6	1.6
Flip angle (degrees)	25	25	30	30	30	30
Field of view (mm)	530	530	512	500	512	512
Matrix	512	256	256	256	256	256
Slice thickness (mm)	2.3	2.3	2.1	2.3	2.0	2.1
Voxel size (mm^3)	4.8	24.6*	8.4	14.6*	8.0	10.5*
Duration (sec)	32	36	22	36	27	42
K-space profile ordering	linear	linear	low-high	low-high	low-high	low-high
Reception coil used	Q-body	Q-Body	Q-body	Q-body	Lower leg	Lower leg
Number of prepulses	NA	3	NA	5	NA	4

(no-)sub: multistation non-subtracted and subtracted peripheral MR angiography techniques; fatsat: fat-saturated peripheral MR angiography technique; voxel size refers to true voxel sizes without any interpolation. Voxels of the fat-satured technique (marked with *) were interpolated to half their size; number of prepulses refers to the number of fat-saturating pulses given for each train of phase encodings for a single slice. Q-body = quadrature body coil, NA = not applicable

Non-subtracted fat-saturated CE peripheral MRA

Fat-saturated multistation imaging consisted of three steps: 1) patient positioning and establishment of venous access, 2) acquisition of 2D TOF localizer scans (with identical parameters as described above), 3) acquisition of contrast-enhanced 3D scans during infusion of 35 mL contrast material (Magnevist, Schering, Berlin) with acquisition of the arterial phase ensured by the use of real-time bolus monitoring software as described above. Contrast material was injected at 0.4 mL/s for the first 15 mL and at 0.3 mL/s for the remaining 20 mL. Tubing and veins were flushed with 20 mL of saline at 0.3 mL/s. A lower dual phase injection rate was chosen for the fat-saturated technique because we wanted to lengthen total bolus duration because of the increased total scantime and because we speculated it could prolong the time to venous enhancement.

To suppress the signal from fatty tissues we used spectral presaturation with inversion recovery (SPIR). Signal from fatty tissues is suppressed by flipping its longitudinal magnetization 120° with a frequency selective prepulse and subsequently dephasing the transverse magnetization with a spoiler gradient. After waiting 10 msec, when the longitudinal magnetization of protons in fat is zero the excitation pulse at the Larmor frequency for the bulk water protons is given, resulting in fat-suppressed images. To ensure that the optimal center frequency was used a separate preparation phase was carried out for the pelvic, upper and lower leg stations, which was recalled from the memory of the scanner when the actual contrast-enhanced sequence was acquired. An additional degree of freedom when programming a fat-suppressed sequence is the number of phase encoding steps that are acquired after each SPIR pulse. Although the most efficient suppression of fat signal is achieved by applying SPIR every TR, scantimes may become too long and consequently venous enhancement may occur. On the basis of previous work by Ho et al it was shown that in a time frame of 42 seconds for each station venous enhancement was not a significant issue.(1) When defining the protocol we decided that the maximum duration that a given station could last was 42 seconds and within this time we maximized the number of fat-saturating pulses we could give. Scanparameters for the 3D fat-saturated CE scans are also tabulated in table 1.

Digital subtraction angiography

Intra-arterial DSA images were acquired according to standard protocol with various amounts and flowrates of Iohexol (300 mg I / mL; Nycomed Amersham, Breda, The Netherlands). We used an X-ray system (Integris, Philips Medical Systems, Best, The Netherlands) with a programmable stepping C-arm. The arteries were imaged by puncturing the common femoral artery in all subjects and placing a 5-French catheter in the distal aorta just above the aortic bifurcation. In all patients who underwent IA-DSA film hardcopies were obtained in the posteroanterior and oblique views.

Image evaluation

After acquisition and reconstruction of magnitude images, the datasets were sent to an offline workstation (Sun UltraSparc, Sun Microsystems, Sunnyvale, CA, USA) with dedicated postprocessing software (EasyVision, version 4.1, Philips Medical Systems, Best, The Netherlands). Section by section subtraction was carried out for the non fat-saturated datasets. For image evaluation purposes the peripheral vascular tree was divided into the following segments: infrarenal aorta, left and right common iliac, external iliac, common femoral, superficial femoral (3 segments), popliteal, anterior tibial, posterior tibial and peroneal artery, for a total of 21 vascular segments in each patient. In all MR angiograms SNR and CNR ratios were calculated for all vessels segments that could be evaluated. Signal was measured in an intravascular user defined region of interest (ROI). Noise was measured by taking the standard deviation of air outside the patient, or if not available, in a region of homogeneous tissue inside the patient, corrected for magnitude effects by the Rayleigh correction.

(8) Image contrast was calculated as the difference between the signal within the artery and that measured in an ROI of the same size in a region immediately adjacent to the vessel. In the subtracted MR angiograms signal, contrast and noise were measured in the subtracted partitions. In all other MR angiograms signal, contrast and noise were measured in original partitions.

For qualitative image evaluation venous enhancement (venous enhancement score, VES), subjective interpretability (subjective interpretability score, SIS) and subtraction artifacts were scored for each vessel segment on 3 point scales. Venous enhancement was scored as 0 when no veins were visible, 1 when some veins were visible but not hindering interpretation and 2 when veins were visible and hindering interpretation of the vessel segment. Subjective interpretability was scored as 0 when the vessel segment was well interpretable, 1 when the observer thought it was suboptimally interpretable and 2 when there was poor interpretability, which was considered as non-diagnostic. For the subtracted multistation CE-MR angiographic exams the presence of subtraction artefacts was recorded and if present were scored as 0 when there was no effect of subtraction on interpretability, 1 if there were some subtraction artefacts visible but not hindering interpretation (as confirmed in original partitions) and 2 if subtraction artefacts made interpretation impossible.

(Non-)subtracted and fat-saturated MR angiograms were evaluated for presence and extent of peripheral arterial atherosclerotic disease on whole volume maxi-

	Technique		
	Non-subtracted	Subtracted	Fat-saturated
Mean SNR (SD)			
Pelvic (n=10)	28.4 (8.4)	19.1 (5.8)	90.7 (23.6)
Upper leg (n=10)	48.1 (8.2)	32.4 (5.1)	73.9 (17.6)
Lower leg (n = 10)	68.3 (22.1)	43.4 (16.4)	189.9 (74.0)
Mean CNR (SD)			
Pelvic (n=10)	22.6 (8.2)	18.8 (5.7)	78.6 (21.1)
Upper leg (n=10)	40.8 (7.4)	32.3 (5.0)	65.8 (16.9)
Lower leg (n=10)	54.8 (21.6)	42.2 (16.3)	150.7 (67.8)

SD: standard deviation; SNR: signal-to-noise ratio; CNR: contrast-to-noise ratio

Table 2 Mean (SD) of SNR and CNR for vessel segments in each field-of-view of non-subtracted, subtracted and fat-saturated MR angiographic techniques.

mum intensity projections (MIP) and on subvolume rotated MIPs around a craniocaudal axis with increments of 30°. Each observer defined the subvolume to be used for the rotational MIPs at his own leisure. Left and right axes were evaluated separately and the most severe lesion per vessel segment was scored on a five-point scale ranging from 0-20% stenosis, 21-49% stenosis, 50-74% stenosis, 75-99% stenosis and occlusion. Images of both techniques were evaluated by two observers experienced in reading MR angiograms, blinded for each other's results and the results of IA-DSA. A final grade of stenosis was determined in a consensus procedure if the two observers in their respective judgements gave a different grade of stenosis. X-ray angiograms were read by an experienced vascular radiologist, blinded for the results of the MR angiograms. Results of the three MR angiographic techniques were compared using the IA-DSA results as the standard of reference.

Statistical analysis

Mean differences in SNR and CNR as well as venous enhancement and subjective interpretability scores were compared on a station-by-station basis using the Wilcoxon signed ranks test for two related samples with a commercially available software package (SPSS 10.0, Chicago, IL, USA). To determine interobserver variation for detection and grading of stenoses and obstructions kappa values were calculated for the fat-saturated and (non-)subtracted techniques. Significance was assumed when *P*-values were <.05.

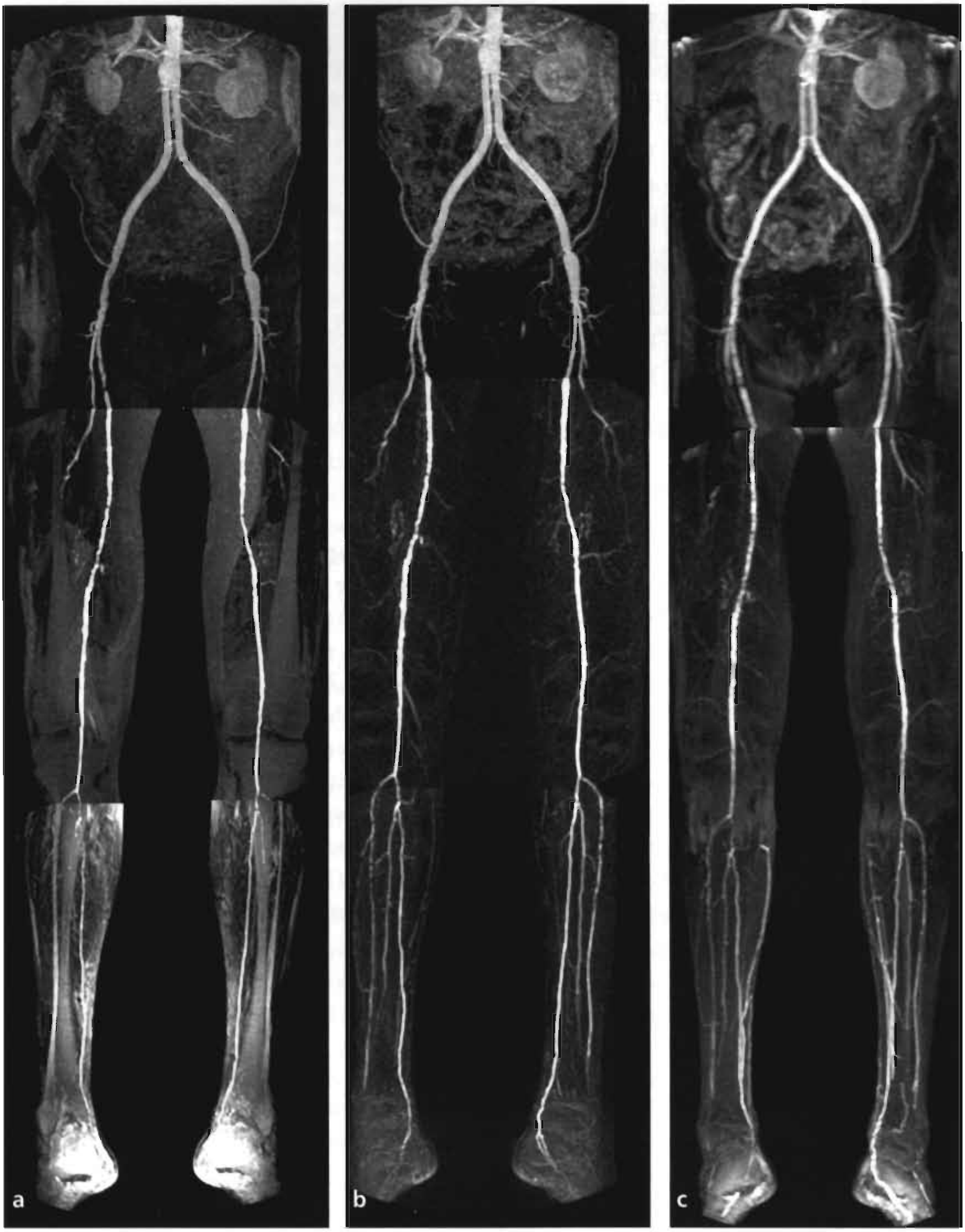

Figure 1 a,b,c Coronal maximum intensity projection (MIP) of contrast-enhanced MR angiograms in a 69-year old male patient with intermittent claudication.(a): MIP image of non-subtracted technique; (b): MIP image of subtracted technique; (c): MIP image of fat-saturated technique. Note that in the middle panel (subtracted technique) more small vessel braches can be seen (compared with the other two panels), there is less venous enhancement and the vessels appear sharper than in the right panel.

	Technique			
	(Non-)subtracted		Fat-saturated	
	Obs 1	Obs 2	Obs 1	Obs 2
Mean VES (SD)				
Pelvic (n=10)	0.01 (0.04)	0.00 (0.00)	0.09 (0.19)	0.00 (0.00)
Upper leg (n=10)	0.41 (0.49)	0.09 (0.15)	0.44 (0.45)	0.23 (0.33)
Lower leg (n=10)	0.64 (0.69)†	0.28 (0.51)†	1.16 (0.68)	0.73 (0.59)

SD : standard deviation ; VES : venous enhancement score ; Obs 1: observer 1; Obs 2 = observer 2. † = significantly lower (less venous enhancement) than fat-saturated technique.

Table 3 Mean (SD) VES for vessel segments in each field-of-view for (non)subtracted and fat-saturated techniques.

Results

All subjects tolerated the MR angiography examinations without side effects. Out of a potential 210 vessel segments a total of 197 segments were available for SNR and CNR comparison with the non-subtracted, subtracted and fat-saturated MR angiographic techniques. In three vessel segments no SNR and CNR measurements could be made because of poor delineation due to venous enhancement. In four vessel segments no measurements could be made due to occlusion (n = 2) or congenital absence of the vessel (n=2) and in six vessel segments no measurements were made because of stents. In figure 1 typical non-subtracted, subtracted and fat-saturated MR angiography exams in a patient are shown. Signal- and contrast-to-noise ratios of the three MR angiographic techniques are tabulated in table 2. For all stations, fat-saturated MR angiography had significantly higher SNR and CNR (P = .005 for all comparisons) than either the non-subtracted or subtracted techniques. Also, for all stations SNR and CNR were significantly higher for the non-subtracted versus the subtracted techniques (p = 0.005 for all comparisons except CNR of non-subtracted versus subtracted techniques in the lower leg station where the P-value was .009). Results of the VES for (non)-subtracted versus fat-saturated techniques are shown in table 3. Results of the SIS for the three techniques and for each observer are shown in table 4. VES were significantly lower for the most distal station with the (non)-subtracted techniques in both observers (observer 1: P = .007; observer 2: P = .012), meaning that more venous enhancement was seen in the fat-saturated lower leg images (figure 2). For the iliac and upper leg stations no significant differences were found with regard to venous enhancement. Results of the SIS comparison for the three techniques and for both observers showed that subjective interpretability was significantly better for the subtracted MR angiography images compared to both fat-saturated and non-subtracted MR angiography in the lower leg station (observer 1: P = .007 / P = .005; observer 2: P = .028 / P =

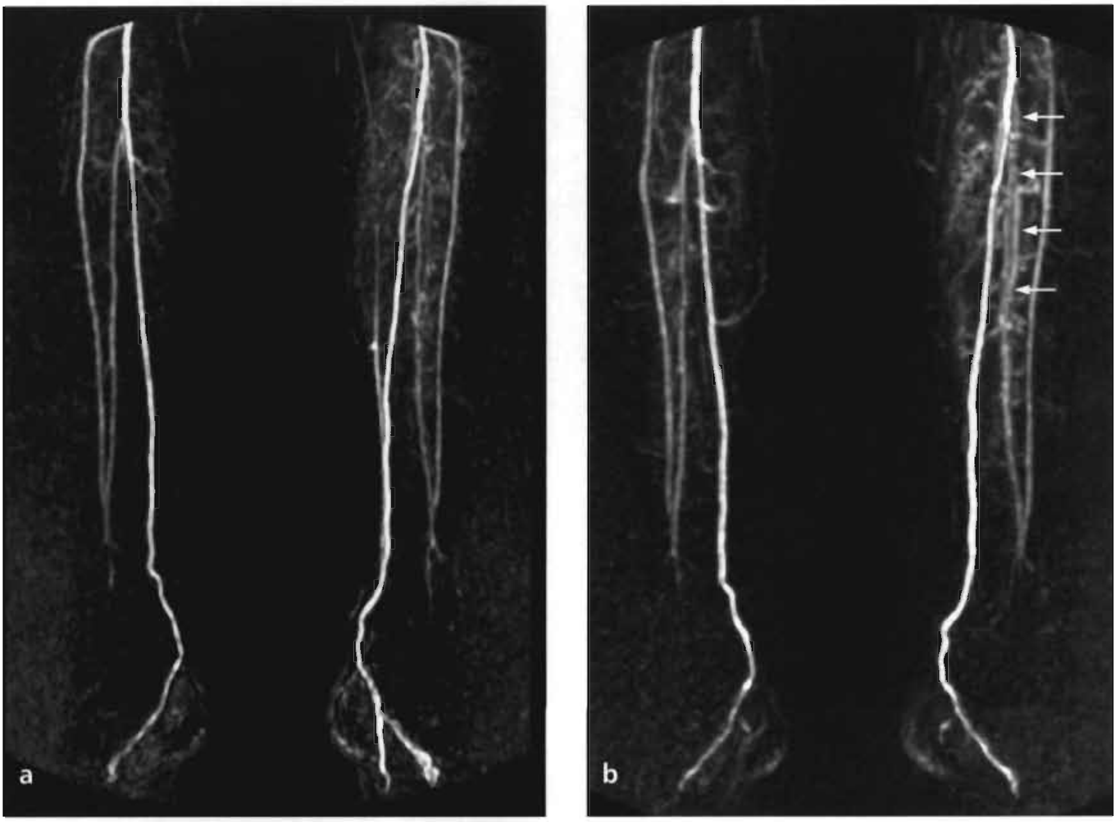

Figure 2 a,b Coronal maximum intensity projection (MIP) of subtracted (a) and fat-saturated (b) MR angiograms in a 57-year old male patient with intermittent claudication. With the fat-saturated technique, deep venous enhancement has occurred and the left fibular artery is not interpretable (arrows).

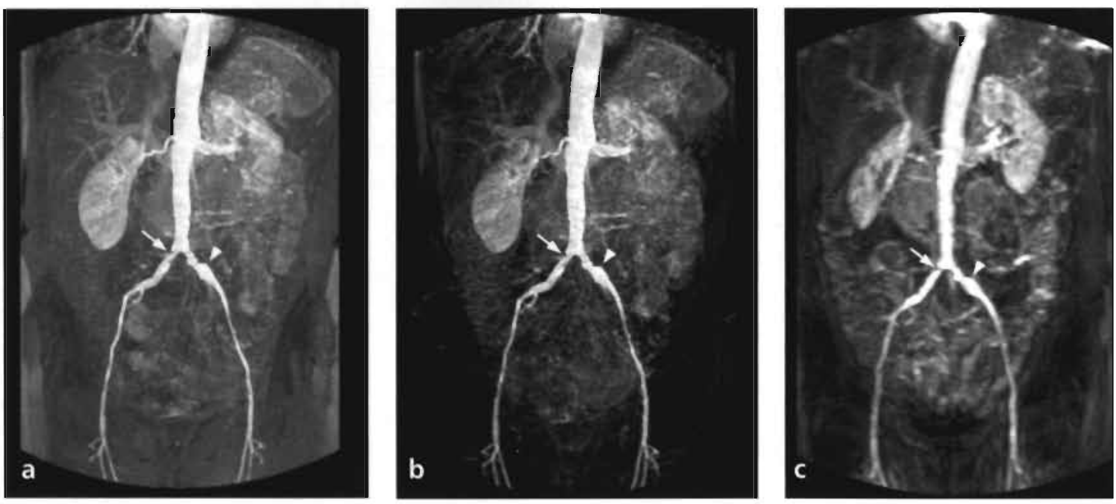

Figure 3 a,b,c Coronal maximum intensity projection (MIP) of non-subtracted (a), subtracted (b) and fat-saturated (c) contrast-enhanced MR angiograms in 67-year old male patient with a stenosis in the right common iliac artery (arrow) and an aneurysm in the left common iliac artery (arrow head). Note that in the a and b panels, arteries can be more sharply delineated than in the right image, allowing better subjective interpretability.

Table 4 Mean (SD) SIS for vessel segments in each field-of-view for non-subtracted, subtracted and fat-saturated MR angiographic techniques.

	Technique					
	Non-subtracted		Subtracted		Fat-saturated	
	Obs 1	Obs 2	Obs 1	Obs 2	Obs 1	Obs 2
Mean SIS (SD)						
Pelvic (n=10)	0.34 (0.39)	0.25 (0.16)'	0.27 (0.39)*'	0.13 (0.21)'	0.61 (0.48)	0.57 (0.39)
Upper leg (n=10)	0.08 (0.19)	0.05 (0.07)'	0.06 (0.19)	0.01 (0.03)'	0.26 (0.34)	0.23 (0.27)
Lower leg (n=10)	1.18 (0.45)	1.01 (0.46)	0.58 (0.53)*'	0.23 (0.23)*'	0.88 (0.55)*	0.58 (0.56)*

SD : standard deviation; SIS : subjective interpretability score; Obs 1: observer 1; Obs 2 = observer 2.
* = significantly lower (better subjective interpretability) than non-subtracted technique; ' = significantly lower (better subjective interpretability) than fat-saturated technique.

Table 5 Comparison between number of stenoses found with the compared MR techniques and intra-arterial digital subtraction angiography (IA-DSA) in patients where a comparator examination was available

	Technique			
	Non-subtracted consensus	Subtracted consensus	Fat-saturated consensus	IA-DSA
Total number of stenoses ≥50%	96	96	115	standard of reference
Diseased vessel segments with IA-DSA as comparator	19	17	17	16
comparison with IA-DSA	9 concordant	12 concordant	5 concordant	
	7 overestimated	1 overestimated	5 overestimated	
		2 underestimated	2 underestimated	
	3 not visible on DSA	2 not visible on IA-DSA	5 not visible on IA-DSA	

.005). In the pelvic station this was only the case for observer 1 (P = .043 / .008). In the lower leg station fat-saturated MR angiograms also had significantly better interpretability than non-subtracted MR angiograms (observer 1: P = .007; observer 2: P = .005). In the upper leg station no one technique was superior over two others. (figure 3). Separate analysis of SIS in diseased versus healthy vessel segments also yielded significantly better scores for subtracted MR angiography images for both observers (observer 1: P<.016, observer 2: P<.001) versus the other two techniques. In the subtracted datasets, both observers found that none of the vessel segments were uninterpretable because of subtraction arte-

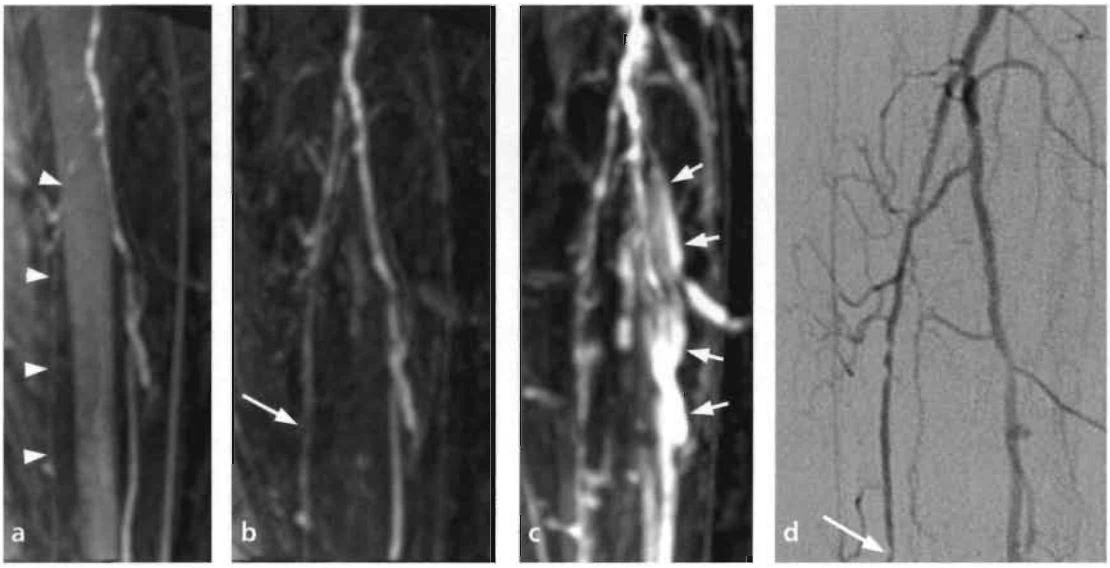

Figure 4 a,b,c,d Zoomed coronal maximum intensity projection (MIP) of non-subtracted (a), subtracted (b) and fat-saturated (c) MR angiograms of the left tibioperoneal trunc in a 61-year old male patient with intermittent claudication. In the non-subtracted (a) image, the posterior tibial artery appears severely stenosed due to suboptimal suppression of signal from fat in the tibial bone marrow (arrowheads). In the subtracted image, the posterior tibial artery appears patent, but stenosed, which is in accordance with the findings on intra-arterial digital subtraction angiography (b,d; long arrows). In the fat-saturated image there is no signal from bone marrow or subcutaneous fat, but due to the longer acquisition time venous enhancement has occurred and the vessels are not interpretable.

facts. Kappa values for detection and grading of stenoses and obstructions were 0.45 (95% CI: 0.35-0.56) for the fat-saturated technique and 0.53 (95% CI: 0.43-0.63) for the (non-)subtracted technique, indicating moderate agreement between observers for the techniques. After the consensus procedure, evaluation of the arterial system for stenoses and obstructions revealed a total of 96 lesions for both the subtracted and non-subtracted techniques and a total of 115 lesions for the fat-saturated MR angiographic technique. Three patients underwent IA-DSA where 16 abnormalities were found. On MR angiography 17 lesions were found with subtracted and fat-saturated techniques and 19 lesions with the non-subtracted technique. For the latter technique 9 lesion were classified as having the same grade of stenosis, 8 lesions were overestimated, 2 lesions were not interpretable, and no lesions were underestimated. For the subtracted technique 12 lesions were classified as having the same grade of stenosis, 2 lesions were not interpretable, 1 lesion was overestimated and 2 lesions were underestimated. With the fat-saturated technique only 5 lesions were classified as having the same grade of stenosis, 5 lesions were not interpretable, 5 lesions were overestimated and 2 lesions were underestimated (table 5). In figure 4 an example of the three MRA techniques and the corresponding IA-DSA for evaluation of the proximal lower leg vessels is shown.

Discussion

With this work we have shown that despite the theoretical objections of subtracted multistation MR angiography this technique is to be preferred over non-subtracted and fat-saturated multistation MR angiography, because of significantly better subjective interpretability. Although the absolute values of SNR and CNR were significantly higher for the fat-saturated and non-subtracted techniques, the subtracted MR angiography method exhibited more than enough vessel-to-background contrast for confident assessment of atherosclerotic peripheral arterial disease. Higher SNR for the fat-saturated technique was achieved because of larger voxel size, mainly for the pelvic arteries (4.8 vs 12.3 mm^3), and lower values measured for noise in the fat-saturated technique. However, because using fat-saturation takes time and we wanted to stay within a 42 seconds acquisition, scanning with larger voxels was unavoidable. Concerning the significantly lower SNR en CNR values for subtracted versus non-subtracted partitions, it is known that image subtraction increases noise. This is because all acquisition parameters are the same for pre- and postcontrast imaging and one expects from elementary theory of error propagation that noise in the subtracted images increases with approximately a factor $\sqrt{2}$.(9) Comparing SNR and CNR values for subtracted and non-subtracted images in absolute terms will therefore always yield a significantly higher value for non-subtracted images. Perhaps the difference between SNR and CNR of the same dataset is therefore a better measure of comparison. In another study investigating the value of image subtraction in peripheral MRA this expected almost 30% decrease in SNR was, surprisingly, not found.(10) In the same study no significant differences in sensitivity and specificity were found between subtracted and non-subtracted datasets when compared to IA-DSA. Because of the limited number of patients with IA-DSA correlation in the current study, no definitive statements can be made concerning a possible difference in sensitivity and specificity. However, the authors of that study compared a non-subtracted, fat-saturated sequence with a subtracted fat-saturated sequence. We speculate that if no fat-saturation had been used, different results would have been obtained, especially with regard to the lower legs.

Venous enhancement occured significantly more often with the fat-saturated technique, most likely because it took a longer time to finish the acquisition of the 3D scanning sequence (122 s vs 89 s). Although we based the maximum duration of our scans on work in which venous enhancement was not a major source of image degradation(1), in the current study venous enhancement occurred significantly more often in the scans with longer duration. The inherent danger of venous enhancement, given the lower resolution of the fat-saturated images, is that arteries and veins may be more difficult to separate because of partial volume effects, even when looking at original partitions.

Although one of the reasons for undertaking this study was the potentially disturbing effect of subtraction on image interpretability, two observers independently found no vessel segments that were uninterpretable on subvolume MIPs of section-by-section magnitude subtracted images. This finding indicates the robustness of the subtracted MR angiographic technique when care is taken with patient positioning and instruction and corroborates findings of other authors that used subtracted multistation peripheral MR angiography.(2,3) Despite adequate patient instruction, however, artefacts may be encountered if patients move between acquisition of the mask and contrast-enhanced scans. On the other hand, if a vessel segment is suboptimally interpretable due to subtraction artifacts it is always possible to evaluate original non-subtracted contrast-enhanced partitions.

In this study we found that subtracted images are subjectively perceived as significantly better interpretable than both fat-saturated and non-subtracted images by both observers. This significance was not dependent on the presence of pathology in vessel segments because significantly better interpretability was also found for vessels assessed as being normal or having only mild irregularities (0-20% stenosis). The most likely reason for this finding is that subtracted images have a higher resolution compared with fat-saturated images which may allow more confident exclusion and assessment of pathology. This was also reflected by the number of lesions found with the three MRA techniques (table 5). More vessel segments were classified in consensus as being diseased with both the fat-saturated and non-subtracted technique with IA-DSA as the standard of reference. The reason that non-subtracted images are judged as being less well interpretable than subtracted images is most likely that signal from fatty tissues close to the surface coil used for imaging the lower leg arteries makes interpretation very cumbersome.

The major drawback of using fat-saturation is that it takes time, which is, with current MR hardware limitations, at a premium. Scanning longer increases the chance of venous enhancement, which is one of the most significant sources of suboptimal image interpretability. Even with the lower injection rate we used for the fat-saturated technique we observed significantly more venous enhancement. With regard to the fat-saturation used in our experiment we have to mention that we used a commercially available sequence. Use of experimental contrast-selective fat-saturation pulse sequences might have yielded better results in shorter time. (11,12)

For instance if we could have used fat-saturation for only the contrast-determining K-space profiles, substantial shortening of scan duration could probably have been made. Also, if thicker slices or a larger bandwidth had been used with the fat-saturated technique we might have been able to shorten scantime and possibly could have reduced venous enhancement. A disadvantage of using inversion prepulses to suppress signal from fatty tissues is that signal from fat is suppressed on the basis of it's T1 value and that signal from other tissues with similar T1 (for instance arteries with small amounts of contrast material in them) can also be suppressed. In addition, artifactual intravascular signal intensity loss may occur when using fat-suppression algorithms, which may lead to misinterpretation of vessels. (13) Although Siegelman et al describe signal loss secondary to lung parenchyma adjacent to the subclavian artery, this phenomenon can potentially also be seen next to gas-filled bowel segments, stents or hip replacements, making the use of fat-saturation in these patients unattractive.

In order to review contrast-enhanced peripheral MR datasets and to present them in a readily accessible format for the referring clinician, some kind of background suppression is needed, especially when using dedicated surface coils to increase SNR. With the use of faster hardware in the future, capable of ultrashort TR values in the order of 1 msec and stronger T1 reducing contrast agents such as the 1.0 molar gadolinium chelates, currently in phase III trials around the world it may be possible to achieve much better T1 weighted sequences which have inherently better background suppression. These improvements may eventually abolish the need for reduction of background signal with subtraction or fat-saturation techniques. However, another advantage of using subtraction techniques is when acquiring multiple phases of arterial and venous filling, selective enhancement of arteries or veins can be obtained by use of subtraction.(14)

Although we have shown significantly better interpretability and significantly less venous enhancement when using subtracted multistation MR angiography our study also has limitations. Perhaps better results would have been achieved if we had been able to use a less time consuming form of fat saturation. However, the aim of our study was to compare both techniques on a commercially available system so that the results can be extrapolated to a wide range of currently available MR imaging systems. Another drawback of the study was the limited number of patients in which we were able to obtain X-ray angiographic correlation. A larger number of correlations would have perhaps shown more conclusively if there was a statistically significant difference for detection and grading of lesions between the three investigated MRA techniques. Also, if we would have scanned a larger sample of patients we might have encountered subtraction misregistration artefacts that hinder image interpretability. Ongoing retrospective analysis of a large amount of cases (>200) in which we used subtracted multistation peripheral MR angiography in our institute however has shown that these artefacts occur only sporadically, i.e. in less than 5% of all exams, and led to suboptimally or uninterpretable vessel segments on MIPs in less than 1% (unpublished results). Finally it cannot be ruled out that the use of different injection schemes led to differences with regard to image interpretability and venous enhancement. However, considering that despite the lower injection rate SNR and CNR were significantly higher for the fat-saturated technique it is unlikely that the significantly lower image interpretatability in the lower legs was due to differences in injection protocol.

Conclusions

With this work we have shown that despite lower signal and contrast to noise ratios subtracted multistation peripheral MR angiography yields objectively and subjectively better image quality than non-subtracted and fat-saturated peripheral MR angiography when using commercially available pulse sequences. When comparing the results of both techniques with intra-arterial DSA the subtracted MR angiographic technique also yielded better results. The value of subtraction was greatest for the lower leg arteries but depends on the type of hardware one has available.

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Use of a three station phased array coil to improve peripheral contrast-enhanced magnetic resonance angiography

submitted

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Abstract

Purpose

The purpose of this study was to explore a new three-station, dedicated phased array coil for contrast-enhanced MR angiography (CE-MRA) in patients with peripheral arterial occlusive disease (PAOD). Specific aims of the study were to a) use the expected increase in signal-to-noise ratio (SNR) to avoid venous enhancement, b) to improve spatial resolution, and c) to increase anatomical coverage to include the pedal arch in the lower leg station.

Subjects and methods

Nineteen consecutive patients (13 men, 6 women, mean age 61 years; range, 40-81) referred for CE-MRA secondary to suspected or proven peripheral arterial disease were enrolled in the study. In 12 patients the vascular surgeons requested information about the pedal vasculature. Prior to the CE-MRA studies, SNR measurements were made to quantify the increase in SNR due to the use of the coil. In all stations imaged, the presence of disturbing venous enhancement was assessed on a three-point scale for all main-stem named vessel segments from the infrarenal aorta through the pedal arch.

Results

For the iliac station SNR increased 64%, for the upper leg station 51% and for the lower leg station 167% when the new peripheral coil was used instead of the standard quadrature body coil. Use of the coil enabled acquisition of high resolution peripheral vasculature images in all cases. In 12/12 (100%) requested cases the entire pedal arch was depicted. The true acquired voxel sizes for the iliac and upper leg stations were 5.7 mm^3, and the voxel size for the lower leg station was 1.8 mm^3. In no case severe deep venous enhancement (rendering images non-diagnostic) was seen.

Conclusions

A three-station dedicated peripheral vascular coil substantially improves peripheral MR angiographic acquisition quality and coverage and allows for station-specific protocol optimization.

Introduction

As an alternative to intra-arterial digital subtraction angiography (IA-DSA) for patients with peripheral arterial occlusive disease (PAOD), excellent diagnostic results have been reported using three dimensional (3D) contrast-enhanced magnetic resonance angiography (CE-MRA).(1-4) Although different MR approaches to peripheral arterial imaging have been described, the most often used technique at present is the acquisition of three or more partially overlapping coronal 3D gradient recalled echo scans during intravenous injection of a single bolus of 0.2-0.3 mmol/kg extracellular gadolinium chelate contrast medium. The contrast-enhanced acquisitions are performed in rapid succession using a large field-of-view (FOV), translating the patient table as quickly as possible between subsequent scans. In all but one reported study using this single bolus injection approach, the 3D scans employ identical scanning parameters for each of the three separate stations.(5) Although studies reporting station-specific figures of sensitivity and specificity are few, image quality is clearly worse for the most distal station than for the more proximal stations.(6,7) One explanation for this is that the relatively long delay between injection and acquisition of the lower leg station often allows superficial and deep veins to opacify, leading to suboptimal lower leg arterial interpretability. In addition, lower leg arteries are of much smaller diameter (2-3 mm) than the more proximal arteries, and when scanned at the same resolution as these larger arteries, may lead to partial volume artifacts, further decreasing the diagnostic accuracy. This is particularly true for severely diseased distal arteries. In addition, most techniques fail to visualize the pedal arch. Consequently, serious doubts remain regarding the adequacy of lower leg station image quality in single-bolus peripheral CE-MRA. One straightforward method of improving lower leg arterial image quality is through the use of a dedicated lower extremity reception coil. In theory, using such a coil provides a higher signal-to-noise ratio (SNR) which can in turn be used to achieve higher resolution or shorter scan times without sacrificing vessel-to-background contrast.

The purpose of this study was to explore a new three-station, dedicated phased array coil for CE-MRA in patients with PAOD. Specific aims of the study were to a) use the expected increase in SNR to avoid venous enhancement, b) to improve spatial resolution, and c) to increase anatomical coverage to include the pedal arch in the lower leg station.

Patients and Methods

All acquisitions were performed using commercially available pulse sequences on a 1.5 T MR scanner equipped with a gradient strength of 30 mT/m and a rise time of 200 msec (Gyroscan Intera, release 8.1, Philips Medical Systems, Best, The

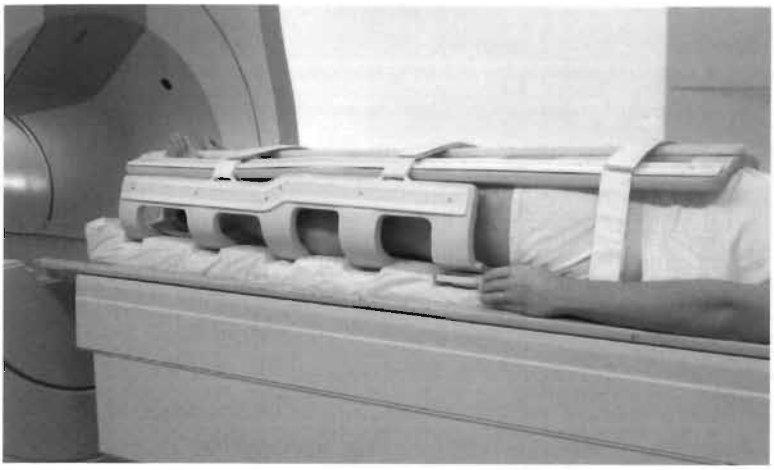

Figure 1 Patient positioning in the three station phased array coil. Note that the feet are inside the anteroposterior area covered by the coil.

Netherlands). The study protocol was approved by the institutional review board, and all patients signed informed consent.

Peripheral vascular coil

The peripheral vascular coil (Philips Medical Systems, Best, The Netherlands) is a bilateral, 12-element phased-array coil in a flexible two-piece design, with one piece placed posterior to the patient and one piece placed anterior to the patient (figure 1). The coil provides a craniocaudal coverage of 129 cm, and anterioposterior coverage can be individually adapted to the patient. The caudal end of the anterior coil part has openings which allow for inclusion of the feet into the 3D imaging volume used for the distal station. Imaging of the peripheral arteries can be performed in three partially overlapping scans using a FOV of 45 cm, with 3 cm overlap between scans. During acquisition of each separate station, two anterior and 2 posterior elements of the coil can be selected via the software and used simultaneously for signal reception. To better understand the capabilities of this coil, we first compared SNR between 1) the new peripheral coil (all three stations); 2) the standard built-in quadrature body coil (all three stations); and 3) a phased array spine coil (lower leg station only). In order to compare only the influence of the coil on SNR, signal intensity measurements were made on original partitions of gradient recalled echo scans performed on a single volunteer. Signal intensity was measured in tibial bone marrow in the lower leg, medial femoral condyle bone marrow in the upper leg, and retroperitoneal fat in the midline for the aortoiliac station. An identical region of interest was used for each coil. From these data SNR was calculated by dividing the signal intensities in marrow or fat by the standard deviation of measurements in air outside the volunteer.

	Aortoiliac	Upper legs	Lower legs
TR (msec)	4.2	3.3	3.8
TE (msec)	1.3	1.2	1.3
FA (degrees)	40	40	30
FOV-freq (mm)	450	450	450
FOV-phase (mm)	270	293	293
Matrix (freq)	432	320	432
Matrix (phase)	149	208	293
Slice thickness	2.8	2.2	1.7
Voxel size (mm^3)	5.3*	4.4*	1.8*
Bandwith (Hz/pix)	310 Hz/pix	624 Hz/pix	434 Hz/pix
Acquisition duration	15-17 sec†	10-12 sec†	60-75 sec†
Partial echo	yes	yes	yes
Half scan	yes	yes	no

FOV = field-of-view; FA = flipangle; freq = frequency encoding direction; phase = phase encoding direction; pix = pixel; * Actually measured voxel sizes, these voxels were later reconstructed to half their size by zero interpolation in the slice direction. † the exact duration of each station varied per patient with the number of partitions used in each station.

Table 1 Scanparameters for each FOV in patients scanned with flexible parameters

MRA patients

Nineteen consecutive patients (13 men, 6 women, mean age 61 years; range, 40-81) referred for CE-MRA secondary to suspected or proven peripheral arterial disease were enrolled in the study. Clinical indications were as follows: mild to moderate intermittent claudication (n=10), severe intermittent claudication (n=5), rest pain (n=1) and rest pain with ulcerations/gangrene (n=3). Four patients had adult onset diabetes mellitus, two of which also had ulcerations.

CE-MRA protocol

In order to prescribe the 3D imaging volumes, transverse time-of-flight (TOF) scout views were first acquired to outline aortoiliac and lower limb arterial anatomy. Time-of-flight imaging parameters were identical for each station (TR (msec) / TE (msec) / flipangle / acquisition time : 11 / 6.9 / 50° / 88 sec). Maximum intensity projections (MIPs) were generated in three orthogonal directions for purposes of prescribing the subsequent 3D imaging volumes. For each patient, the 3D imaging volume was chosen to encompass only the arteries of interest in each of the three separate stations, and care was taken to avoid scanning redundant partitions which did not contain any arteries of interest. For all examinations, the FOV in the phase-encoding (left-right) direction for each station was reduced to the smallest possible value while still avoiding wrap-around artifacts. To decrease the chance of lower leg venous enhancement, we attempted to image the aortoiliac and upper leg stations as rapidly as possible, investing the time savings (as compared to a protocol with the same parameters and duration in every station) in increasing the number of partitions and resolution for the lower leg station. Station-specific imaging parameters using this approach are shown in table 1. We used linear K-space view ordering for the aortoiliac station, and elliptical centric K-space ordering for the upper and lower leg stations. Approximately 7 seconds elapsed between completion of one scan and the start of the next scan (including scanner controlled table movement). Each patient received 35 mL of gadolinium DTPA (Magnevist, Schering, Berlin, Germany) adminstered at a rate of 1.8 mL/sec for the first 15 mL, and 0.6 mL/sec for the remaining 20 mL (total injection duration: 42 sec), followed by a saline flush of 20 mL at 0.6 mL/sec. This dual phase injection rate was chosen empirically based on prior experience with somewhat lesser injection rates while using slower, higher SNR aortoiliac and upper leg sequences. The injection rate was increased compared to protocols described in the literature (1-4) because we felt that the dedicated coil alone would not entirely compensate for the loss in SNR due to shorter aortoiliac and upper leg scan times and the use of halfscan (i.e. half NEX or half fourier imaging in the phase encoding direction). Scan delay was determined using real time bolus monitoring software (BolusTrak, Philips Medical Systems, Best, Netherlands). When enhancement was first seen in the descending aorta, the patient was given a breathhold command and immediately after completion of the command (4-5 sec) image acquisition was started. When the referring vascular surgeon specifically requested information about outflow vessels (n =12), it was attempted to include the pedal arterial arch into the imaging volume of the lower legs. For all MR examinations, vessel-to-background contrast was increased by subtraction of non-enhanced scans acquired before the injection of contrast medium.

In all stations imaged, the presence of disturbing venous enhancement was assessed for all main-stem named vessel segments from the infrarenal aorta through the pedal arch. Venous enhancement was classified on a four-point scale (0 = no venous enhancement, 1 = superficial venous enhancement present but not disturbing interpretation, 2 = superficial and deep venous enhancement present but not disturbing interpretation and 3 = superficial and/or deep venous enhancement rendering the vessel segment not interpretable).

Results

All MR examinations were successful, and no patients experienced any side effects. In particular, none of the 19 patients included in this study complained

Figure 2 a,b Peripheral MR angiogram of a 61-year old male patient with the LeRiche syndrome. The left image (a) is a coronal, three station maximum intensity projection (MIP) image of the peripheral arteries and shows occlusion of the infrarenal abdominal aorta, left and right common iliac, external iliac and common femoral arteries. From the right, sagittal MIP image (b), it can clearly be appreciated that volumes with different thickness were used for the aortoiliac, upper and lower leg stations. Note that the lower leg volume scanned with the coil allows for imaging of the pedal arch and has more than double the anteroposterior coverage of the upper leg volume.

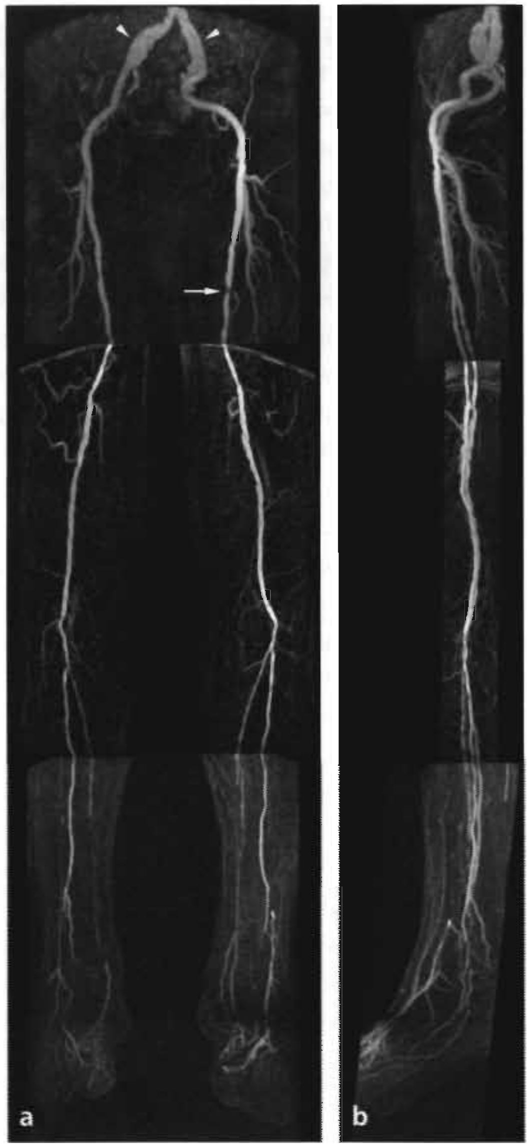

Figure 3 a,b Peripheral MR angiogram of a 79-year old male patient suffering from critical ischemia and tissue loss in right foot. Coronal (a) and sagittal (b) three station maximum intensity projection (MIP) images from the aortic bifurcation down to and including the pedal arch. In both common iliac arteries there are aneurysms.(arrow) There is a high-grade stenosis in the left superficial femoral artery.(arrowheads)

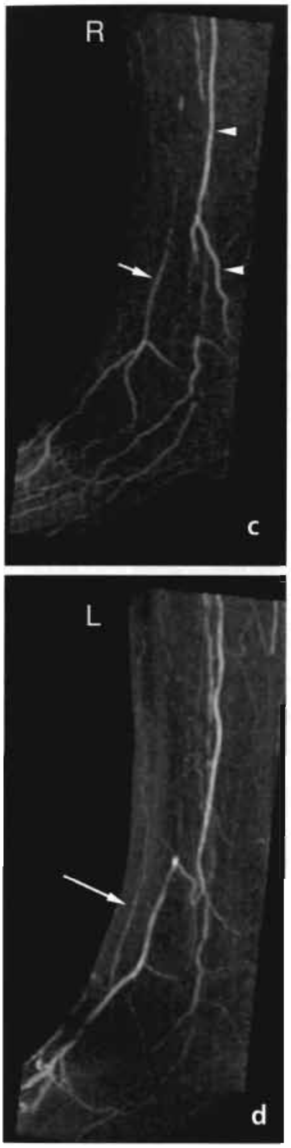

Figure 3 c,d *Zoomed sagittal MIPs are shown of the right (R,c) and left (L,d) distal lower leg vessels and the pedal arch. The pedal arch in the right foot is supplied by a collateral vessel (bottom arrowhead) arising from the distal fibular artery (top arrowhead) and by the severely diseased anterior tibial artery (short arrow). There is slight superficial venous enhancement in the left lower leg, not disturbing image interpretability (long arrow).*

Figure 4 a,b *Coronal (a) and sagittal (b) maximum intensity projections of the three station peripheral MR angiogram of a 59-year old male patient suffering from rest pain of the left leg. The patient had undergone common femoral endarterectomy and below-knee femoropopliteal bypass grafting in the right leg two years previously. The external iliac, common femoral, superficial femoral and popliteal arteries on the left side are completely occluded. The left tibioperoneal trunc is partly occluded. Collateral branches arising from the left internal iliac artery (asterisk) supply the deep femoral artery which fills the anterior tibial (long arrow) and fibular (short arrow) arteries. There is superficial venous enhancement in the left lower leg (arrowheads) which was considered not disturbing because of the three dimensional nature of the dataset.*

of claustrophobia while in the peripheral vascular coil. Comparison of the SNR measurements between the different coils showed that substantial differences in SNR existed (table 2). For the iliac station SNR increased 64%, for the upper leg station 51% and for the lower leg station 167% when the new peripheral coil was used instead of the standard quadrature body coil. An increase in SNR of 71% over the standard quadrature body coil was seen when the phased array spine coil was used for the lower leg station. The dedicated peripheral vascular coil had 56% higher SNR in the lower leg station as compared to the spine coil.

Images from the infrarenal aorta down to and including the entire pedal arterial arch were obtained as requested by the referring vascular surgeons in 12/12 (100%) patients (figures 2 and 3). In five patients, imaging of the pedal arch was sacrificed in order to more fully cover the descending aorta, and in two patients the referring clinicians also wanted information about the thoracic aorta, and therefore the feet were excluded from the distal coverage of the peripheral vascular coil (figure 4). The true acquired voxel size for the iliac staion was 5.3 mm^3, for the upper leg station 4.4 mm^3, and the voxel size for the lower leg station was 1.8 mm^3. Of the 19 patients imaged, 9 patients exhibited no venous enhancement whatsoever (grade 0). Seven patients exhibited superficial lower leg venous enhancement, and one patient exhibited upper leg superficial venous enhancement, none impairing study interpretation (grade 1). In 2 lower limbs of 2 different patients, slight deep venous enhancement was seen (grade 2), also not impairing interpretation. Of the three patients with ulcers or gangrene, one demonstrated no venous enhancement, and two had slight superficial lower leg venous enhancement (grade 1). Of the 4 patients with diabetes mellitus, 3 exhibited superficial lower leg venous enhancement, and the remaining patient slight deep venous enhancement in the upper leg station. In no case was severe deep venous enhancement seen.

Discussion

This work demonstrates that a full-length dedicated lower extremity coil can be used for multiple station, single injection peripheral CE-MRA to increase acquisition speed, image resolution and/or anatomical coverage. The use of station specific parameters permitted inclusion of the entire pedal arch in all requested cases while maintaining good image quality in the aortoiliac and upper leg stations. The gain in SNR due to the use of a dedicated peripheral vascular coil such as was evaluated here can be used to choose scanning parameters which decrease SNR, such as a shorter TR, a larger bandwidth or half scan, without a qualitatively noticeable overall loss in image interpretability. For the purpose of this study, we chose to use the SNR gain to scan faster in the aortoiliac and upper leg stations, and to invest the time saved for these proximal stations to arrive more quickly and

	Signal to noise ratio		
	Aortoiliac station	Upper leg station	Lower leg station
Quadrature body coil	5.3	11.2	9.7
Peripheral vascular coil	8.7	16.9	25.9
Spine coil	NA	NA	16.6

NA = not applicable (it is only possible to use the spine coil for a single station)

Table 2
Comparative signal to noise ratios with three different coils

scan longer in the lower legs. Use of this strategy enabled us to scan these small and distal vessels at a much higher resolution (lower leg station 1.8 mm^3 vs upper leg station 5.7 mm^3 and aortoiliac station 5.3 mm^3). Also, with the use of this coil, we were able to increase the anatomic coverage in the anteroposterior direction to include the pedal arch, something not yet reported in the single injection, multiple station peripheral CE-MRA literature. Inclusion of the pedal arch is particularly important in patients being considered for bypass surgery to the arteries in the distal lower leg and foot, as patency of the arch is of high prognostic significance for medium and longterm patency of surgical bypass grafts to arteries below the knee.(8-10) Although a recent study also reported on the advantages of the use of a dedicated coil for peripheral CE-MRA (11), to our knowledge, we are the first to use the advantages of such a coil to depict the entire peripheral arterial tree from the infrarenal aorta through the pedal arch in a single bolus exam while maintaining good image quality (figures 2 and 3).

One of the most troublesome aspects of CE-MRA in patients with PAOD is venous enhancement, particularly in the lower leg station. In various recent reports, venous enhancement disturbing image interpretation in up to 25% of lower leg stations has been reported.(3,4,12,13) In the current study, venous enhancement did not render images non-diagnostic because slight deep venous enhancement was only found in 2/19 patients and viewing of the original partitions was diagnostic in these patients. All other venous enhancement (9 patients) was superficial and thus not problematic due to the 3D nature of the MR datasets. This finding is encouraging, especially considering the relatively fast first part of the dual phase injection rate (1.8 mL/s for the first 15 mL of contrast media) we used.

Venous enhancement is particularly prevalent in certain patient groups, for instance patients with diabetic ulcers.(13) In the current study, 2/3 patients (67%) with ulcers, and all 4 patients (100%) with diabetes mellitus exhibited slight venous enhancement. It is these patients, however, that often have predominantly distal PAOD, and thus a high resolution MR angiogram without confusing venous overlay is necessary to optimally explore surgical therapeutic options. The ability to image the pedal arch and selectively increase the resolution in the lower leg station resolution using this new coil is one step in the needed direction. In all patients in which information on outflow vessels and arch patency was requested (12/12), we were able to depict the pedal vessels at high resolution without substantial venous enhancement, in part because of the new coil. In 7 out of 19 patients we did not image the entire pedal arch, as the referring clinicians were more interested in covering sufficient length of the descending aorta. We must comment, however, that only 3 patients with ulcers and 4 patients with diabetes mellitus (in total 5 out of 19 examinations [26%]) were examined, and that in these patients a single bolus strategy ultimately may not be the best option for imaging the lower leg without venous enhancement. An alternative method of preventing lower leg venous enhancement is through the use of a time-resolved two-dimensional projectional technique as described by Wang et al.(13) With this technique images of the lower leg vessels are acquired approximately every 2 seconds during injection of a small amount (5-7 mL) of gadolinium chelate contrast medium, giving projectional information analogous to that provided by IA-DSA. Using a two dimensional (2D) technique, the chance of obtaining a selective arterial phase regardless of how rapidly venous enhancement occurs is much greater than with a 3D single bolus injection technique. A drawback to 2D techniques, however, is that the information obtained is projectional, and therefore (as with IA-DSA) does not allow for evaluation from different viewing angles without performing additional contrast medium injections. A second alternative for obtaining images with a substantially smaller chance for lower leg station venous enhancement is by using a separate contrast injection for each station.(14,15) Using this strategy, the lower leg station can be acquired first, ensuring acquisition occurs simultaneous to arterial contrast arrival, rather than delayed as with a single injection approach, when the risk for venous enhancement is greater. The disadvantages of this approach are that it takes longer to perform, the amount of contrast that can be injected for each station is about one third that of single injection protocols, possibly decreasing vessel to background contrast and, the presence of residual contrast medium in arteries and veins, potentially reducing vessel-to-background contrast for the second and third acquisitions.(16)

A limitation of the current study is that we did not obtain intra-arterial digital subtraction angiographic (IA-DSA) correlation, so no conclusions can be made concerning sensitivity and specificity of the evaluated protocol in this study. However, the accuracy of contrast-enhanced peripheral MRA in comparison with IA-DSA as the standard of reference has been extensively evaluated in two recent meta-analyses(6,7) and was not the objective of the current study. At our institution, a tertiary referral hospital with a large vascular surgical department, images as presented in the current study are used in clinical practice for percutaneous as well as surgical planning without the need for additional IA-DSA.

In conclusion, although experience is preliminary and obtaining diagnostic images in peripheral MRA depends on complex interactions between many variables, the use of a full length peripheral vascular coil is beneficial for single bolus peripheral CE-MRA. Because of the increased SNR with this new coil, resolution can be increased selectively for the lower leg station, and high quality imaging of the pedal arch becomes a possibility. The use of a full length peripheral vascular reception coil in combination with an optimized scanning protocol may dispel concerns about lower leg image quality and substantially improve the utility of single bolus peripheral CE-MRA.

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Multicenter phase II trial of safety and efficacy of NC100150 for steady-state contrast-enhanced peripheral magnetic resonance angiography

submitted

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Abstract

Purpose

To test the safety and efficacy of NC100150 injection for steady-state contrast-enhanced peripheral MR angiography in a multicenter phase II trial.

Subjects and methods

33 patients underwent NC100150 enhanced MR angiography (5 mg Fe/kg bodyweight). Safety assessment consisted of pre- and post-injection (2, 24 and 72 hours) monitoring of vital signs, physical examination, laboratory and electrocardiographic parameters. To determine sensitivity and specificity for detection of hemodynamically significant stenoses (HSS; >50% luminal reduction) MR angiograms were compared with intra-arterial digital subtraction angiography (IA-DSA), which was considered the standard of reference.

Results

In 33 patients a mean of 12.8 mL NC100150 was injected. Eleven patients reported 13 mild and 2 moderate adverse events. Five mild and one moderate adverse event were considered due to NC100150 injection. There were no significant changes in vital signs, laboratory or electrocardiographic parameters. Sensitivity and specificity (in %) for detection of HSS were 87 and 87, 56 and 96 and 75 and 94, for iliac, femoral and popliteal arteries, respectively.

Conclusions

NC100150 high-resolution steady-state MR angiography can be performed safely and is feasible for the detection of peripheral arterial HSS. Arterial-venous separation in small lower extremity arteries is challenging on NC100150 CE-MRA using currently available techniques.

Introduction

Contrast-enhanced magnetic resonance angiography (CE-MRA) of peripheral arteries has improved in recent years. The typical imaging technique employs a heavily T1-weighted three dimensional (3D) gradient echo pulse sequence, acquired during the initial arterial passage of an extracellular 0.5 molar gadolinium chelate contrast medium. The use of fast table translation enables a multi-station exam during injection of a single bolus and has generated images comparable to intra-arterial digital subtraction angiography (IA-DSA).(1-4) However, CE-MRA using an extracellular gadolinium chelate contrast agent also has limitations. The two most important limitations are the limited relaxivity of 0.5 molar gadolinium chelates (approximately 4-5 $mmol^{-1}\ s^{-1}$ at 20 MHz, 37 °C) and the rapid clearance from the arterial circulation with a half time of at the most several minutes.(5) Practically, when using a gadolinium chelate for CE-MRA this means there is only a very limited temporal window for image acquisition, which in turn places restrictions on image acquisition time and the resultant achievable spatial resolution. These limitations are particularly notable during bolus chase peripheral MRA whereby several 3D acquisitions must be tailored to accommodate the often quick arterial transit of contrast medium over several consecutively imaged stations. These disadvantages have sparked the search for other contrast media with higher T1 relaxivities which stay longer in the arterial circulation, thereby effectively increasing the temporal window for imaging and by default improving the achievable spatial resolution for CE-MRA.(6) One category of these new contrast media are ultrasmall superparamagnetic iron oxide particles (USPIOs), which are particles with a diameter in the nanometer range, which have an intravascular halflife between one and two hours and which have relaxivities several times those of extracellular gadolinium chelates.(7-10) NC100150 is an example of a contrast agent with a longer intravascular half-life (a.k.a. "blood-pool" contrast agent) and has been shown to be beneficial for CE-MRA of the coronary, renal and aortoiliac arteries.(9,10) The contrast medium exerts a relatively high T1 relaxivity (20 $mmol^{-1}\ s^{-1}$) and a weak T2 relaxivity (35 $mmol^{-1}\ s^{-1}$) (20 MHz, 37°C), making it suitable for applications which require strong T1 enhancement, such as CE-MRA.(11)

The objective of this phase II multi-center study was to test the safety and efficacy of NC100150 injection for CE-MRA of the peripheral arteries in patients with known peripheral arterial occlusive disease.

Subjects and Methods

Patients

Thirty-three patients (27 males, 6 females, mean age 61 (range 29-78 years), weight range 48-100 kg) with suspected peripheral arterial occlusive disease and complaints of intermittent claudication participated in the study. All patients were either scheduled for diagnostic IA-DSA with or without percutaneous intervention (e.g. stenting) or had undergone IA-DSA without an intervention up to six weeks before inclusion. Patients with liver problems, iron-metabolism diseases, a history of allergy and anaphylaxis and women who were breast-feeding or pregnant were not allowed to participate in the study. Women of child-bearing age underwent pregnancy testing and were only allowed to participate after pregnancy was ruled out. Institutional review boards at all participating institutions approved the study and patients were required to give full written informed consent before they were enrolled in the study.

Contrast medium and dose

NC100150 (Feruglose [Clariscan®], Nycomed Amersham, Oslo, Norway) is a preparation of ultrasmall superparamagnetic iron oxide crystals (approximately 12 nm in diameter) with an oxidised starch coating prepared as a 30 mg Fe/mL colloidal solution. Every patient received a dose of 5 mg Fe/kg bodyweight in a single injection which was immediately followed by 15-30 mL normal saline flush. All injections were given intravenously with a remote controlled MR compatible power injector (Medrad Spectris, Indianola, PA) with an injection rate not exceeding 3.0 mL/s. The dose of 5 mg Fe/kg was based on the results of phase I studies, in which this dose was found to result in prolonged and sufficient shortening of arterial T1 times (below 100 msec).(11,12)

MR imaging

Imaging was performed on a 1.5 T MR scanner (Signa CVi, GE Medical Systems, Waukesha, WI; Philips ACS NT PT6000, Philips Medical Systems, Best, The Netherlands [2 centers]; Vision Symphony, Siemens Medical Systems, Erlangen, Germany). MRA consisted of a T1-weighted 3D gradient recalled echo pulse sequence (repetition time [TR; msec] 4.9-9.5; echo time [TE; msec] 1.4-2.9; flip angle 20-50 degrees, 1 excitation) performed using either a quadrature body coil or a phased array surface coil (especially lower legs). Non-interpolated voxel sizes were chosen smaller than or equal to 1.0 mm^3 (dimensions in frequency, phase and slice encoding direction all 1.0 mm) in all steady state sequences. Acquisition times varied between 150 and 304 sec per scan. In every patient steady-state scans were made of the pelvic, upper and lower leg arteries.

Digital subtraction angiography

All patients had either undergone or were scheduled to undergo IA-DSA within a period of six weeks of the MR examination. The IA-DSAs were performed at the respective institutions according to their standard protocols. In all patients vascular access was gained through the left or right groin where the common femoral artery was punctured. Subsequently, a catheter was advanced into the infrarenal aorta from which the entire peripheral vascular tree was imaged with various amounts and flow rates of standard iodinated contrast media. In 2 out of 33 cases antegrade puncture angiography was performed and only one leg was imaged.

Safety and patient tolerance

Before any contrast material was given, the medical and surgical histories were obtained for each patient, including any medication a patient was taking at that time. At screening, less than 2 hours before injection and at 2, 24 and 72 hours post-injection, all patients underwent physical examination and standard clinical laboratory evaluations (serum chemistry, iron-metabolism, hematology, coagulation and urinalysis). At the same time-points a 12-lead electrocardiogram (EKG) was recorded. Before and after the injection of the contrast medium and at every follow-up visit to the hospital, vital signs (blood pressure, heart rate, respiratory rate, temperature) were recorded. Patients were asked to report any adverse events they experienced after injection of the compound. Adverse events were classified as mild (easily tolerated), moderate (interfering with normal activity) or severe (causing inability to perform usual work or activity). If an adverse event occurred, the site investigator who gave the drug determined the relationship with NC100150 injection. Also, any changes in laboratory values, vital signs and EKG were recorded. Scatter plots of all post-injection values of the parameters above versus baseline were generated and examined for trends and relatively large individual changes from baseline.

Data analysis

For image evaluation the peripheral arterial tree was divided into the following segments: both left and right common, internal and external iliac, superficial and deep femoral and popliteal arteries. The superficial and deep femoral arteries as well as the lower leg arteries were divided into a proximal and distal part. In a subset of patients (n=10), signal intensity measurements were made using an operator-defined region of interest in the arterial lumen, the tissue immediately surrounding the artery and outside the patient. From these data signal-to-noise ratios (SNRs) were calculated by dividing the intravascular signal intensities by the standard deviation of the measurements outside the patient. Contrast-to-noise ratios (CNRs) were calculated by subtracting the signal intensity of the tissue immediately adjacent to the artery from the intravascular signal intensity and dividing the result by the standard deviation of the measurement outside the patient. SNR and CNR values were calculated for pelvic, upper leg and lower leg arteries.

To assess the sensitivity and specificity of NC100150 for detection and grading of peripheral arterial occlusive disease, all MR scans and hardcopies of all IA-DSA exams were transferred for a central, blinded read. NC100150-enhanced MR angiograms were evaluated using maximum intensity projections (MIP), multiplanar reformation (MPR) and source images by vascular radiologists experienced in reading MR angiograms, who where unaware of the results from angiography. IA-DSA images were read by other experienced vascular radiologists who were unaware of the results of the NC100150-enhanced MR angiograms. Before stenoses and obstructions were scored the reviewer had to indicate if a vessel segment was evaluable or not. In all vessel segments for which X-ray angiography was available, the most severe stenosis was recorded on a five-point scale ranging from 0 (normal vessel), 1 (1-49% stenosis), 2 (50-74% stenosis), 3 (75-99% stenosis) and 4 (occlusion). Because of anticipated observer difficulties with the visual differentiation of arteries from veins in the lower leg using source images and commercially available post-processing techniques (MIP and MPR), the arteries below the knee were not included in the blinded reads.

Results

All patients tolerated the NC100150 injection well and no serious adverse events were reported. A mean volume of 12.8 mL of NC100150 was injected (range 8-16.7 mL) at a mean injection rate of 0.4 mL/s (range 0.1-2.0 mL/s). Eleven patients reported a total of 13 mild and 2 moderate adverse events. One of the moderate and 5 of the mild adverse events were considered by the responsible investigators at the respective institutions to have a likely relationship with the injection of the drug. There was no clear relationship between adverse events and the different injection rates. The moderate adverse event considered likely due to NC100150 injection was dizziness, starting about nine hours after injection and

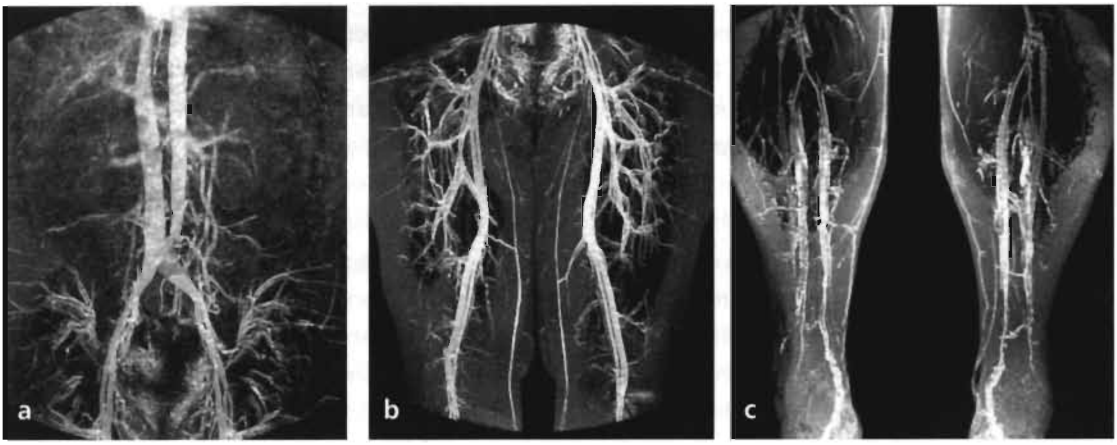

Figure 1 a,b,c Coronal, whole volume maximum intensity projections of a representative study of the abdominal and pelvic (a), upper (b) and lower leg (c) vasculature enhanced with NC100150. Arteries and veins are enhanced simultaneously with comparable intensity while background tissue is almost non-enhanced.

lasting 45 minutes. The mild adverse events considered due to the NC100150 injection were: hypoesthesia starting immediately after injection and lasting two minutes, a case of fatigue starting approximately 4 hours after injection and lasting about 4 hours, an increase in prothrombin time after two hours, an increase in coagulation time after two hours and an increase in creatinine after two hours. All increases in laboratory parameters considered related to the drug injection resolved spontaneously within 24 hours. Other adverse events, deemed unlikely due to drug injection were influenza-like symptoms (of moderate intensity), nausea, dizziness and walking difficulties after the MR exam (likely due to uncomfortable patient positioning). For the remaining five mild adverse the relationship with NC100150 injection was unknown. These adverse events were: rhinitis, increase in prothrombin time and three cases of hematuria (all at one center). Two of these three cases of hematuria resolved within the 72-hour safety follow-up period. The third case of hematuria was already present before injection of the contrast medium and remained present throughout the 72 hour follow-up period. There were no significant changes in any vital sign parameter or the EKG variables. Of all the laboratory parameters only ferritin, total iron and total iron binding capacity (TIBC) showed (expected) significant changes. Ferritin values were increased from a mean of 10.5% over baseline at 2 hours postinjection to 318% over baseline at 72 hours postinjection; total iron increased to 267% over baseline at two hours postinjection and returned to 5% below baseline at 72 hours and TIBC increased to 308% over baseline two hours post-injection and returned to 9% below baseline at 72 hours post-injection.

Of the 33 patients enrolled, the MR images of 29 patients were compared with IA-DSA. In one patient, the MR angiograms were not evaluated because the patient declined to undergo IA-DSA and thus no comparison existed. A further three patients from a single center were not evaluated because MR images were

	SNR	(SD)	CNR	(SD)
Pelvis	20	(2.6)	16	(2.4)
Upper legs	25	(3.1)	22	(2.7)
Lower legs	64	(8.7)	56	(8.4)

Table 1 Mean arterial SNR and CNR (SD) values in 10 patients

Note – In the pelvic and upper leg station the standard quadrature body coil was used and for the lower legs a dedicated quadrature phased array lower extremity coil was used. SNR = signal-to-noise ratio, CNR = contrast-to-noise ratio.

considered to be not evaluable due to too intense venous overprojection. In the 29 evaluated patients, both arteries and veins enhanced very strongly after injection of the contrast medium, with almost no enhancement of background tissue (figure 1). Results of the SNR and CNR measurements are tabulated in table 1. In 29 patients a total of 261 vessel segments were available for comparison with IA-DSA. Of these 261 segments 11 were considered not evaluable on both IA-DSA and CE-MRA and a further 18 segments were considered not evaluable on CE-MRA alone. Artefacts encountered and which rendered CE-MRA images uninterpretable were blurring of borders, local signal loss, motion artifacts, presence of surgical clips and too low resolution. The results of sensitivity and specificity analyses are tabulated in table 2. Overall sensitivity and specificity figures were 70% and 93% respectively. In figure 2 a typical example is shown of a stenosis in the iliac arteries as detected with NC100150 MRA and with the comparator IA-DSA.

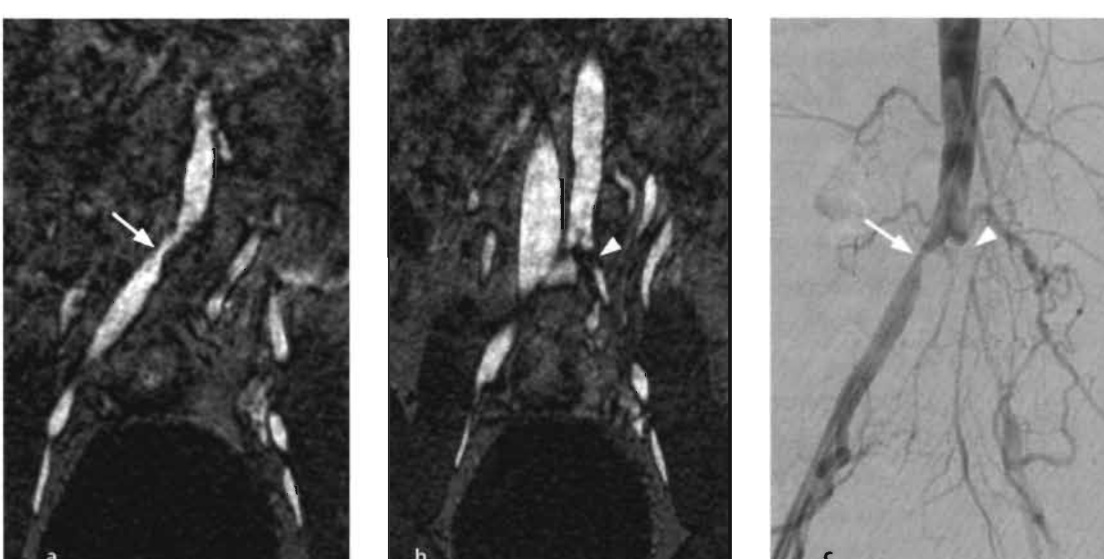

Figure 2 a,b,c Coronal source images of right iliac artery (a), left iliac artery (b) and the corresponding IA-DSA image (c) in a patient with a medium grade stenosis in the right iliac artery (arrow) and an occlusion of the left iliac artery (arrowhead) show perfect agreement with regard to location and grade of peripheral arterial disease between CE-MRA images and IA-DSA.

Table 2 Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for discriminating diseased vessel segments (50% stenosis or occlusion) from non-diseased (<50% stenosis) vessel segments

	Overall	Iliac	Femoral	Popliteal
Sensitivity (%)	70	87	56	75
Specificity (%)	93	87	96	94
PPV (%)	67	65	77	50
NPV (%)	94	96	90	98

Discussion

With this work we have shown that steady-state CE-MRA of the peripheral arteries using NC100150 as contrast agent is feasible, safe and generally well tolerated. In 33 patients no serious adverse events occurred and two adverse events of moderate intensity were reported of which one was considered due to injection of the drug. No adverse events necessitated medical or surgical treatment and all adverse events considered due to injection of NC100150 resolved within the 72 hour safety follow-up period. This compares favourably with other NC100150 clinical trials.(9,10,12)

To our knowledge this is the first study reporting on the use of a blood pool agent in humans to image the peripheral vasculature across a variety of imaging platforms and using IA-DSA as the standard of reference. The sensitivity and specificity figures for arteries below the inguinal ligament obtained in this study are lower than those with extracellular gadolinium-chelate enhanced images, which have reported sensitivities and specificities in the 85-100% range.(13) However, the major difference between the acquisition strategy reported here and the studies using extracellular gadolinium-chelates as contrast media is that the images evaluated in this study were obtained in the steady state and not during first pass of the contrast medium. The ability to image arteries during the steady state enables the acquisition of higher spatial resolution images (voxel sizes $\leq$ 1.0 mm^3) and removes the technical concerns related to the synchronization of image acquisition with arterial transit of the contrast bolus. However, the concurrent venous enhancement on steady state images presents a significant challenge to image interpretation that compromises the current ability to detect and grade peripheral arterial occlusive disease and results in a decline in overall study sensitivity for lesion detection.(14)

In vascular beds where arteries and veins can be separated visually with the aid of appropriate reformatting techniques such as maximum intensity projections and multiplanar reformations, acceptable levels of sensitivity and specificity can be achieved. For instance, for the iliac arteries we report a sensitivity and specificity of both 87% which is comparable to values obtained with extracellular agents. However, for the femoral and popliteal arteries sensitivity values lag behind those of first-pass studies using traditional extracellular contrast agents (56 and 75% for

Figure 3 Coronal source image (1.0 mm measured thickness, reconstructed to 0.5 mm) of posterior tibial artery in a patient with suspected narrowing in this vessel segment (arrow). Arteries and veins are intensely enhanced at about equal signal intensity. As demonstrated on this image, differentiation of small caliber arteries of the lower leg from adjacent veins and assessment of precise grade and length of an arterial stenosis can be extremely difficult.

the femoral and popliteal arteries, respectively). In areas with very small caliber arteries (e.g. the lower legs) or extensive venous beds surrounding them (e.g. the upper and lower legs) separation of arteries and veins can become so difficult with currently available post-processing techniques that vessel narrowing and occlusion may not be detected reliably and reproducibly. Separating arteries from veins will be even more difficult in the presence of severe disease with extensive narrowing, occlusions and collateralisation, an example of which is shown in figure 3. Because NC100150 can be administered as a bolus injection, images can also be acquired during the first arterial pass of the contrast medium and a preliminary study has shown that this approach can increase sensitivity and specificity for detection of stenoses and occlusions in patients with peripheral arterial disease. In this study (15), first pass images during injection of NC100150 were acquired after which images were acquired of the entire peripheral vascular tree in the steady state. Afterwards, the first pass information with selective arterial enhancement was used to segment arteries and veins. Using this strategy, sensitivity and specificity could be increased from 71% to 100%, 94% and 98% for the iliac, upper leg and lower leg arteries.(15) Grist et al used a similar arterial phase and steady state data acquisition scheme to segment arterial images using MS-325, a gadolinium based intravascular contrast agent.(14) An additional method for arterial-venous segmentation of equilibrium phase images is to supplement conventional T1-weighted high spatial resolution steady state images, as used in the present study, with a phase contrast technique.(16) Phase contrast MRA could preferentially differentiate arterial from venous structures based on their inherent blood flow properties.

Venous illustration in patients with peripheral arterial occlusive disease, however, is not entirely without merit. High-resolution, large field-of-view and high SNR venous images could actually assist pre-operative planning by providing the vascular surgeon with information about the suitability of autologous veins to function as bypass grafts. In clinical practice, however, image interpretation should not only be reliable and accurate but also facile and expeditious. In order to derive information about stenoses and occlusions in an easy and reproducible way, as is currently the case when using extracellular contrast media, either current post-processing techniques have to be improved (semi-automated) or new techniques will have to be developed. As mentioned, techniques which will enable the quick and reliable separation of arteries from veins could greatly improve the accuracy and thus the utility of an intravascular contrast agent for peripheral CE-MRA.

A strength of the current phase II study was that we have tested the feasibility of imaging peripheral arteries on different imaging systems, with a relatively free choice of imaging parameters and coils to be used. This indicates that NC100150 enhanced peripheral MRA can be performed on a broad range of commercially available MR imaging platforms. However, a more uniform acquisition and post-processing protocol may have yielded higher values for sensitivity and specificity.

In this phase II clinical trial of patients with peripheral arterial occlusive disease, steady-state MR angiography of the peripheral arteries using NC100150 injection was shown to safely provide excellent vessel-to-background contrast for ultrahigh sub-millimeter spatial resolution imaging. When using IA-DSA as the standard of reference and standard image interpretation techniques, sensitivity and specificity values for hemodynamically significant lesion detection in large arteries were comparable to those reported with CE-MRA using extracellular gadolinium chelate agents; but lower for lesion detection in smaller arteries below the inguinal ligament. However, experience with CE-MRA using NC100150 injection is early and further pulse sequence optimizations are necessary. Dedicated post-processing techniques for improved arterial-venous segmentation and/or the addition of first-pass acquisitions could improve for the ability to detect and grade peripheral arterial disease with NC100150, especially in arteries of very small diameter or surrounded by extensive venous networks.

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Magnetic resonance angiography detects more patent arteries than intra-arterial angiography in patients with chronic critical ischemia and tissue loss

submitted

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Abstract

Purpose

In order to prevent amputation, intra-arterial digital subtraction arteriography (IA-DSA) is the standard procedure for demonstration of arteries suitable for distal bypass grafting in patients with chronic critical ischemia and tissue loss. However, it is known to be suboptimal for this purpose in a substantial number of patients. This study aimed to assess the value of multiple station contrast-enhanced magnetic resonance angiography (CE-MRA) for demonstration of such arteries and the potential impact of CE-MRA on clinical management of these patients.

Subjects and methods

23 patients with critical ischemia and tissue loss were examined with IA-DSA (16 using a selective technique) and CE-MRA. The number and suitability for bypass surgery of arteries were assessed by two vascular surgeons in a blinded fashion. Both vascular surgeons formulated treatment plans for all patients which were compared with actual treatment which was based on all available information. Magnetic resonance imaging was done with a commercially available 1.5 T scanner. The main outcome was the number of arteries that could be detected with CE-MRA and IA-DSA.

Results

In comparison to IA-DSA, both surgeons detected significantly more arteries with CE-MRA, both above and below the knee (surgeon 1: above knee 7.0 vs 5.2 (P=.002) and below knee 5.4 vs 8.5 (P<.001); surgeon 2: above knee 5.4 vs 7.1 (P=.004) and below knee 5.9 vs 8.3 (P<.001)). Both surgeons also considered significantly more arteries suitable for bypass grafting based on the CE-MRA images (surgeon 1: 2.6 vs 4.0 (P=.003); surgeon 2: 3.2 vs 4.7 (P=.001)). In 8/23 (35%) patients the CE-MRA based treatment plans were different from those formulated based on IA-DSA and in exact accordance with actual treatment.

Conclusions

In this study CE-MRA detected more patent and graftable arterial segments in patients with chronic critical ischemia and tissue loss compared to IA-DSA and changed treatment planning in the experimental setting in a substantial number (35%) of these patients. These findings indicate the potential of CE-MRA as a usefull addition to or replacement of conventional catheter-based intra-arterial angiographic techniques in the decision making process in patients with chronic critical ischemia.

Introduction

The prevalence of symptomatic peripheral arterial occlusive disease (PAOD) is approximately 2% in the general population over 50 years of age and increases to 7% in the age group over 70 years old.(1) In most patients symptoms are limited to intermittent claudication (weakness, discomfort or pain upon exercise, relieved by resting the affected limb). A minority of patients with intermittent claudication subsequently progresses to critical ischemia; that is, the oxygen and nutrient supply of the distal lower extremity falls below the level for maintenance of normal cellular processes in resting conditions. Clinically, this is manifested by rest pain and tissue loss (i.e. non healing ulcers and gangrene).

In patients with critical ischemia, the primary aim is to provide sufficient blood flow to relieve the rest pain and heal skin lesions. This can be achieved by percutaneous transluminal angioplasty (PTA) and/or arterial reconstructive bypass surgery.(2) With technical advances in vascular surgical techniques it is now possible to successfully bypass stenoses and obstructions of the lower leg and to make distal anastomoses of bypass grafts to arteries at the level of the ankle or even in the foot.(3) For these vascular surgical reconstructions precise morphological information about degree and length of stenoses and obstructions is needed for the entire peripheral vascular tree from the infrarenal aorta down to the pedal arch of the affected limb. In current clinical practice this information is usually obtained with intra-arterial digital subtraction angiography (IA-DSA). However, there are persistent concerns using IA-DSA with regard to contrast medium toxicity (especially in patients with critical ischemia and diabetes)(4), local and systemic complications associated with the invasiveness of the IA-DSA procedure, and most important, failure to visualize patent crural and foot arteries, that are demonstrated with other modalities.(5-7)

An alternative way to map the extent of PAOD is contrast-enhanced magnetic resonance angiography (CE-MRA). With this technique arteries are imaged during intravenous bolus-injection of paramagnetic contrast medium while acquiring multiple separate MR scans in rapid succession. Several reports have shown that the diagnostic accuracy of this technique is comparable to IA-DSA for aortoiliac and femoropopliteal arteries in patients with intermittent claudication. However, the non-invasiveness and three-dimensional nature of CE-MRA offers substantial benefits over IA-DSA.(8,9) Experience with CE-MRA in patients with chronic critical ischemia is limited. Except for the encouraging study by Kreitner et al of only distal crural and pedal vessels, it is not yet clear if CE-MRA offers any advantage over IA-DSA in this patient group.(10)

The purpose of this study was to assess the potential of CE-MRA to adequately visualize arteries from the infrarenal aorta down to the foot in patients with chronic critical ischemia and tissue loss and to determine the potential impact of CE-MRA on clinical decision making.

Table 1 patient characteristics and disease severity

Sex	M/F	12/11
Diabetes mellitus	number (%)	15 (65%)
Age	years range	72 (56-86)
$TcPO_2$	mmHg (SD)	20 (22)
Absolute ankle pressure (n=13)	mmHg (SD)	45 (25.7)*
Toe pressure (n=17)	mmHg (SD)	15 (32.6)[†]
Creatinine	µmol/L (SD)	105 (43)

All clinical parameters are presented as mean values (standard deviation) except for sex and the presence of diabetes mellitus. $TcPO_2$ = transcutaneous oxygen pressure measured over the dorsum of the foot. * In 8 patients ankle pressures could not be measured reliably because of uncompressible arteries and in 3 patients no measurements were made because they were not tolerated by patients due to pain and/or the presence of wounds. [†] Toe pressures were not measured in 7 patients because of necrosis of the first digit.

Patients and Methods

Over a 9 month period (july 2000 – april 2001) 23 consecutive patients with rest pain and tissue loss due to arterial insufficiency were prospectively enrolled in the study. The criteria of chronic critical ischemia as defined in the revised version of the recommended standards for reports dealing with lower extremity ischemia (11) were fulfilled by 21/23 (91%) patients. Of the remaining two patients, one had an absolute ankle pressure of 90 mmHg and suffered from diabetes mellitus. In this patient the transcutaneous oxygen pressure measured over the forefoot of the affected limb was 67 mmHg. The second patient had extensive aortoiliac arterial disease and an absolute ankle pressure of 75 mmHg with a transcutaneous oxygen pressure of 60 mmHg. In table 1 patient characteristics are summarized. All patients underwent CE-MRA and IA-DSA within two days. The order of the examinations was dictated by availability of the MR scanner. Approval of the institutional review board had been obtained before the study was started and all patients had to sign the informed consent form before they were included in the study.

Magnetic resonance imaging

All MR arteriograms were acquired on a 1.5 T commercially available scanner (Intera, Philips Medical Systems, Best, The Netherlands; software version 7 [first 14 patients] and version 8 [last 9 patients]) with patients placed in the magnet in the supine position. For the first 20 patients a dedicated reception coil for the lower legs only (43 cm coverage) was used and for the last 3 patients a dedicated reception coil was uses for the entire lower extremity (129 cm coverage). To image the arteries of the lower extremity three independent three-dimensional (3D)

	Imaging parameters			
	inflow scan	aortoiliac station	upper legs	lower legs
TR (msec)	11	4.2-7.6	3.3-5.3	3.8-5.8
TE (msec)	6.9	1.3-1.9	1.2-1.5	1.3-1.6
Slice thickness (mm)	2.5	2.5-2.8	2.1-2.2	1.7-2.0
FOV (freq/phase; mm)	512x282	432-530/259-292	432-512/281-325	432-512/281-282
Matrix (freq/phase)	256x100	432-512/149	320-512/172-325	432-512/281-282
Duration (sec)	155	17-32	11-21	31-69
Resolution (mm^3)	NA	4.9-5.1*	2.1-4.9*	1.7-2.0*

TR: repetition time; TE: echo time; FOV: field-of-view; freq: frequency encoding direction; phase: phase encoding direction; * Actually measured voxel sizes; these voxel sizes were later reconstructed to half their size by calculating from the measured set double the number of slices

Table 2

scans for the aortoiliac, upper legs and the lower legs were used. To prescribe the spatial position of the 3D imaging volumes in relation to the arteries in the three stations, inflow-sensitive non contrast-enhanced scans lasting 30 seconds in each region were made. On the basis of these images the scanparameters were optimized for the 3D imaging volume so that anatomically tailored volumes with different imaging times and resolutions for each region could be used. For the upper and lower legs sequences were performed so that contrast sensitive information was acquired in the first part of the scans. The imaging parameters used are shown in table 2. To enhance intravascular signal, 35 mL of gadodiamide (Omniscan, Nycomed-Amersham, Oslo, Norway) was used per patient. The contrast agent was administered as a single continuous bolus in an antecubital or hand vein at a rate of 1.5-1.8 mL/sec for the first 15 mL and 0.6 mL/sec for the remaining 20 mL. Immediately after injection of the contrast material 25 mL of normal saline were administered at a flowrate of 0.4 mL/sec to flush tubing and veins. The total injection duration varied between 104-106 seconds. All injections were done using a remote controlled MR compatible injection system (Medrad Spectris, Indianola, PA, USA). Non-enhanced scans acquired before the administration of contrast material were later subtracted from the enhanced acquisitions to suppress signal from background tissue. The total procedure time per patient was between 25 and 30 minutes.

Digital subtraction angiography

All IA-DSA examinations were performed by experienced interventional radiologists. Eighteen patients were imaged with Philips Integris V5000 (Philips

Medical Systems, Best, The Netherlands) and 5 patients with Siemens Polystar (Siemens Medical Systems, Erlangen, Germany) digital angiography equipment. In 15 of 23 patients (65%) selective arteriograms were obtained by puncturing the common femoral artery of the affected limb retrogradely with a 19 gauge (1.0 mm diameter) needle and subsequently advancing a 4 French (1.35 mm diameter) endhole catheter (Cordis, Miami, FL, USA) into the external iliac artery. In 7 patients (30%) non-selective arteriograms were made by puncturing the common femoral artery contralateral to the ischemic limb and retrogradely placing a 4 French universal flush catheter in the distal infrarenal aorta. In one patient selective antegrade puncture arteriography was performed by puncturing the common femoral artery of the affected limb and advancing a 4 French endhole catheter as far distally as possible. For the latter two procedures catheters of the same manufacturer were used. The total amount of contrast medium that was used varied between 60-80 mL of Iohexol (Omnipaque, Nycomed-Amersham, Oslo, Norway) and was administered in a variable number of runs. Contrast medium was administered with a power injector (Medrad, Indianola, PA, USA). None of the 23 patients were given vasodilative drugs because it was assumed that vessels would already be maximally dilated due to the ischemia. The number of contrast injections and view angles varied per patient and were chosen by the interventional radiologist who performed the IA-DSA.

Image evaluation

Magnetic resonance arteriograms were transferred to an offline workstation where they were postprocessed in a standardized format. From the CE-MRA datasets rotational maximum intensity projections (MIPs) of the affected limb were generated at 18° increments over a total of 180°, allowing to view the datasets from multiple angles. In addition to the projectional images, source data were also available for review to confirm the findings from the MIPs. Commercially available postprocessing software (EasyVision version 4.1, Philips Medical Systems, Best, The Netherlands) could also be used to generate additional views of the vasculature. For evaluation purposes, two vascular surgeons experienced in distal arterial bypass grafting procedures and familiar with reading IA-DSAs, MR arteriograms as well as workstation software, reviewed all datasets. Hardcopies (n = 9 patients) or digital images (n = 14 patients) of the IA-DSA datasets were read on either a light-box or on a workstation. Images of all anatomical regions that were imaged were reviewed.

CE-MRA as well as IA-DSA datasets of the affected limb were retrospectively reviewed at random with at least a four-week period between the reading sessions of images of the same patient. Observers were blinded for patients' identities. When reviewing the datasets the vascular surgeons had to make an assessment of the visibility of named arteries and if visible, stenoses (50% diameter reduction) and obstructions, potential suitability for anastomosing a bypass graft (distal to the superficial femoral artery) and subjective interpretability. In every patient a maximum of 21 vessel segments were analyzed and these were: infrarenal aorta, common and external iliac, common femoral, superficial femoral (three equal parts), popliteal (three parts), anterior tibial (three equal parts), posterior tibial (two equal parts), fibular (2 equal parts), dorsal pedal and lateral plantar arteries. In addition, the tibioperoneal trunc and the pedal arch connecting the dorsal pedal and lateral plantar arteries were evaluated. Subjective image quality of the arterial segments was scored on a 4-point scale (0 = not visible, 1 = non-diagnostic, 2 = diagnostic but mediocre image quality, 3 = diagnostic and good image quality).

Formulation of treatment plans

After reviewing the images and assessing what arteries were present each vascular surgeon retrospectively formulated two separate sets of treatment plans based on IA-DSA and CE-MRA for all patients. Before treatment plans were formulated the vascular surgeons were given the patients' sex, age, creatinine level (μmol/L), transcutaneous oxygen pressure of the forefoot (mmHg), resting systolic ankle and toe pressure (mmHg), whether the patient had diabetes mellitus and the location and extent of the lower limb tissue loss. Treatment options were percutaneous intervention (e.g. angioplasty or stenting), bypass surgery, primary amputation (above or below the knee joint) or conservative (medical) treatment. In case surgery was chosen in the treatment plan the surgeon had to specify the type of surgery and the location of the intended treatment. In case arterial bypass surgery was chosen the arterial segments of proximal and distal anastomosis had to be named. All treatment decisions were recorded on standardized forms. Reviewers were blinded with regard to the identity of the patient and to the treatment decisions made by the other surgeon. To determine the potential impact CE-MRA had on the clinical management of the included patients, the separate treatment decisions based upon IA-DSA or CE-MRA were compared with the actual treatment which was based upon all clinically available information (IA-DSA, CE-MRA and any other diagnostic procedures (e.g. duplex ultrasonography)).

Statistical analysis

Interobserver agreement for the visibility of arterial segments, stenoses and occlusions were calculated separately for both IA-DSA and CE-MRA using the linear weighted kappa statistic. The indicated number of arterial segments present and, separately, the number of arterial segments suitable for bypass grafting were compared on patient level between IA-DSA and CE-MRA using the Wilcoxon signed ranks test. This comparison was repeated separately for patients that underwent selective IA-DSA. Mean subjective image quality scores per patient for IA-DSA and CE-MRA images were compared on patient level also using the Wilcoxon signed ranks test. In a separate comparison, only vessel segments depicted with both imaging modalities were compared on patient level. For all statistical tests *P* values below .05 were considered to be significant.

Results

Of the 23 attempted IA-DSA examinations 22 were successful. In the remaining patient, the IA-DSA was only done for the aortoiliac vasculature because the patient was not able to tolerate the entire examination. Concerning the CE-MRA examinations, one patient was claustrophobic and consented to undergo CE-MRA of the femoropopliteal and lower leg regions only, while his head remained outside of the magnet. In all other patients CE-MRA examinations were perfomed as planned. There were no additional side effects or adverse events associated with the CE-MRA exams.

Interobserver agreement between the two surgeons with regard to visibility and the presence of stenoses and/or occlusions yielded linear weighted kappa values of 0.76 (95% CI 0.71-0.81) for IA-DSA and 0.73 (95% CI 0.66-0.80) for CE-MRA. Comparative subjective image quality scores are shown in table 3. Both observers assessed subjective image quality of the CE-MRA images significantly better in the overall comparison (observer 1: $P<.001$; observer 2: $P<.001$). Figures 1 and 2 show representative examples of a CE-MRA examination with the corresponding IA-DSA. For the vessel-to-vessel comparison of only those arteries that were depicted with both CE-MRA and IA-DSA surgeon 1 found CE-MRA images significantly better ($P=.010$) but surgeon 2 found no significant difference ($P=.066$).

The mean number of vessel segments found with IA-DSA and CE-MRA as well as the mean number of graftable vessel segments per patient are shown in table

	Overall comparison		Vessel-to-vessel comparison	
	IA-DSA (SD)	CE-MRA (SD)	IA-DSA (SD)	CE-MRA (SD)
Surgeon 1	1.3 (0.7)	2.1 (0.4)*	2.7 (0.4)	2.9 (0.3)*
Surgeon 2	1.4 (0.6)	2.0 (0.5)*	2.6 (0.4)	2.8 (0.4)

* Significantly higher (better image quality) than IA-DSA

Table 3 Mean (SD) subjective image quality scores at patient level for both observers

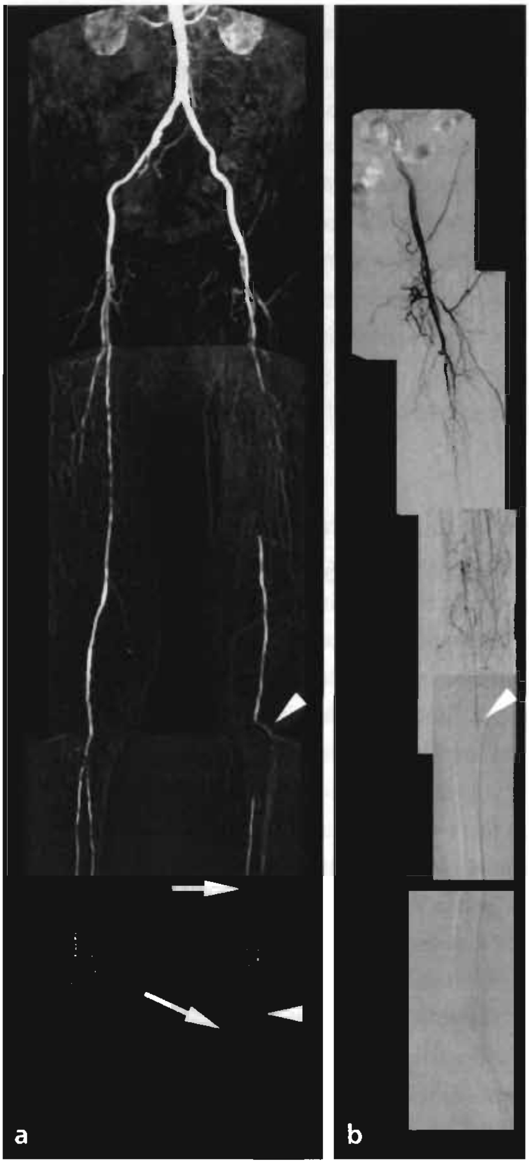

Figure 1 a,b Total outflow CE-MRA (left) and corresponding selective IA-DSA (right) in a 64-year old male diabetic patient with a necrotic ulcer on the left forefoot. Note the superior depiction of the run-off vessels in the left lower leg with CE-MRA compared to IA-DSA. Due to occlusion of the left superficial femoral artery the arteries below the knee opacify very poorly at IA-DSA except for the origin of the anterior tibial artery (top arrowhead) and some collateral vessels. In the distal lower leg and foot (lateral projection) no arteries are seen. On the CE-MRA images three lower leg arteries and their branches in the foot can be identified very clearly: the anterior tibial artery (arrowheads), the fibular artery (short arrow) and (faintly) the posterior tibial artery (long arrow).

4. With CE-MRA, both observers identified more vessel segments compared to IA-DSA. This difference was statistically significant between the two imaging techniques for above- and below-knee vessels (observer 1: P=.002/P<.001; observer 2: P=.004/P<.001). Both observers also classified significantly more vessel segments as graftable on the basis of the CE-MRA findings than on the basis of IA-DSA findings (observer 1: P=.003; observer 2: P=.001). When patients that underwent selective IA-DSA (n=16) were analysed separately, both surgeons still detected significantly more arteries above and below the knee with CE-MRA (surgeon 1: P=.004/P=.001; surgeon 2: P=.005/P=.005) and also significantly more graftable arteries (surgeon 1: P=.041; surgeon 2: P=.015). In 11 out of

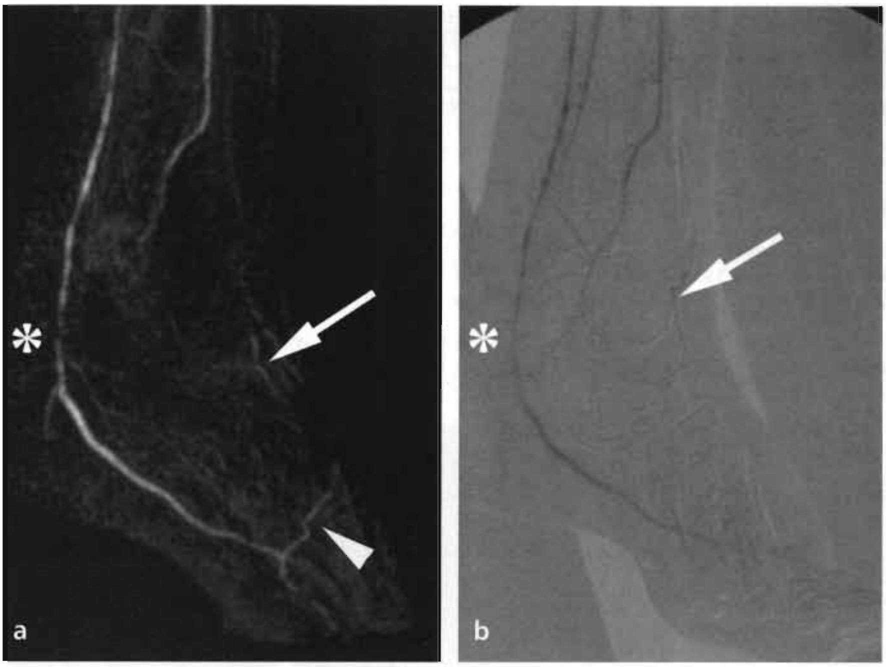

Figure 2 a,b Lateral CE-MRA (a) and IA-DSA (b) projections of arteries in the distal lower leg and foot in an 85-year old male diabetic patient with a necrotic ulcer on the right lower leg. On the CE-MRA image the pedal arch (arrowhead) connecting the plantar arteries with the dorsalis pedis artery is better visualized than on the IA-DSA image. The dorsal pedal artery (arrow) can be seen on both images. Because of the high resolution MR imaging protocol used for the lower leg and foot, disease severity as seen with the two different imaging modalities matches perfectly (asterisk), indicating the robustness of the CE-MRA technique.

23 patients (48%) both observers detected at least one vessel segment with CE-MRA that they considered graftable and that was not visible on IA-DSA.

Actual treatment of the 23 patients included in the study was PTA in seven patients (once in common iliac artery; 6 times in superficial femoral artery), bypass surgery in 10 patients and conservative treatment in six patients. In the group that underwent radiological interventions one patient underwent amputation below the knee within a 30 day-period after PTA. In the surgically treated group 3 patients underwent amputation (2 below- and 1 above-knee) within 30 days. In the conservatively treated group one patient had died after 30 days.

In table 5 the treatment decisions as made in the experimental setup by both surgeons are compared with each other and with the actual treatment the patients received. In 8 out of 23 patients (35%) CE-MRA changed or modified the decision made by both surgeons on the basis of the IA-DSA images alone in the experimental setup (figure 3). Five of these eight patients underwent selective IA-DSA. In two patients bypass surgery was abandoned in favour of radiological intervention, in one patient a foreseen amputation was changed to arterial bypass

	Mean number (SD) of segments visible (above knee/below knee)*		Mean number (SD) of vessel segments considered graftable†	
	IA-DSA	CE-MRA	IA-DSA	CE-MRA
surgeon 1	5.2 (2.1)/5.4 (2.8)	7.0 (1.6)‡/8.5 (1.8)‡	2.6 (2.6)	4.0 (2.7)‡
surgeon 2	5.4 (2.0)/5.9 (2.8)	7.1 (1.6)‡/8.3 (2.2)‡	3.2 (2.5)	4.7 (2.7)‡

The maximum number of arterial segments above the knee (defined as above tibial plateau) was 8 and the maximum number of segments below the knee was 13; † Graftability was assessed for all vessel segments considered present distal to the superficial femoral artery; ‡ significantly higher (more vessel segments) than IA-DSA.

Table 4 Number of vascular segments visible and potential graftability at patient-level for both observers

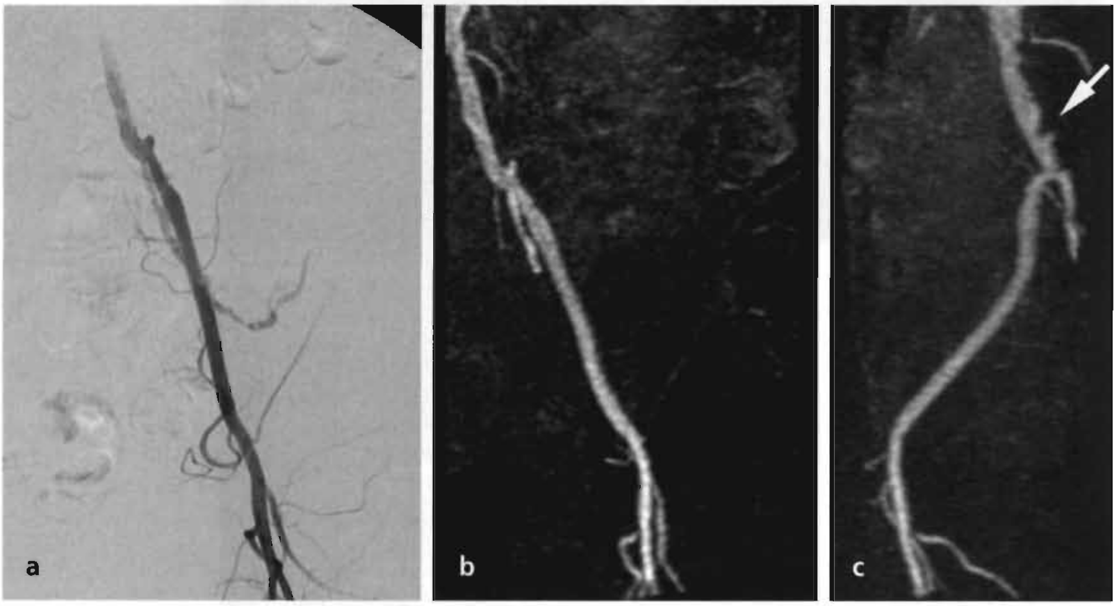

Figure 3 a,b,c Detail of IA-DSA and CE-MRA in a 56-year old female patient with a necrotic ulcer on the left foot. In the left panel (a) a coronal view of the IA-DSA of the left external iliac and common femoral arteries is shown. In the middle panel (b) the corresponding view of the CE-MRA is shown. Note that, although smaller, first and second order branches can be better seen on the IA-DSA due to the superior in-plane spatial resolution. However, on the coronal CE-MRA (b) the distal part of the common iliac artery is also opacified (upper left corner). In the right panel (c) a sagittal view is seen of the distal common iliac artery which was rendered from the same dataset as image (b). There is a stenosis in the common iliac artery of about 60% luminal reduction (arrow), which was missed at IA-DSA.

surgery, in one patient amputation was changed to conservative treatment, in one patient amputation was converted to radiological intervention and in three patients the site of the distal anastomosis at bypass surgery was changed on the basis of the CE-MRA findings. The initial outcome (at 30 days after intervention or imaging) of the patients in which the treatment decision was altered by CE-MRA was that two patients had undergone amputation. The overall limb salvage rate was 78% (18/23 patients) at 30 days post-imaging or intervention.

Patient	surgeon 1		surgeon 2		actual treatment	change by CE-MRA
	IA-DSA	CE-MRA	IA-DSA	CE-MRA		
1	bypass	bypass	bypass	PTA	bypass	no
2	conservative	PTA	conservative	PTA	conservative	no
3	conservative	PTA	conservative	PTA	conservative	no
4	bypass	conservative	bypass	conservative	bypass	no
5	conservative	PTA	PTA	PTA	conservative	no
6	conservative	PTA	PTA	PTA	PTA	no
7	bypass	PTA	PTA	PTA	bypass	no
8	conservative	bypass	conservative	bypass	conservative	no
9	bypass	bypass	bypass	bypass	conservative	no
10	bypass	bypass+PTA	bypass	bypass+PTA	bypass	no
11	amputation	PTA	amputation	PTA	PTA	yes
12	bypass	bypass	bypass	bypass	bypass	yes, changed anastomosis
13	PTA	PTA+bypass	bypass	PTA	PTA	no
14	PTA	PTA	PTA	bypass	PTA	no
15	bypass	PTA	bypass	PTA	PTA	yes
16	conservative	bypass	bypass	bypass+PTA	bypass	no
17	bypass	PTA	bypass	PTA	PTA	yes
18	amputation	bypass	amputation	bypass	bypass	yes
19	amputation	bypass	amputation	bypass	conservative	yes
20	bypass	conservative	bypass	conservative	bypass	no
21	PTA	PTA	PTA	PTA	PTA	no
22	bypass	bypass	bypass	bypass	bypass	yes, changed anastomosis
23	bypass	bypass	bypass	bypass	bypass	yes, changed anastomosis

Table 5 Treatment decisions by both vascular surgeons versus actual treatment

Discussion

In this study CE-MRA detected more patent and graftable arterial segments in patients with chronic critical ischemia and tissue loss compared to IA-DSA and changed treatment planning in the experimental setting in a substantial number (35%) of these patients. These findings indicate the potential of CE-MRA as a usefull addition to or replacement of conventional catheter-based intra-arterial angiographic techniques in the decision making process in patients with chronic critical ischemia. According to the transatlantic intersociety consensus

(TASC) document precise anatomical information is needed with regard to degree and length of stenoses and occlusions when an intervention is considered.(12) Information about vessel patency is of prognostic value in patients with PAOD because it determines what treatment options are available and because it correlates with short and long term outcome after intervention.(13)

The results of the current study corroborate those of Owen et al who used a non contrast-enhanced (inflow or time-of-flight) MR angiographic technique. In their study 22% of the run-off vessels detected by magnetic resonance angiography were not seen on conventional X-ray angiography.(7) However, of the 23 patients studied only 11(48%) had critical ischemia and tissue loss, compared with 21/23 (91%) in the current study. This means that in the current study patients suffered from more severe PAOD, which strengthens the results. In addition, it is not clear if the previous version of the strict criteria of Rutherford (14) were used to define the presence of critical ischemia. Finally, it is well known that time-of-flight MR angiography suffers from artefacts that may cause overestimation of the severity and length of stenoses. Furthermore, it is very time consuming because of inherent technical limitations.(15) For a complete inflow and outflow examination up to two hours are needed, making the technique potentially less suitable for patients with rest pain that are unable to keep the ischemic leg perfectly still during the entire examination. However, in the current study we applied the advantages of the faster and easier CE-MRA technique and were able to obtain diagnostic CE-MRA examinations in all but one aortoiliac region in one patient. The results we report here are also in accordance with a study by Kreitner et al which showed that CE-MRA detected up to 40% more patent vessel segments at the level of the distal lower leg and foot in patients with diabetes suffering from chronic critical ischemia (Rutherford grade III ischemia).(10) However, in that study images were obtained of the distal calf and foot vessels only whereas in the present study magnetic resonance arteriograms of the entire ischemic limb and the infrarenal aorta were obtained in all but one patient. Depiction of the proximal vascular tree is important because of the high prevalence of atherosclerotic lesions at multiple levels in the peripheral arterial tree in this patient category. Precise knowledge about inflow status is clinically important because patency rates after distal interventions decline if inflow is limited.(12,13) In the current study we found additional lesions in the common iliac artery and aorta in 5 patients which were not seen on IA-DSA because these vessel segments were not depicted due to the use of selective imaging (figure 3).

In addition to detecting more patent vessel segments with CE-MRA, the two observers also considered more vessel segments suitable for bypass grafting. Both vascular surgeons detected vascular segments on the MR arteriograms that were considered graftable and that were not seen at all on IA-DSA. The important implication of this observation is that part of the additional vessel segments identified are not severely diseased and have the potential to modify patient management. Potentially, this may lead to higher limb salvage rates. The reason why additional vessel are visualized by CE-MRA compared to IA-DSA is not precisely known but an explanation may be suboptimal IA-DSA technique. Preferably, all patients with chronic critical ischemia in which demonstration of distal arteries is necessary prior to revascularisation should undergo selective injection into the ipsilateral external iliac artery or antegrade puncture angiography.(16) In the current study this was the case in 16/23 (70%) patients, but even in this group CE-MRA detected significantly more and graftable arteries in the opinion of two vascular surgeons and in 5/16 (31%) patients that underwent selective IA-DSA treatment was changed. Also, no vasodilating agent was used during the IA-DSA procedures because of the assumption that the chronic critical ischemia had already caused maximum dilatation of lower leg arteries. It is possible that the number of detectable vessel segments may have been higher under medical vasodilation, although this is subject to debate because giving vasodilators may produce worse IA-DSA images due to a steal effect.(17) Further, contrast kinetics in relation to image acquisition is fundamentally different with CE-MRA. Data acquisition takes several orders of magnitude longer and may be less sensitive than IA-DSA in relation to contrast bolus duration since information about image contrast is collected over the entire scanning period. An additional explanation for the difference in vessel segments found may be that iodinated contrast media can cause vasoconstriction, as is known from studies in rats.(18)

Despite the fact that the mechanism of visualization of additional vessel segments is not precisely known, this study again raises the important point that routinely performed IA-DSA is apparently not the most sensitive modality to visualize runoff arteries in patients with chronic critical ischemia. In a recent study by Wilson et al duplex ultrasonography also detected more patent lower leg and crural vessels than IA-DSA.(6) On the basis of the current study and previously published studies we believe that when no patent runoff arteries are seen on IA-DSA the limitations of this technique should be kept in mind.

A key issue for acceptance of a diagnostic test is that different observers come to the same conclusion on the basis of the test results. An important result of this study is that we found a kappa value of 0.76 for detection and grading of disease with IA-DSA and a value of 0.73 with CE-MRA. This indicates that interobserver variation is similar for IA-DSA and CE-MRA, and that although low, these diagnostic tests are apparently not unambiguous.(19) Overall and vessel to vessel comparison of image quality of the magnetic resonance arteriograms versus the X-ray arteriograms yielded significantly higher values for CE-MRA. We believe the reason for this finding is that with IA-DSA more vessel segments are classified as being of only mediocre quality or even non-diagnostic because of impaired filling of arteries, cortical overprojection or a limited number of projections obtained. Although it is a subjective measure, high image quality may expedite review and increase confidence with regard to the absence of artifacts.

The CE-MRA technique we used makes optimum use of the high signal-to-noise and threedimensional spatial resolution capabilities of a state-of-the-art magnetic resonance scanner. This is achieved by combining dedicated surface coils, the intravenous injection of a gadolinium-chelate contrast medium and the use of flexible scanning parameters for aortoiliac, upper and lower leg arteries.(20) Because multiple field-of-views were imaged, this means that distal arteries with a small diameter could be scanned at higher resolution than large, proximal arteries. If the same scanning parameters were used for all regions, resolution had to be compromised and much more venous enhancement was probably seen in the lower legs. This would have adversely affected image quality because venous enhancement is well known to disturb image interpretation of magnetic resonance arteriograms, especially in patients with diabetes and tissue loss.(21)

How can the findings of this study affect the management of patients with chronic critical ischemia? In a growing number of vascular surgical centers there is an increasing tendency to attempt arterial reconstructive bypass surgery to vessels at the level of or below the ankle. Patency rates of these bypasses are influenced to a large extent by the presence of adequate outflow vessels and the material used to construct the conduit.(2,13) Thus, an important consideration in the decision if a patient is otherwise eligible for distal bypass surgery is the detection of suitable outflow vessels and a technique with a high sensitivity for finding these vessels should be used. In retrospective analysis, there were 8 patients (35%; 5 with selective IA-DSA) for which both vascular surgeons independently proposed identical treatment plans on the basis of CE-MRA that matched the actual treatment received. The experimental setting of the treatment decisions makes it difficult, however, to quantify the exact influence of CE-MRA on the decision making process. In clinical practice CE-MRA and IA-DSA are likely to be read by a surgeon and a radiologist together and a treatment decision is usually taken by a team of experts (e.g. interventional radiologists and vascular surgeons) in consensus. In addition, other elements that influence the decision making process such as operative risk due to concommitant disease or patient preference were not taken into account in the experimental setup of this study. Despite these limitations, CE-MRA detected more vessel segments in the critically ischemic limbs this study and it is most likely that in clinical practice treatment is indeed influenced. If the currently considered standard of reference, (selective) IA-DSA, fails to identify distal runoff vessels in patients with chronic critical ischemia there is a substantial chance that CE-MRA will detect additional outflow vessels that may be suitable for reconstruction.

Despite these encouraging results our study also has limitations. A shortcoming of this study is that we did not use another standard of reference with regard to the visualisation of the vessel segments. Approaches that have been used by others to determine more definitively if arteries detected with other imaging modalities than IA-DSA were indeed patent are intraoperative angiography, surgical exploration of vessels and/or completion angiography after construction of arterial bypass grafts.(7,10) On the other hand, the weak point of these validation strategies is that they require pathology amenable to surgical treatment in order to be applied.

In conclusion, CE-MRA can detect more patent runoff vessels deemed suitable for arterial bypass surgery than (selective) IA-DSA in patients with chronic critical ischemia. CE-MRA potentially changes or modifies the treatment decision taken in a substantial number of these patients. CE-MRA should be part of the clinical workup of patients with chronic critical ischemia when (selective) IA-DSA does not show distal runoff vessels. If the use of CE-MRA in diagnosis and treatment planning leads to lower amputation rates in the long term compared to the current situation remains to be determined.

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The comparative accuracy of color duplex ultrasonography and contrast-enhanced magnetic resonance angiography for the diagnosis of peripheral arterial occlusive disease

submitted

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Abstract

Introduction

Recent studies indicate that contrast-enhanced magnetic resonance angiography (CE-MRA) and color duplex ultrasonography (DU) are reliable alternatives to invasive diagnostic X-ray arteriography for the diagnosis of aortoiliac and femoropopliteal peripheral arterial occlusive disease (PAOD). Little is known about the comparative accuracy of CE-MRA and DU, especially in the same populations. In this study we prospectively compared the accuracy of both imaging modalities in a large cohort of patients in comparison to X-ray arteriography as the standard of reference.

Methods

CE-MRA and DU were performed in 302 patients referred for diagnostic and preinterventional workup of PAOD. Magnetic resonance angiograms were acquired during intravenous injection of gadolinium and were reviewed twice for the presence or absence of ≥ 50% luminal reduction which indicated hemodynamic stenosis. At DU a peak systolic velocity ratio ≥2.5 indicated hemodynamic stenosis. Primary outcome measures were the interobserver variation between the two CE-MRA reads and the difference in sensitivity and specificity for detection of a hemodynamic stenosis as seen on X-ray arteriography.

Results

There were 257 patients with each one or more hemodynamically signifant lesions on either CE-MRA or DU or both. 166 patients underwent X-ray arteriography. The kappa value for detection of greater than 50% stenosis on CE-MRA was 0.80. Sensitivity of DU was 71% and specificity 94%. Sensitivity and specificity of CE-MRA were 85% and 97%. Sensitivity of CE-MRA was significantly higher (P=.001); specificities did not differ significantly (P=.12).

Conclusions

This prospective comparison between CE-MRA and DU provides evidence that CE-MRA is a highly accurate, reproducible and more sensitive method than DU for the diagnosis and preinterventional workup of PAOD.

Introduction

The diagnosis of peripheral arterial occlusive disease (PAOD) can be made with near certainty on the basis of the typical history, physical examination and resting and post-exercise ankle-brachial index (ABI) measurements.(1,2) About 5% of patients presenting to medical attention with intermittent claudication will eventually undergo endovascular or surgical treatment.(2) In the US alone, over 100,000 patients annually undergo percutaneous or surgical treatment for PAOD.(3) The major determinants of the available treatment options are the precise location, length and severity of the atherosclerotic lesion.(2)

To determine the location, length and severity of aortoiliac and femoropopliteal stenoses and obstructions color duplex ultrasonography (DU) is a widely used tool. It was developed in the 1980s to avoid invasive intra-arterial angiography with its associated local and systemic complications and to provide direct physiological information about affected arteries in patients with PAOD. Reported sensitivity and specificity of DU for detection and grading of PAOD are generally high, ranging from 70-90%.(4) In recent years contrast-enhanced magnetic resonance angiography (CE-MRA) has been developed as an alternative imaging modality to assess peripheral arterial anatomy prior to an intervention.(5-7) Despite the widespread acceptance of CE-MRA no definite proof exists of the efficacy of this method as a screening tool for PAOD. Thus far, mainly studies that have compared CE-MRA with intra-arterial digital subtraction angiography (IA-DSA) in patients already referred for IA-DSA have been reported (8,9) and there are limited data available on the comparative accuracy of DU and CE-MRA for the diagnosis of PAOD, especially in the same patient group.

The aims of this study were to assess the interobserver variability for detection and grading arterial stenoses and obstructions with CE-MRA in a large cohort of patients with PAOD and to prospectively compare the diagnostic accuracy of DU and CE-MRA for the diagnosis of PAOD. IA-DSA was considered the standard of reference.

Methods

Study design

Patients were eligible for inclusion if they had complaints of intermittent claudication, rest pain or tissue loss and were referred for DU by their vascular surgeon. Referral for DU was based on history and physical examination (typical skin changes, audible bruits in the groin or over the abdominal aorta, palpation of lower extremity pulses and diminished/absent pulsations on pocket doppler). All included patients underwent ankle-brachial index measurements, DU and

CE-MRA. If either DU or CE-MRA or both tests were positive for the presence of a treatable stenosis (≥50% luminal reduction) in the aortoiliac or superficial femoral arteries IA-DSA was recommended, and was considered the standard of reference. For medical ethical reasons patients with negative test results on both DU and CE-MRA did not undergo the standard of reference and were assumed to have no treatable lesions. We expected treatable lesions in the aortoiliac and superficial femoral arteries in 55% of the patients and assumed that in 20% of patients DU and CE-MRA would differ for the presence of such lesions. A minimum difference in sensitivity between DU and CE-MRA of 10% was considered clinically significant. At a significance level of 0.05 (two-sided) and a power of 80%, target enrollment was set at 300 patients. The study was approved by the institutional review board and all patients signed informed consent before participating in the study.

Duplex Ultrasonography

DU examinations were performed by qualified, experienced vascular technologists, blinded for the findings of CE-MRA using Aloka 2000 or 5500 (Aloka Co., Tokyo, Japan) color duplex ultrasound devices. The abdominal aorta, common and external iliac and common femoral arteries were insonated using a 5 MHz convex transducer. Patients were asked to fast 8-9 hours before the examination. In the presence of excessive bowel gas or obesity a 3.5 MHz convex transducer was used. If the superficial femoral arteries were scanned a 7.5 MHz linear transducer was used. In every vessel segment the peak systolic velocity ratio (PSVR) was measured and classified on a 5-point stenosis scale. In the aortoiliac and common femoral arteries the end diastolic velocity was also measured. The different categories were: 1) PSVR < 1.5 for 0-19% stenosis; 2) 1.5 ≤ PSVR < 2.5 for 20-49% stenosis; 3) PSVR ≥ 2.5 for 50-74% stenosis; 4) PSVR ≥ 2.5 and end diastolic velocity > 60 cm/s for 75-99% stenosis and 5) no doppler signal for occlusion. For the superficial femoral artery no differentiation was made between 0-19 and 20-49% stenosis and between 50-74 and 75-99% stenosis.

CE-MRA

All MR acquisitions were done with a commercially available whole-body 1.5T MR scanner with standard hardware and software (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands). To depict the aortoiliac and peripheral arteries a stepping table approach was used. With this scanning technique high-resolution three dimensional (3D) images of the peripheral arterial system from the abdominal aorta down to the ankles were obtained making by three separate volumetric acquisitions (for the aortoiliac, upper and lower leg arteries) in rapid succession. Full technical details of the CE-MRA scans are available in chapter 3.(10) To enhance intravascular signal every patient was injected a standard dose of 35 mL of 0.5 mmol/mL gadolinium-DTPA (Magnevist, Schering, Berlin, Germany). Contrast medium was administered with an MR compatible power injector (Medrad, Indianola, PA, USA) as a single continuous bolus at rates which varied between 0.4 to 1.8 mL/s. After image acquisition CE-MRA images were transferred to a dedicated postprocessing workstation.

Digital subtraction angiography

All IA-DSA examinations were supervised by experienced interventional radiologists and were done on standard digital subtraction angiography equipment. Arteriograms were made using a 4 French universal flush catheter (Cordis, Miami, FL) placed in the distal infrarenal aorta. Contrast medium (Iohexol, Omnipaque, Nycomed Amersham, Eindhoven, The Netherlands, 300 mg I/mL) was injected with a flowrate ranging from 4 to 12 ml/sec for a total of 50-175 mL. In 13 patients antegrade angiography was performed using a 5 French sheath (Cordis, Miami, FL). The total amount of contrast medium used in these cases varied between 60-80 mL. The IA-DSA datasets were read in consensus by two observers after inclusion of the study had ended.

Image evaluation

For both CE-MRA and IA-DSA the presence of stenoses and obstructions were recorded in those vessel segments that were also imaged with DU. The following vessel segments were evaluated: infrarenal aorta, common and external iliac (evaluated as a single vessel segment), common femoral and superficial femoral arteries. The common and external iliac arteries were evaluated as a single vessel segment because the presence of a stenosis in either vessel would lead to the same treatment. In every vessel segment only the most severe stenosis was recorded. Severity of stenoses was classified on the same 5-point scale as with DU and were calculated by dividing the luminal diameter at maximum stenosis by the luminal diameter of the closest adjacent normal vessel diameter. For evaluation of CE-MRA data, coronal, sagittal and rotational maximum intensity projections (MIPs) were available. Rotational MIPs were generated at 30° increments from 0° to 150° for a total of 6 projections, allowing to view the vasculature from multiple angles. For IA-DSA, standard anteroposterior views were obtained for all vascular regions. For the aortoiliac region additional left and right anterior oblique projections at 25° were obtained.

To determine interobserver agreement, all CE-MRA datasets were read twice. Four observers, experienced in reading MRA datasets assessed grade of atherosclerotic lesions in the vessel segments as defined previously. Every observer was blinded for the results from the other observers, the results of DU and of IA-DSA. No dataset was read twice by the same observer.

Different results from DU and CE-MRA with regard to stenosis classification in a vessel segment were considered discrepancies and were classified as minor and major. Discrepancies were considered minor when DU and CE-MRA both indicated a non-significant or significant stenosis but of different degree (e.g. DU indicating 75-99% stenosis and CE-MRA indicating 50-74% stenosis). Major discrepancies were those that signified a change in patient management; i.e. the difference between less than or more than 50% stenosis. For all major discrepancies of 2 or more stenosis categories that had IA-DSA available as the standard of reference, the reason for discrepancy was retraced.

Statistical analysis

The McNemar test was used to test for significant differences in sensitivity and specificity between DU and CE-MRA on vessel segment level. Ninety-five percent confidence intervals of sensitivity and specificity were calculated using the binomial distribution. Agreement between the two CE-MRA readings was expressed by the linear weighted kappa statistic.(11) To test whether there was a difference in the distribution of delay times between DU and the CE-MRA for patients with and without major discrepancies the Mann-Whitney test was used. *P*-values below .05 were considered to indicate statistical significance.

Results

Patients

From September 1997 to June 2001, 1430 patients were referred for aortoiliac and/or superficial femoral DU. Patients referred for follow-up of an intervention (n=327) and those that participated previously (n=45) were excluded from participation. Of the remaining 1058 patients, 396 were contacted by taking a random sample of names from the vascular laboratory agenda every week. We were not able to include consecutive patients because we could accommodate a maximum of 5 patients per week on our MR scanner. Of those contacted, 94 patients did not participate in the study. Reasons for non-participation were: claustrophobia (n=9), pacemaker (n=6), other metal implants (n=2), not available when scanner available (n=8) and non-willingness (n=69). A total of 302 of the contacted

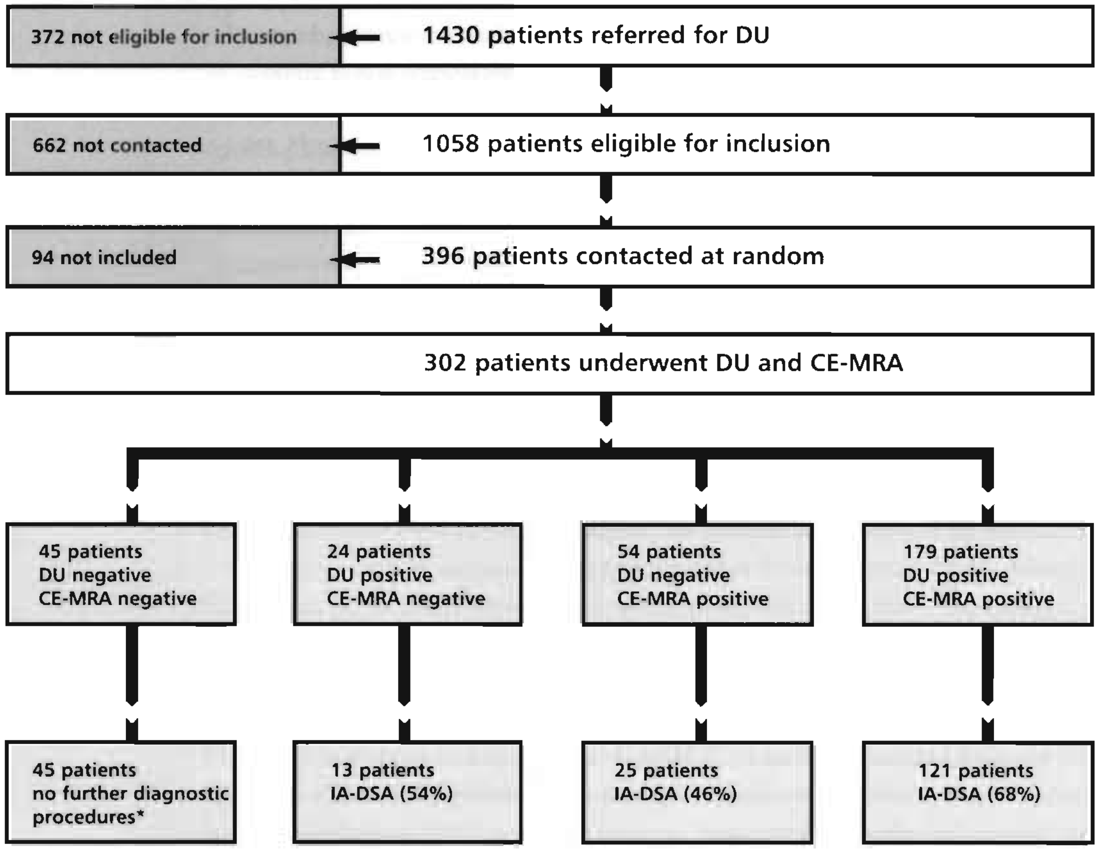

*Figure 1 DU: duplex ultrasonography; CE-MRA: contrast-enhanced magnetic resonance angiography; "positive" indicates presence of a ≥ 50% lesion in any vessel segment; * seven patients underwent IA-DSA for a lesion located distal to the superficial femoral artery (in these patients DU of these arteries was not done and was considered "negative").*

patients were enrolled in the study and underwent both DU and CE-MRA. Figure 1 shows the patient flow diagram. A typical example is shown in figure 2. The sequence of the imaging procedures was determined by availability of the MR scanner. There were 97 women (32%) en 205 men (68%) with a mean (± SD) age of 63 ± 10 years (range, 39 to 87). Disease severity, mean resting and post-exercise ABI of symptomatic extremities and risk factors are listed in table 1.

Results of DU and CE-MRA

All 302 patients underwent CE-MRA and DU without side-effects. The mean delay (± SD) between DU and CE-MRA was 1.0 ± 15 days (range 60 days before to 63 days after CE-MRA). In addition to aortoiliac DU, 99 extremities (49 right; 50 left) also underwent superficial femoral DU. In 257 patients we found at least one hemodynamically significant lesion per patient. One-hundred and sixty-six of

Characteristic	Total (n=302)	IA-DSA (n=166)	no IA-DSA (n=136)
Mean age (years; SD)	63 (10)	63 (10)	63 (10)
males (%)	205 (68)	107 (64)	98 (72)
Ankle-brachial index (n= 456 symptomatic extremities)			
Mean resting ABI (SD)	0.64 (0.18)	0.61 (0.18)	0.68 (0.19)
Mean post-exercise ABI (SD)	0.45 (0.22)	0.41 (0.22)	0.49 (0.23)
Disease Severity* (% of all patients†)			
Grade 0 Mild claudication	76 (25)	32 (19)	44 (32)
Grade I Moderate/Severe claudication	209 (69)	120 (72)	89 (65)
Grade II chemic rest pain	12 (4)	10 (6)	2 (1)
Grade III Tissue loss	5 (2)	4 (2)	1 (1)
Risk Factors (% of all patients†)			
Smoking	181 (60)	96 (58)	85 (63)
Diabetes mellitus	51 (17)	31 (19)	20 (15)
Hypertension	148 (49)	80 (48)	68 (50)
Hyperlipidemia	166 (55)	93 (56)	73 (54)
Symptomatic coronary artery disease	112 (37)	61 (37)	51 (38)
Symptomatic carotid artery disease	36 (12)	17 (10)	19 (14)
Creatinin elevation (> 125μmol/L)	30 (10)	8 (5)	22 (16)

* According to the revised edition of the recommended standards for reports dealing with lower extremity ischemia. (18) †Due to rounding errors percentages may not total to 100

Table 1 Disease severity, risk factors and concommitant disease

these patients (65%) underwent IA-DSA (figure 1). Although all patients with a hemodynamically significant lesion were due to undergo IA-DSA, this was not the case in 91 patients because the vascular surgeon thought conservative treatment (i.e. medical therapy and walking exercise) was the preferred therapy (for instance in patients with a long superficial femoral artery occlusion) or they declined to undergo invasive imaging and treatment. Because not all patients with stenoses on DU and/or CE-MRA underwent IA-DSA as the standard of reference we tested for but did not find a significant difference with regard to age, sex, resting and post exercise ankle brachial index between the patients that underwent IA-DSA and patients that did not (table 1).

Fourteen hundred and forty-five corresponding vessel segments were depicted with DU and CE-MRA in 302 pts. There were 643 corresponding aortoiliac and superficial femoral vessel segments available for comparison between DU, CE-MRA and IA-DSA in 166 patients. The number and grade of lesions found with DU, CE-MRA and IA-DSA is shown in table 2.

	Stenosis severity (%)					% in exact agreement with IA-DSA
	0-19	20-49	50-74	75-99	100	
Aortoiliac (n=589)						
DU	282	175	69	34	29	59
CE-MRA	348	100	94	16	31	77
IA-DSA	362	85	88	20	34	NA
Superficial femoral (n=54)						
DU	21[†]	NA	10[‡]	NA	23	89[†‡]
CE-MRA	17	3	7	2	25	94[†‡]
IA-DSA	16	1	10	1	26	NA
Overall (n=643)						
DU	299	179	79	34	52	60
CE-MRA	365	103	101	18	56	77
IA-DSA	378	86	98	21	60	NA

† no distinction is made between 0-19 and 20-49% stenosis ; ‡ no distinction is made between 50-74 and 75-99% stenosis; NA: not applicable

Table 2 Number and grade of lesions found with DU, CE-MRA and IA-DSA for vessel segments for which IA-DSA was available as the standard of reference for DU and both MRA reads

Interobserver agreement between CE-MRA reads

The linear weighted kappa value over the five categories of stenosis between both CE-MRA reads was 0.80 (95% CI: 0.78-0.83). The kappa value between the CE-MRA reads for the agreement concerning the presence of a more than or less than 50% stenosis was 0.84 (95% CI: 0.79-0.88).

Accuracy of DU and CE-MRA in comparison to the standard of reference

Because not all patients underwent the standard of reference, sensitivity and specificity based on validated patients only may be too high. In order to correct for this we assumed that 1) patients with negative results on both CE-MRA and DU were true negatives and 2) in the patients with either DU or CE-MRA or both tests positive for the presence of disease but that did not undergo IA-DSA the prevalence of diseased vessel segments as determined on IA-DSA was the same as in the validated patients. In order to estimate the absolute values of sensitivity and specificity for all patients the rate of true positive (TP), true negative (TN),

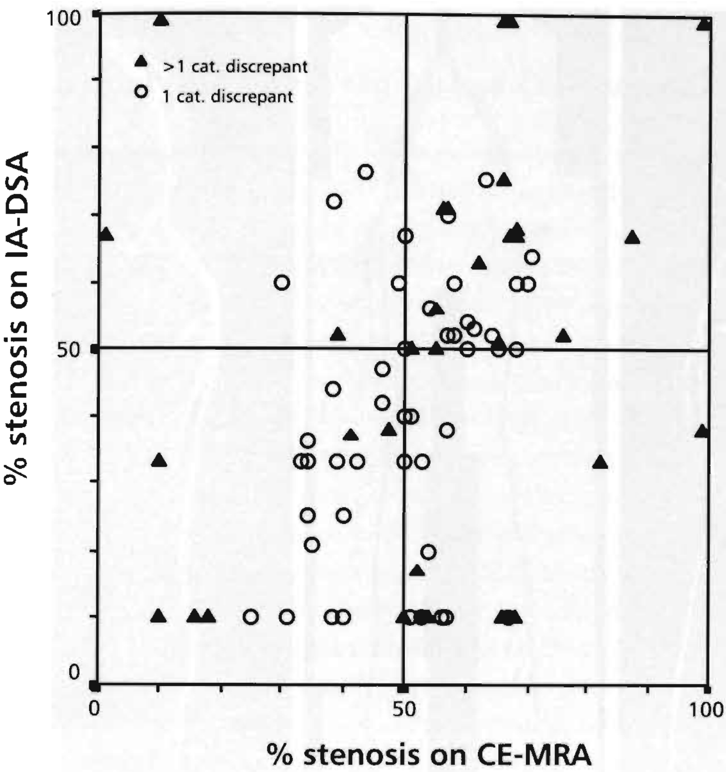

Figure 3 *Every point represents a major discrepancy between DU and CE-MRA, where IA-DSA is available as the standard of reference (vessel segments where DU and CE-MRA agreed for the category of stenosis or vessel segments where DU and CE-MRA showed a minor discrepancy are not shown in this figure). Points in the left upper and right lower quadrants are discrepancies where DU was in agreement with the standard of reference. Points situated in the left lower quadrant and right upper quadrant are discrepancies where MRA was in agreement with the standard of reference. The percentage of stenosis measured on CE-MRA was taken as the mean of the two reads when both reads were discrepant with DU; in case only one CE-MRA read was discrepant with DU the percentage of stenosis from that single read is shown.*

false positive (FP) and false negative findings (FN) determined for the three different test combinations of DU and CE-MRA (DU positive and CE-MRA negative; DU negative and CE-MRA positive; both DU and CE-MRA positive) were extrapolated to the patients that did not undergo IA-DSA. In table 3 these absolute numbers of TP, TN, FP and FN for patients that underwent IA-DSA and, the estimated numbers of TP, TN, FP and FN for all 302 patients are listed in crosstables.

Estimated absolute sensitivity and specificitiy for detection and grading of hemodynamically significant stenoses were 71%/94% for DU and 85%/97% for CE-MRA. The difference in sensitivity between DU and CE-MRA was statistically significant (P=.001). The specificities of DU and CE-MRA were not significantly different (P=.12).

Table 3 *Absolute numbers of TP, TN, FP and FN for patients that underwent IA-DSA and estimated numbers of TP, TN, FP and FN for all 302 patients*

	patients with IA-DSA (n=166)					patients (n=302)			
	IA-DSA+		IA-DSA-			IA-DSA+		IA-DSA-	
	MRA+	MRA-	MRA+	MRA-		MRA+	MRA-	MRA+	MRA-
DU+	125	9	5	26	DU+	197	20	8	58
DU-	30	15	15	418	DU-	61	26	30	1045

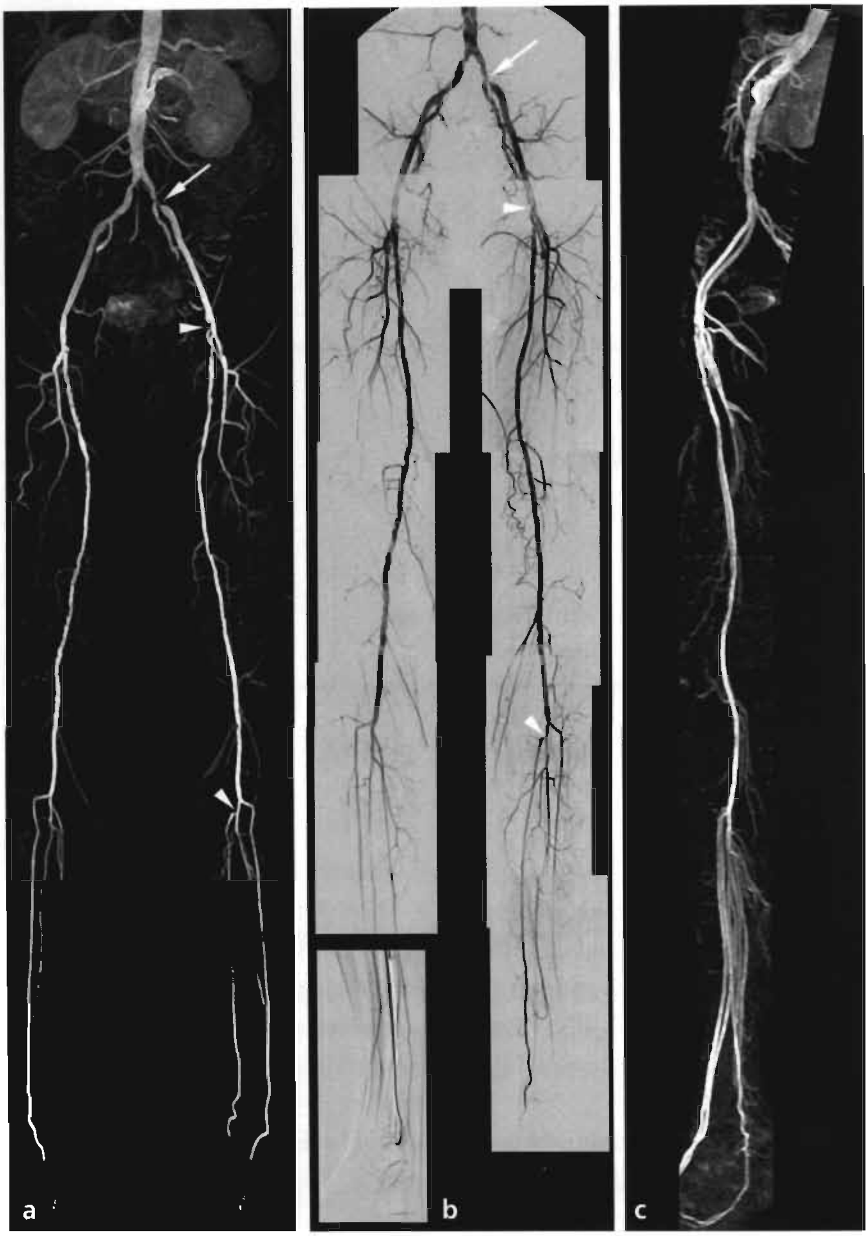

Figure 2 a,b,c Contrast-enhanced MR angiogram and IA-DSA in a 56-year old male patient with bilateral ischemic rest pain (Fontaine grade III peripheral arterial disease). The left panel (a) shows a coronal maximum intensity projection (MIP) image of the acquired dataset. The middle panel (b) shows the corresponding IA-DSA and the right panel shows a sagittal (lateral) view of the same CE-MRA dataset (c). There is a high grade stenosis in the left external iliac artery (arrow). DU of this arterial segment showed a peak systolic velocity ratio of 6.8, also indicating high grade stenosis. Extent and the grade of disease as shown by CE-MRA matches very well with the corresponding IA-DSA image (arrowheads). CE-MRA and IA-DSA also detected a significant stenosis in the right common iliac artery which was missed with DU because this arterial segment was not interpretable. Note that with CE-MRA image quality of lower leg arteries is at least as good as the IA-DSA. Due to the magnetic field inhomogeneity there is slight curving of the lower leg arteries where the upper and lower leg fields-of-view overlap. In the IA-DSA (b) panel the right lower leg is detached from the coronal image because this was a lateral projection.

Discrepancies between DU and CE-MRA

There were 429 minor discrepancies between DU and CE-MRA. Major discrepancies between DU and CE-MRA occurred in 169 vessel segments in 124 patients. Seventy-six major discrepancies (45%) were validated by comparison with IA-DSA. DU was in accordance with the standard of reference 19 times and CE-MRA 57 times. Figure 2 shows a graphic representation of the major discrepancies between DU and CE-MRA where IA-DSA was available as the standard of reference. Retrospective analysis of major discrepancies of 2 or more stenosis categories (n=36) showed that DU located a lesion in the wrong vessel segment 6 times, was false positive 7 times and false negative 12 times. CE-MRA located a lesion in the wrong vessel segment once, was false positive 2 times and was false negative 4 times. An additional three false positive lesions on CE-MRA were, in retrospect, also present on the IA-DSA and were therefore not true discrepancies. A final discrepancy where both DU and CE-MRA saw a vessel segment as patent which was occluded at IA-DSA was probably due to occlusion of that vessel segment before IA-DSA (which was 51 days later). There was no significant difference in the distribution of delay times between DU and the CE-MRA for patients with and without major discrepancies (P=.88).

Discussion

The results of this prospective comparison between DU and CE-MRA provide evidence that CE-MRA is a more sensitive technique than DU for the detection of hemodynamically significant stenosis in the diagnostic workup of patients with intermittent claudication. This study was motivated by the fact that there was little information available about the comparative accuracy of DU and CE-MRA for the detection of suspected aortoiliac and superficial femoral PAOD in patients with intermittent claudication.

A limitation of this study is that due to logistical reasons we were not able to include consecutive patients. However, we tried to avoid bias by contacting random patients from those due to undergo DU in a given week during the inclusion period. Another limitation is that not all patients with atherosclerotic lesions on either DU or CE-MRA or with a lesion on both imaging modalities underwent the standard of reference. The reason for this is that many patients were treated conservatively and did not want to undergo or were not referred for IA-DSA for diagnostic purposes only. On the other hand, the group of patients in which invasive over conservative treatment was chosen (i.e. the group with the most severe complaints and thus clinically relevant discrepancies) was validated.

Because we did not validate all patients with significant lesions on either DU or CE-MRA we are only able to approximate the absolute values for sensitivity and specificity in these patients. However, the difference in sensitivity is derivable from our data and was statistically significant.

The agreement between the two reads of the CE-MRA data was high with a kappa value of 0.80 and compares favourably to the kappa value reported in recent study for aortoiliac DU (0.57).(12) The high kappa value for CE-MRA indicates that dedicated readers are interchangeable. Unfortunately we were unable to calculate a kappa value for DU. However, this would have meant that patients had to undergo DU twice which was not feasible for logistical reasons. It is likely that the kappa value for CE-MRA readings of the entire vascular tree is lower, but the arteries that are most important and accessible for therapeutic purposes in the current patient group, the aortoiliac and superficial femoral arteries, were evaluated in the reported kappa values. The kappa value may also be lower in other patient groups with more severe disease.

The results of the present study corroborate the findings of the recent meta-nalysis by Visser et al in which greater discriminatory power of CE-MRA was found over DU in the diagnostic workup of patients with PAOD.(13) In that study, the total number of patients enrolled in the 10 MRA studies that were analyzed was 295. For DU, 21 studies with a total of 1291 patients were analyzed. The pooled sensitivities for CE-MRA and DU were 97.5% and 87.6%, respectively. Specificities were 96.2% for CE-MRA and 94.7% for DU. In this respect, the sensitivity reported here for DU is somewhat lower. At this time, two studies have been published that have compared DU with CE-MRA in the same patients.(14,15) Both studies reported results similar to those found in the current study with sensitivity (specificity) for DU in both studies of 72% (88 and 97%). For CE-MRA these figures were 81 and 86% and 88 and 92% for sensitivity and specificity, respectively. In the study by Wikström et al 30 non-consecutive patients with an iliac artery stenosis found at DU also underwent CE-MRA and IA-DSA.(14) In the study by Lundin et al, 39 patients already referred for IA-DSA also underwent CE-MRA and DU.(15) In contrast, in the current, prospective study patients were randomly selected from those that were referred for non-invasive evaluation because of complaints of intermittent claudication by their vascular surgeons. In contrast to the two previously published studies that compared CE-MRA with DU, all patients enrolled in the current study underwent CE-MRA and DU, irrespective of the results of one of these tests.

In a substantial number of patients discrepancies were found between the results of DU and CE-MRA. We analyzed our data according to clinically significant discrepancies, i.e. discrepancies that would lead to another treatment (e.g. common femoral endarterectomy instead of iliac artery percutaneous transluminal angioplasty). In the majority of the discrepancies that were validated CE-MRA was in accordance with the standard of reference, indicating the usefullness of this new technique.

In contrast to DU information about stenoses obtained with IA-DSA and CE-MRA is purely morphological and not functional. However, when percutaneous or surgical therapy is considered in a patient with PAOD, the precise location, grade and length of an atherosclerotic lesion is key information needed to decide which is the most appropriate therapy.(2) Traditionally, IA-DSA has been used to provide this information. Recently, several published meta-analyses have shown that CE-MRA is able to provide this information with accuracy similar to IA-DSA.(8,9) Although we chose IA-DSA as the standard of reference a better standard of reference would have been intraarterial pressure measurements. This is because it is known that stensosis percentages as measured on IA-DSA do not always correlate with the pressure gradient across a stenosis.(14)

For evaluation of the CE-MRA datasets it would have been better if source images had also been available. It is known that reading source images of CE-MRA datasets increases diagnostic yield.(8,16) For the current study this means that sensitivity and specificity of CE-MRA would have probably increased. It should also be mentioned that not every patient is a suitable candidate for CE-MRA, because of contraindications such as claustrophobia or the presence of a pacemaker or intracerebral ferromagnetic vascular clips. A technical limitation of CE-MRA is that it is not able to provide information about stenoses and obstructions in most stents because of artefacts. Also, to acquire CE-MRA images of the peripheral arteries succesfully, one has to be familiar with technical details. In contrast to DU, CE-MRA requires injection of contrast material which somewhat increases the chance for procedure related complications.(17)

In conclusion, the findings of this study indicate that CE-MRA is a highly accurate and safe imaging technique for detection and grading of PAOD, given the necessary equipment and expertise. CE-MRA has significantly higher sensitivity than DU but both modalities are equally suited to rule in disease, because of the similar specificities. On the basis of these findings and the posibility of CE-MRA to provide inflow and outflow information we believe that CE-MRA should become the diagnostic procedure of choice in investigating suspected peripheral arterial disease.

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Comparison of treatment plans for peripheral arterial disease made with multi-station contrast-enhanced magnetic resonance angiography and duplex ultrasonography

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Abstract

Introduction

to investigate the effect of substituting multi-station total outflow contrast-enhanced magnetic resonance angiography (CE-MRA) for color duplex ultrasonography (DU) on treatment planning in the diagnostic workup of patients with suspected or known peripheral arterial occlusive disease (PAOD).

Subjects and methods

100 consecutive patients (mean age, 64; 65% men) referred for suspected or proven PAOD to a University Hospital underwent both aortoiliac DU and multi-station total outflow CE-MRA. Twenty-seven patients also underwent femoropopliteal DU. Three experienced vascular surgeons separately formulated two sets of treatment plans based on standardized clinical parameters and either DU or CE-MRA. The main outcome measures were the number of treatment plans that could be formulated without additional diagnostic intra-arterial digital subtraction angiography (IA-DSA) and how well treatment plans were in concordance with actual treatment.

Results

With CE-MRA treatment plans could be formulated in 92, 90 and 91 out of 100 patients (surgeons 1, 2 and 3). With DU treatment plans could be formulated in 60, 59 and 66 patients (P<.001 for all surgeons). Based on CE-MRA significantly more treatment plans could be formulated compared with patients that underwent aortoiliac DU only (P<.001 for all surgeons) and patients that underwent both aortoiliac and femoropopliteal DU (surgeon 1: P<.001; surgeon 2: P=.021; surgeon 3: P=.070). In patients presenting for the first time (n=55) or patients that previously underwent surgery (n=20) CE-MRA was significantly more often able to formulate a treatment plan than DU (surgeon 1: P<.001/.008; surgeon 2: P<.001/.012; surgeon 3: P<.001/0.008). Treatment plans based on DU exactly matched actual treatment in 44/60 patients (surgeon 1); 39/59 patients (surgeon 2) and 46/66 patients (surgeon 3). Treatment plans based on CE-MRA exactly matched actual treatment in 61/92 patients (surgeon 1); 56/90 patients (surgeon 2) and 54/91 patients (surgeon 3).

Conclusion

Compared to aortoiliac and femoropopliteal DU, multi-station total outflow CE-MRA is a more effective tool for treatment planning in most patients with known or suspected PAOD. This difference is especially apparent in patients presenting for the first time or patients that underwent previous vascular surgery.

Introduction

Peripheral arterial occlusive disease (PAOD) is a significant source of morbidity in western society with an estimated incidence of 2-10 new cases per 1000 persons per year.(1) Patients with PAOD usually present to their physician with complaints of intermittent claudication and the diagnosis of PAOD can be made with reasonable certainty on the basis of the typical history and physical examination.(2) The first line treatment of patients with complaints attributable to PAOD is modification of risk factors, such as smoking, hypertension and hypercholesterolemia and participation in exercise training programs.(3-5)

When a patient experiences too much impairment in daily routine despite the above measures, percutaneous or surgical intervention is usually considered. Before an intervention, precise mapping of the site and extent of PAOD is needed. For this purpose duplex ultrasonography (DU) is routinely used in many centers and has shown to predict with reasonable accuracy the presence of stenoses and occlusions in the aortoiliac and femoropopliteal arteries and in arterial bypass grafts.(6) Despite its widespread application for treatment planning, DU has the disadvantage that it is operator dependent, time-consuming and that obese

Table 1 Patient characteristics

	Number of patients
Rutherford score*	
Grade 0	25
Grade I	70
Grade II	4
Grade III	1
Total number of patients	100
Presenting for the first time	55
Previous percutaneous interventions	25
Previous surgical interventions	20
Smokers	60
Adult onset diabetes mellitus	17
Hypertension	47
Hyperlipidemia	52
Cardiac disease	31
Carotid artery disease	12
Kidney transplantation	2
Pulmonary disease	13
Mean resting ABI (SD)	0.65 (0.21)
Mean post-exercise ABI (SD)	0.46 (0.26)

patients or patients with excessive bowel gas or calcified arteries are difficult to examine.(7) These limitations are the main reason why a substantial number of patients still have to undergo diagnostic intra-arterial digital subtraction angiography (IA-DSA) before the exact extent and severity of PAOD is known and lesions amenable for therapy can be identified. Although a reasonably safe procedure, diagnostic IA-DSA demands intraarterial catheterisation, hospitalisation for at least a day, involves X-ray exposure and the administration of nephrotoxic iodinated contrast-media.

Recently contrast-enhanced magnetic resonance angiography (CE-MRA) has evolved as an alternative modality for depicting the peripheral arterial tree.(8) With CE-MRA, images similar to IA-DSA can be obtained from the infrarenal aorta down to the ankles. CE-MRA has been compared to IA-DSA and has shown to accurately predict grade and length of PAOD.(9,10) Despite these encouraging findings, the utility of CE-MRA as a tool for interventional planning has not been investigated extensively, specifically not in comparison with DU.

The purpose of this study was to investigate the effect of substituting total outflow CE-MRA for DU on treatment planning in the diagnostic workup of patients with suspected or known PAOD.

Patients and Methods

Patients and current diagnostic workup algorithm

During a 17-month period (september 1999-january 2001) 100 consecutive patients, referred for DU by their vascular surgeons because of known or suspected PAOD also underwent CE-MRA of the peripheral arterial tree. There were 35 women and 65 men with a mean (± SD) age of 64 ± 9.4 years (range, 41 to 81) with 158 symptomatic extremities. Other patient characteristics are listed in table 1. All patients were prospectively followed to determine the nature and type of any interventions. Before DU and CE-MRA were performed, all patients underwent resting and post exercise ankle brachial index (ABI) measurements. The post exercise ABI was measured after a standardized walking test on a treadmill, lasting a maximum of five minutes. The study design and diagnostic workup algorithm for patients with intermittent claudication as used in our hospital is shown in figure 1. Patients were not included in the study if they were claustrophobic (n=2), had a pacemaker (n=1) or non MR compatible ferromagnetic implants (e.g. certain intracranial aneurysm clips or hearing ossicles (n=0). The mean delay (± SD) between CE-MRA and DU was 4.9 days ± 4.2 days (range, 13 days before - 21 days after) and was subject to availability of the MR scanner. The institutional review board had approved the study protocol and all patients signed informed consent before they were included in the study.

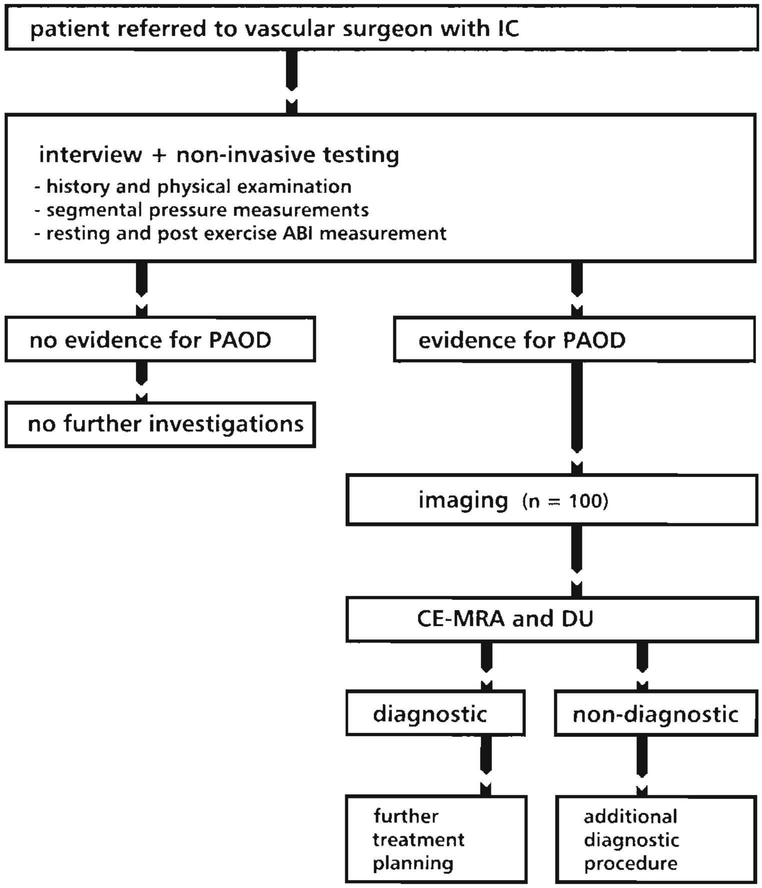

Figure 1 Study design and diagnostic workup algorithm

Duplex ultrasonography

On the basis of the history and the findings at physical examination the referring vascular surgeons determined the extent of the DU examination (aortoiliac only or including the femoropopliteal arteries). The DU examinations were performed by qualified, experienced vascular technologists, unaware of the findings of the CE-MRA examinations. For the DU examination patients were placed in the supine position and the abdominal aorta, common and external iliac and common femoral arteries were insonated using a 5 MHz convex transducer. In the presence of excessive bowel gas or obesity a 3.5 MHz convex transducer was used. When the femoropopliteal arteries were scanned a 7.5 MHz linear transducer was used. In every named vessel segment, the peak systolic velocity ratio (PSVR) was measured and recorded on a standard reporting sheet, indicating the grade of stenosis on a 5-point scale. The PSVR was calculated by dividing the velocity measured at the point of maximum stenosis by the velocity in the closest adjacent normal vessel segment. The cutoff points used for aortoiliac DU were: 1) PSVR

< 1.5 for 0-19% stenosis; 2) 1.5 ≤ PSVR < 2.5 for 20-49% stenosis; 3) PSVR ≥ 2.5 for 50-74% stenosis; 4) PSVR > 2.5 and end diastolic velocity > 60 cm/s for 75-99% stenosis and 5) no doppler signal for occlusion. For the femoropopliteal arteries the cutoff points used were: 1) PSVR < 2.5 for 0-50% stenosis; 2) PSVR ≥ 2.5 for 50-99% stenosis and 3) no doppler signal for occlusion. All DU examinations were done using Aloka 2000 or 5500 color-aided duplex ultrasound devices (Aloka Co, Tokyo, Japan). Total patient handling time for aortoiliac duplex was about 45-60 minutes, including the femoropoliteal arteries about 60-90 minutes.

MR angiography

All MR acquisitions were done with a 1.5 T MR scanner (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands) using commercially available pulse sequences. Patients were placed in the supine position on the scanner table. To depict the arteries of the lower limb a stepping table approach was used. With this scanning technique high-resolution three dimensional (3D) images of the arterial system from the abdominal aorta down to the ankles can be obtained scanning three separate volumes (for the aortoiliac, upper and lower leg arteries) in rapid succession. The CE-MRA procedure consisted of three steps: 1) acquisition of localizer scans, 2) acquisition of 3D mask scans and 3) acquisition of the same 3D scans during administration of 35 mL of Gd-DTPA contrast material (Magnevist, Schering, Berlin, Germany). On the basis of orthogonal maximum intensity projections (MIPs) of the localizer dataset the high resolution 3D scans were prescribed. To increase vessel-to-background contrast non-enhanced scans were subtracted from the corresponding CE-MRA scans after acquisition. The full technical details and parameter settings of the CE-MRA scanning procedure have been described in chapter 3.(11) After image acquisition CE-MRA images were transferred to a dedicated postprocessing workstation (EasyVision rel. 4.2, Philips Medical Systems, Best, The Netherlands) where they were read by a radiologist experienced in reading CE-MRA datasets. For every named vessel segment starting from the infrarenal aorta down to the ankles the presence of stenoses and obstructions were recorded. Stenoses were classified on the same 5-point scale as the DU examinations and were calculated by dividing the luminal diameter at maximum stenosis by the luminal diameter of the closest adjacent normal vessel diameter. In every vessel segment only the most severe stenosis was recorded. In addition to the information about grade of stenoses as determined by the radiologist, coronal and sagittal maximum intensity projection images of all three stations were printed on film and made available for the vascular surgeons taking the treatment decisions. Total patient handling time for the CE-MRA procedure was about 20 minutes. For postprocessing and interpretation of the data an additional 15-20 minutes were needed.

Table 2
Treatment options

0	**no treatment / conservative treatment**
1	**PTA (with or without primary stenting) in iliac arteries**
2	**PTA in femoral arteries**
3	**Aortobifemoral bifurcation graft**
4	**Unilateral iliac artery bypass**
5	**Surgical endarterectomy of common femoral artery**
6	**Femorofemoral crossover bypass**
7	**Femoropopliteal bypass (distal anastomosis above-knee)**
8	**Femoropopliteal bypass (distal anastomosis below-knee)**
9	**Femorotibial bypass**
10	**Amputation***

PTA: percutaneous transluminal angioplasty; * exact level of amputation had to be specified

Further diagnostic and treatment plans

Three experienced vascular surgeons familiar with interpreting both DU reports and CE-MRA images retrospectively formulated two sets of treatment plans for all patients. Treatment plans were formulated on the basis of standardized clinical information and the results of either DU or CE-MRA. After the study was completed, the two sets of treatment plans were compared with each other and the actual treatment the patients had undergone. Standardized clinical information consisted of: age and sex of the patient, previous vascular interventions (e.g. angioplasty, stenting, operations), pain free walking distance, the presence of rest pain and/or tissue loss, side of complaints (left, right or both), duration of complaints, risk profile of the patient (smoking, hypertension, diabetes, hypercholesterolemia, cardiac, renal, pulmonary and neurological history; according to the categories defined by Rutherford(12)) and resting and post exercise ankle-brachial index (ABI) of both lower extremities.

After receiving the clinical information the vascular surgeon was given the results of either the DU or the CE-MRA examination. The first decision that had to be taken was if any further diagnostic procedure (e.g. diagnostic IA-DSA) was needed or if the information so far sufficed to formulate a treatment plan. If the vascular surgeon considered the information from the imaging procedure sufficient, he was requested to formulate a treatment plan. It was assumed that the patient was willing to undergo the proposed treatment. Treatment options were chosen from the list shown in table 2.

Over a 4-month period the 3 vascular surgeons reviewed all 100 cases twice and formulated treatment plans on the basis of each of the two imaging modalities in separate sessions. Thus, every vascular surgeon formulated 100 treatment plans based on DU and 100 treatment plans based on CE-MRA. To prevent recall bias, cases were presented at random, and a period of at least four weeks elapsed before a treatment plan was formulated for the same case based on the results of the other imaging modality. The vascular surgeons were kept unaware of each others decisions and of the decisions taken on the basis of the other imaging modality. Any attribute that could possibly identify the patient (patient number, date of birth, name and date of examination, referring physician) was removed from duplex reports and the CE-MRA films. After two treatment plans were formulated for all patients they were compared with the actual clinical treatment decisions made on the basis of all available information (i.e. physical examination, non-invasive tests, DU, CE-MRA, clinical impression and patient preference).

Formulated treatment plans based on DU and CE-MRA were analyzed for discrepancies with actual treatment and for discrepancies between them and were distinguished as serious and minor. Minor discrepancies were defined as different treatments aimed at the same lesion that was actually treated. A discrepancy between actual treatment and proposed treatment was considered serious when the proposed treatment concerned a lesion in another artery than the lesion that was actually treated.

Statistical analysis

The McNemar test was used to test for differences in the number of requested additional diagnostic procedures based on the different imaging modalities.

Table 3 Number of cases with sufficient information to formulate a treatment plan

	Surgeon 1			Surgeon 2			Surgeon 3		
	DU	CE-MRA	P-value	DU	CE-MRA	P-value	DU	CE-MRA	P-value
AoII DU only (n=73)	49 (67%)	66 (90%)	<.001	42 (58%)	65 (89%)	<.001	46 (63%)	65 (89%)	<.001
AoII+fempop DU (n=27)	11 (41%)	26 (96%)*	<.001	17 (63%)	25 (93%)*	.021	20 (74%)	26 (96%)	.070
First presentation (n=55)	34 (62%)	53 (96%)*	<.001	30 (55%)	53 (96%)*	<.001	36 (66%)	53 (96%)*	<.001
Previous intervention (n=45)	26 (58%)	39 (87%)*	.001	29 (64%)	37 (82%)	.096	30 (67%)	38 (84%)	.057
PTA (n=25)	18 (72%)	23 (92%)	.125	21 (84%)	20 (80%)	1.0	22 (88%)	22 (88%)	1.0
Surgery (n=20)	8 (40%)	16 (80%)*	.008	8 (40%)	17 (84%)*	.012	8 (40%)	16 (80%)*	.008
Overall (n=100)	60	92*	<.001	59	90*	<.001	66	91*	<.001

DU: duplex ultrasonography; CE-MRA: contrast-enhanced magnetic resonance angiography; AoII: Aortoiliac; fempop: femoropopliteal; NA: not applicable; * significantly higher than duplex ultrasonography. Except for one patient for surgeon 2 all CE-MRA exams considered not sufficient for treatment planning were due to the presence of implanted vascular stents.

Surgeons	DU All cases	DU Corresponding cases	CE-MRA All cases	CE-MRA Corresponding cases
	(n = 100)	(number)	(n =100)	(number)
1-2	0.63	0.81 (45)	0.59	0.70 (84)
1-3	0.65	0.91 (48)	0.48	0.62 (84)
2-3	0.79	0.80 (53)	0.49	0.59 (84)
Mean	0.69	0.84	0.52	0.64

DU: duplex ultrasonography; CE-MRA: contrast-enhanced magnetic resonance angiography; corresponding cases are patients that have sufficient information available for treatment planning in the opinion of both vascular surgeons.

Table 4 Kappa values comparing different surgeons decisions based on DU and CE-MRA

	Actual treatment	Surgeon 1		Surgeon 2		Surgeon 3	
		DU	CE-MRA	DU	CE-MRA	DU	CE-MRA
Number treated conservatively	42	56	25	53	26	43	22
Because additional diagnostic information needed	2	40	8	41	10	33	9
For other reasons	40	16	17	12	16	10	13
Number of interventional radiological procedures	46	44	59	45	58	52	63
PTA (with or without primary stenting) in iliac arteries	40	35	50	37	52	41	51
PTA in femoral arteries	6	9	9	8	6	11	12
Number of surgical procedures	12	0	16	2	16	5	15
Aortobifemoral bifurcation graft	1	0	3	1	3	3	6
Unilateral iliac artery bypass	1	0	2	0	1	0	0
Endarterectomy of common femoral artery	2	0	4	1	5	1	3
Femorofemoral crossover bypass	1	0	1	0	3	0	3
Femoropopliteal bypass (above-knee distal anastomosis)	5	0	4	0	1	1	3
Femoropopliteal bypass (below-knee distal anastomosis)	1	0	1	0	2	0	0
Femorotibial bypass	1	0	1	0	1	0	0
Amputation	0	0	0	0	0	0	0
Number of treatment plans in exact agreement with actual treatment*		44/60	61/92	39/59	56/90	46/66	54/91
Percentage of treatment plans in exact agreement with actual treatment*		73	66	66	62	70	59

* only for cases with sufficient information for treatment planning

Table 5 Actual treatment received compared with treatment decisions based on DU or CE-MRA for different surgeons

Variation with regard to the formulated treatment plans between vascular surgeons on the basis of both modalities was calculated using the kappa statistic. In addition to overall comparisons, separate analyses were done in the patient groups that had undergone previous interventions (subdivided in previous PTA or vascular surgery) and femoropopliteal DU in addition to aortoiliac DU only. Two-sided *P*-values below .05 were considered to indicate statistical significance.

Results

All patients underwent DU and CE-MRA without experiencing any adverse events. In addition to aortoiliac DU, 27 patients also underwent DU of the femoropopliteal arteries. In total, 46 patients underwent percutaneous treatment and 12 patients underwent surgery. Thirty-eight patients were treated conservatively and in 4 patients no signs of PAOD were found on DU or CE-MRA. Nine patients of the 38 patients that were treated conservatively were advised an intervention but did not want to undergo any additional procedures. Of the 27 patients that underwent femoropopliteal DU in addition to aortoiliac DU, 7 underwent iliac artery PTA, 3 underwent superficial femoral artery PTA, 2 above-knee, 1 below-knee femoropopliteal bypass grafting, 1 iliac artery bypass and 1 endarterectomy of the common femoral artery. Additional diagnostic procedures were ordered for a patient with an abdominal aortic aneurysm (CT-scan) and for a patient with suspected vasculitis (laboratory testing). Two patients that were intended to undergo iliac artery PTA did not have a stenosis at the location specified by DU and CE-MRA so in retrospect IA-DSA was for diagnostic purposes only in these patients. Nine patients had previously implanted vascular stents which rendered CE-MRA inconclusive in these patients except for one patient with a nitinol stent which was evaluable in the opinion of a single surgeon.

Significant differences existed between DU and CE-MRA for all three vascular surgeons in the number of additional diagnostic procedures deemed necessary (table 3). In the experimental setup, all vascular surgeons ordered significantly less additional diagnostic procedures based on CE-MRA compared to DU in the patient group presenting for the first time or the group that had undergone vascular surgery in the past. In the patient group that had undergone femoropopliteal DU in addition to aortoiliac DU, surgeons 1 and 2 also ordered significantly less additional diagnostic procedures based on CE-MRA (table 3). In table 4 kappa values are listed comparing different surgeon's treatment decisions based on DU or CE-MRA. In table 5, the actual treatment that patients enrolled in the study underwent is compared with treatment plans by different surgeons based on DU or CE-MRA. In table 6, agreement between treatment plans proposed on DU and CE-MRA for the different surgeons is shown. In total, there were 15 serious discrepancies between DU and CE-MRA in 11 patients.

	Surgeon 1	Surgeon 2	Surgeon 3
Number of corresponding cases (out of 100 included patients)*	58	53	62
Number of cases with exact agreement between DU and CE-MRA (%)	46 (79)	39 (74)	46 (74)
Number of serious discrepancies between DU and CE-MRA (%)†	3 (5.2)	6 (11.3)	6 (9.7)
Actual treatment conservative	1	1	1
Actual treatment according to treatment plan based on DU	2	3	2
Actual treatment according to treatment plan based on CE-MRA	0	2	3

* Corresponding cases are patients that have sufficient information available for treatment planning with both DU and CE-MRA; † serious discrepancies are discrepancies where proposed treatment concerned a lesion in another vessel segment than the lesion that was actually treated

Table 6 Agreement between treatment plans proposed on DU and CE-MRA for the different surgeons

Discrepancies between treatment plans proposed on DU and actual treatment

The total number of discrepancies for all three surgeons combined between treatment based on DU and actual treatment was 56 of 185 (30%) cases where enough information was available to formulate a treatment plan. Thirty-four discrepancies occurred because in reality treatment was conservative. In 9 of these conservatively treated cases the patient did not want to undergo the proposed treatment.

In the group of patients that actually underwent PTA or surgery there were 22 discrepancies between proposed and actual treatment for the three surgeons combined. With treatment plans based on DU, 10 serious discrepancies (i.e. actual treatment concerned a lesion in another vessel segment than was proposed based on DU) arose in 5 different patients (5.4% of total number of treatment plans). Surgeon 1 was responsible for 2 serious discrepancies, and surgeons 2 and 3 were each responsible for 4. In one case common femoral endarterectomy was proposed where iliac artery PTA was done, in one case iliac artery PTA was proposed where an above-knee femoropopliteal bypass graft was made. In all other cases PTA was done in another vessel segment. Three patients with serious discrepancies presented for the first time and two had undergone interventions (iliac and femoral PTA) in the past.

Discrepancies between treatment plans proposed on CE-MRA and actual treatment

Treatment plans based on CE-MRA led to 102 discrepancies for all three surgeons combined, on a total of 273 (37%) cases with enough information for treatment planning. Seventy-one times conservative treatment was chosen in reality. In total, 31 discrepancies with the proposed treatment plans occurred in the patient group that actually underwent PTA or surgery. Five serious discrepancies (1.8% of total number of treatment plans) arose between proposed and actual treatment in 4 patients; two patients presented for the first time and two patients had undergone an intervention in the past. Surgeon 1 had 1 serious discrepancy, and surgeons 2 and 3 each had two. In all cases iliac artery PTA was proposed but femoral PTA was actually done in 4 cases and in one case an above knee femoropopliteal bypass was done.

Discussion

In this study treatment plans based on standardized clinical information and the results of either DU or total outflow CE-MRA were compared in patients referred to the vascular surgeon with complaints of PAOD. The results of this study demonstrated that vascular surgeons were less likely to order diagnostic IA-DSA when they had CE-MRA available instead of DU to plan treatment on, even when femoropopliteal DU was done in addition to aortoiliac DU. In addition, the vascular surgeons in this study were able to formulate more surgical treatment plans based on CE-MRA without ordering additional diagnostic information.

Since the early 1980s the use of DU as a potential alternative to IA-DSA has been investigated.(6) In recent years CE-MRA has also evolved as a potential alternative for diagnostic IA-DSA in patients with suspected or proven PAOD. With the use of DU or CE-MRA, exposure to, ionizing radiation, administration of iodinated contrast media and local and systemic complications of catheterisation can be avoided. Despite many studies that have investigated the diagnostic accuracy of CE-MRA compared to IA-DSA, questions remain regarding the important issue of the utility of CE-MRA compared to DU as a tool to plan vascular interventions. We conducted this study to investigate the potential of CE-MRA as an alternative to DU for diagnosis and preinterventional treatment planning in patients presenting with complaints of PAOD.

In the current study, three vascular surgeons were independently able to formulate significantly more treatment plans on the basis of CE-MRA (CE-MRA: mean 91/100 vs DU: mean 62/100) without the need for additional diagnostic IA-DSA. If patients with implanted vascular stents are excluded, treatment plans could have been formulated in all but one patient for a single surgeon. In our opinion, the likely explanation for this difference is the availability in all patients of anatomical images from the infrarenal aorta down to the ankles, comprising information about inflow and outflow arteries, closely resembling IA-DSA images. Many vascular surgeons still consider such a 'roadmap' of the lower limb vasculature essential when they plan treatment, a view that is also expressed in the transatlantic intersociety consensus (TASC) document.(1) A limitation of this study is that only selected patients underwent DU of the femoropopliteal arteries in addition to aortoiliac DU. However, in the subset of patients that had undergone femoropopliteal DU, 2 of the 3 vascular surgeons in this study still needed additional information significantly more often to formulate a treatment plan. The rationale for referring only selected patients for femoropopliteal DU is that this examination is not always expected to yield relevant information. Femoropopliteal DU is a reliable technique to locate and grade short stenoses and occlusions in the superficial femoral artery(13) and for surveillance of bypass grafts.(14) However, the accuracy of DU for precise planning of femoropopliteal bypass grafting, where information is also needed on lower leg outflow arteries is still subject of debate.(15)

Overall, agreement rates between proposed and actual treatment with DU were slightly higher than with CE-MRA (mean for DU: 70%; mean for CE-MRA: 62%). What should be kept in mind, however, is that agreement between CE-MRA and actual treatment was based on a much larger number of patients and formulated treatment plans encompassed interventional radiological as well as surgical treatment options (table 5). In the current study, agreement, expressed in kappa values, between the surgeons with regard to formulated treatment plans was higher for DU than for CE-MRA when taking all cases into account (DU: 0.69; CE-MRA: 0.52) but also higher when only taking cases into account which did not require additional diagnostic information (DU: 0.84 [mean number of patients 49]; CE-MRA:0.64 [mean number of patients 84]). The reasons that interobserver agreement is higher with DU are most likely that information is presented in a simpler format (only categories of stenosis per vessel segment and no information about morphology) and in 73/100 of cases DU lacked outflow information which limited the available options to choose from. In addition, higher interobserver agreement with DU comes at the cost of much lower numbers of patients in which a treatment plan can be defined.

In several other studies investigators have compared treatment plans based on IA-DSA with those based on DU and MRA. The study by Mulligan et al found that treatment plans formulated based on DU were more often in agreement with the findings and subsequent treatment planning based on IA-DSA than treatment plans formulated based on MRA in 13 patients undergoing 21 interventions. However, in that study non contrast-enhanced MRA was used, which is known to suffer from prohibitively long examination times and from several sources of artefacts, mainly in the aortoiliac region. (16) This was corroborated in the study by Hoch et al who compared treatment plans also based on non contrast-enhanced MRA with plans based on IA-DSA in 40 patients. (17)

The interesting finding in the latter study was that above the inguinal ligament plans based on IA-DSA were in accordance with actual treatment in all patients and that below the inguinal ligament plans based on MRA were more often in accordance with the treatment that was actually chosen.

The number of serious discrepancies for all three surgeons together, i.e. those cases in which the actual treatment was PTA or surgery for a lesion in another vessel segment amounted to 5.4% (10/185) of all formulated treatment plans for DU and 1.8% for CE-MRA (5/273). In 8/10 serious discrepancies the treatment plan would have involved PTA on a different level (iliac vs femoral) with the resultant (antegrade vs retrograde) approach by the interventional radiologist. For CE-MRA this was also the case in 4/5 patients. These results indicate that in a limited number of patients either DU or CE-MRA do not supply enough information and a combination of the two or additional diagnostic procedures are needed. In the study by Kohler et al who compared treatment plans based on DU from the infrarenal aorta down to the ankles with treatment plans based on IA-DSA in 29 patients this was also the case; a mean of 76% of treatment plans were in exact agreement and serious discrepancies between DU and IA-DSA occured 5/29 (17%) patients.(18)

The present study also has limitations. Because this was a study in which retrospectively formulated treatment plans were compared with the actual treatment based on all available diagnostic information (DU, CE-MRA and any additional other diagnostic procedures), results must be interpreted with caution. This is because it is extremely difficult to capture every bit of relevant information in a standardized way that determines actual treatment. However, because standardized clinical information was given in an identical fashion for DU and CE-MRA, surgeons probably experienced an equal effect of this simplification of reality with both modalities. Another source of variation in this experiment besides the different diagnostic tests under investigation is variation between two different surgeons when making a treatment plan. It is well known that this variation exists(18) and actual treatment decisions in real life are often taken at multidisciplinary expert meetings (e.g. interventional radiological and surgical) where specific patient cases are discussed. An interesting avenue of exploration to correct for this would be to investigate if a team of two surgeons or an interventional radiologist and a surgeon would have come to different treatment plans.

It should also be mentioned that not every patient can undergo CE-MRA, because of contraindications such as claustrophobia or the presence of a pacemaker or intracerebral ferromagnetic vascular clips. A technical limitation of CE-MRA is that it is not able to provide information about stenoses and obstructions in most stents because of artefacts. In the current study this was the case in 9/100 patients. Also, to acquire CE-MRA images of the peripheral arteries succesfully, one has to be familiar with technical details. In contrast to DU, CE-MRA requires injection of contrast material which carries a very small but not neglible risk for procedure related complications.(19)

What are the implications of this study for clinical practice? Apart from patients' preferences and other elements (e.g. comorbidity) that influence treatment options that are considered, information about the exact length and severity of stenoses and occlusions is needed when considering an intervention. CE-MRA is able to provide this data in a format and with accuracy similar to IA-DSA (9,10) and is therefore a valuable addition to the diagnostic workup of patients with PAOD. The morphological information that can be derived from the CE-MRA dataset may also facilitate logistics in the angiography suite because before an interventional procedure is started, information about catheter and stent sizes and grade and localisation of atherosclerotic lesions is available, which may lead to shorter and more targetted interventional procedures. However, because CE-MRA and DU are complementary imaging modalities (DU based on physiological data and CE-MRA providing the necessary anatomical information), the real gain for the patient lies in combining the two modalities when one test provides equivocal information, so diagnostic IA-DSA can be avoided. Of the patients enrolled in the current study, only 2 underwent IA-DSA for diagnostic purposes. Because treatment plans could be formulated with CE-MRA in a larger number of patients it would make sense to use CE-MRA as the first imaging study and to use DU when CE-MRA is non-diagnostic or does not provide the necessary information (i.e. when a borderline lesion is seen or in the presence of stents and metal clips, which are known to generate artefacts on CE-MRA).

In conclusion, this study shows that CE-MRA is a highly valuable tool to plan percutaneous as well as surgical treatment without the need for invasive IA-DSA. The limited time needed for the test and interpretation of the results combined with the ability to provide true three-dimensional information on inflow as well as outflow vessels similar to IA-DSA makes CE-MRA a compelling alternative for DU in selected cases and in centers with the necessary equipment and expertise.

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General discussion

In this thesis a number of studies related to optimization and clinical utility of contrast-enhanced magnetic resonance angiography (CE-MRA) for the diagnosis of peripheral arterial occlusive disease (PAOD) are reported. Since the first description of CE-MRA of the arteries in the lower extremities in 1995 by Douek et al (1), the technique has matured and now enjoys widespread application. In fact, CE-MRA of the peripheral arteries is now a very widely used method for diagnosis and post interventional monitoring of patients with PAOD. The threedimensional (3D) nature of the MR acquisition combined with the rapid and non-invasive nature of the technique make it well suited to examine a broad range of patients. Additional advantages are the absence of ionizing radiation and the use of non-nephrotoxic contrast media.

The diagnostic accuracy of CE-MRA

CE-MRA has a very high diagnostic accuracy for depiction of number, grade and length of stenoses and obstructions in the peripheral arterial tree when compared with the standard of reference in peripheral vascular imaging, IA-DSA, as we have shown in a literature survey in chapter 2.(2) Of the different MRA methods that have been developed, CE-MRA is the fastest, most robust and most accurate technique, which is least prone to known artefacts and pittfalls inherent to magnetic resonance imaging.(3) A strong testimonial to this claim is the fact that within a few years after it's inception CE-MRA for imaging the entire peripheral vascular tree has become implemented in routine clinical practice in many academic as well as non-academic hospitals around the Western world.

Optimization of peripheral CE-MRA

The acceptance and efficacy of peripheral CE-MRA has made a critical step forward through the use of rapid moving bed technology (4,5), which enables scanning the peripheral arteries during the relatively slow injection of a single bolus of gadolinium chelate contrast medium. With this technique 3D high-resolution images of the peripheral arterial circulation can be obtained in less than two minutes (figure 1). Including the necessary preparations before contrast-enhanced images are acquired, scanner occupancy is limited to 15-20 minutes per patient when a routine protocol has been established and radiologists and technicians have the necessary experience.

Because the peripheral arterial tree has a length of over 100 cm and the effective field-of-view (FOV) in commercially available MR scanners is 35-45 cm, it is obvious that multiple FOVs and scans are needed to image the peripheral circulation. To achieve imaging multiple FOV technically, two general approaches have been described which yield images of the entire peripheral arterial circulation. The first approach, as described and used in this thesis, is based on a single injection of contrast media and rapid interscan table movement (in the order of a few seconds), attempting to image three to four stations before venous enhancement occurs. The second approach, usually applied on scanners on which rapid interscan table movement is not possible, or in patients with suspected rapid venous enhancement makes use of a separate injection of contrast medium for each station imaged. Rapid venous enhancement can be expected in patients with diabetes and cellulitis because of altered arteriovenous communication modulated by the autonomous nervous system. A disadvantage of the multiple injection technique is that the total amount of contrast medium has to be divided into three or more separate injections of much less contrast medium, thus decreasing vessel-to-background contrast compared to a full, double to triple dose (0.2-0.3 mmol/kg) injection. Therefore, the most applied and easiest technique is probably the former since it requires only a single injection of contrast medium and demands considerably less time. The advantage of using separate injections for each FOV is that the parameters can be tailored more easily to the specific anatomy of the station in question. In chapter 3 we have presented a technique that combines station-specific scanning parameters with a single injection protocol.(6) For the iliac arteries with a large diameter a different resolution can be chosen to image these vessels than for the lower leg arteries with their much smaller diameter. The reliable detection and grading of PAOD clearly demands differential resolutions for the three different stations.

Technical issues that must be considered before peripheral MRA can be performed successfully are 1) correct patient positioning; 2) correct timing of data acquisition in relation to contrast medium injection; 3) table movement and the acquisition of mask scans, 4) the use of the right scanning parameters and coils for each station and 5) adequate postprocessing of the acquired data. Also, before a patient is scanned the radiologist should know whether or not the patient has an ulcer or cellulitis and whether the patient has diabetes or not, since venous return is altered in patients with these conditions.

patient positioning

The patient should be positioned on the table in such a way that the most economical reduction can be chosen in the phase encoding direction, which is almost always in the left-right direction. Since additional phase encodings steps in this direction increase scantime proportionally, patients' arms should either be positioned on the abdomen or over the head to prevent wrap around artefacts when scanning with a reduced FOV.

Figure 1 Three station CE-MRA examination in a 57-year old male patient with bilateral intermittent claudication. In the left common iliac artery an aneurysm can be seen (arrowhead). Both superficial femoral arteries are occluded over their entire length. Note excellent depiction of the stenosis in the proximal anterior tibial artery (arrow).

Figure 2 a,b Three station CE-MRA examination in a 54-year old female patient who had previously undergone femorofemoral crossover bypass surgery and who now again had complaints of intermittent claudication. On the coronal (a) and sagittal (b) views it can clearly be appreciated that a complete outflow arteriogram of the infrarenal aorta and entire lower extremities is possible, including depiction of the pedal arch. On the sagittal (b) image a stenosis in the right extenal iliac artery can be seen. On the sagittal image it can also be seen that the iliac, femoral and tibial scanning volumes are of different thickness. Also note the total lack of venous enhancement. Acquisition times and acquired resolutions were 16 s / 6 mm^3 (iliac), 10 s / 5 mm^3 (upper leg) and 59 s / 1.7 mm^3 (lower leg).

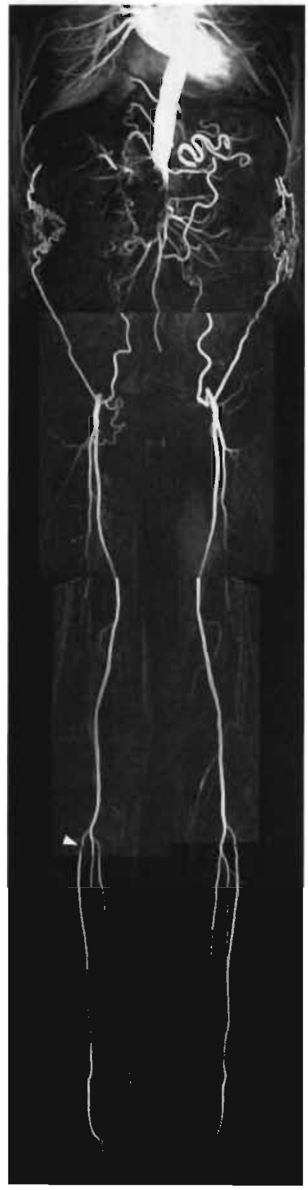

Figure 3 Coronal maximum intensity projection images of a 3D contrast-enhanced MRA dataset in a 63-year old male patient with peripheral arterial occlusive disease and a pain-free walking distance of < 200m. The images were acquired with flexible parameters for each of the four fields-of-view and with a combination of the quadrature body coil (upper station) and a total runoff peripheral vascular coil (lower three stations). The abdominal acquisition lasted 20 seconds, the iliac acquisition lasted 15 sec, the femoral acquisition 10 sec and the tibial acquisition 55 seconds. Acquisition voxel sizes for the respective stations were 10.0, 5.0, 6.0 and 1.7 mm^3 and were all interpolated to half their size by zero filling. Note that despite the long acquisition duration depiction of arteries in the lower legs is without any disturbing venous enhancement. There is occlusion of the infrarenal abdominal aorta down to the superficial femoral arteries (LeRiche Syndrome), nice depiction of collateral vessels, no vascular abnormalities of the lower extremities, except for a medium grade stenosis in the right anterior tibial artery (arrowhead). Because of the high resolution depiction of the lower legs, small digital arteries in the feet can even be seen.

timing the acquisition

Succesful image acquisition with CE-MRA is very dependent on timing because of the non-instantaneous way of MR data acquisition. When acquisition starts too early, no contrast material is present in the arteries and images are non-diagnostic. When acquisition is started too late, arteries are enhanced suboptimally and veins and soft tissue enhancement may render arteries not interpretable. To ensure adequate timing (i.e. scanning during initial arterial bolus passage), either a test bolus technique or real-time bolus monitoring techniques should be used, be it operator controlled or automated.(7)

table movement and the acquisition of mask scans

When a single bolus technique is used table movement between consecutive scans should be completed as fast as possible (several seconds). A longer delay may result in venous enhancement before acquisition has finished. Although major MR vendors have commercially available software packages which allow fast interscan table movement several research groups have described approaches in which the patient table is rapidly translated manually.(4,5,8,9) The advantage of this approach is the rapid way in which table movement can be accomplished (almost always under 5 seconds). The reason why repositioning is necessary is because of the use of a subtraction technique. With this technique, non-enhanced scans acquired with the same scanning parameters are subtracted from the CE-MRA scans. In chapter 4 we have shown that subtraction for peripheral CE-MRA is beneficial and is the most optimal tool to improve image quality, especially in the lower leg station. Although some vessel-to-background contrast is lost when doing this, the depiction of small arteries definitely improves.

the use of different scanning parameters and coils for each station

If at all possible this should be attempted. The minimum requirements for a reliable and successful peripheral CE-MRA exam demands the use of a surface reception coil for at least the lower leg arteries, as we have shown in chapter 5. If such a coil is not used, images can become noisy, lacking sufficient vessel-to-background contrast to reliably differentiate diseased from healthy vessel segments.(10) As mentioned earlier, image quality and reliability will really take a quantum leap if flexible imaging parameters for each FOV are used. When using this approach, three factors can be combined to potentially improve image quality which are: 1) the use of a thinner volume containing less partitions in areas where arteries run very straight and do not curve significantly in the anterior-posterior direction (i.e. upper legs); 2) the use of centric ordered K-space filling to prevent venous enhancement in upper and lower leg stations and 3) the use of thinner (but more) slices and higher matrix values for the lower legs to obtain a higher resolution. The implementation of all these imaging parameters can effectively lead to significant shortening of acquisition times for the pelvic and upper leg arteries and reinvesting this 'saved' scantime into higher resolution scanning with increased coverage in the lower leg station. In practice, imaging this way can yield venous-free station-optimized images with coverage of the entire pedal arterial arch in the foot (figures 2 and 3).

Because of inherent physical contraints the sensitivity of the magnetic resonance imaging process is finite.(11) With the use of current 0.5 molar gadolinium chelates and the development of ever stronger gradient systems and ever shorter scan times the limits of obtainable resolution are in sight. In the near future, stronger T1 reducing contrast media will be needed to maintain acceptable image quality when resolution is increased and scantimes are further shortened. In chapter 6 we report on the use of an iron-oxide bloodpool contrast agent for steady-state, contrast-enhanced peripheral MR angiography. Because of its' slow clearance from the circulation this agent allows imaging of the peripheral arteries over a longer time which offers the possibility to increase resolution without losing signal-to-noise. The drawback of this approach is that veins also opacify and that they have to be separated from arteries later. The application of such bloodpool contrast media seems promising but is still a long way from use in clinical practice. However, there may be substantial use for these agents as first-pass contrast agents.(12)

postprocessing of the acquired data

When CE-MRA datasets are evaluated for presence and severity of PAOD, maximum intensity projections (MIP) or multiplanar reformats (MPR) are usually used to get a quick overview of vascular anatomy. However, the definitive diagnosis should preferably be made on the on the original partitions since this increases the diagnostic yield.(2) Reviewing original partions may reveal stenoses and obstructions not visible on MIPs and conversely, may reveal residual lumen where MIPs shows a complete occlusion.

Clinical Utility of peripheral CE-MRA

The functional severity of PAOD is generally classified according to the Fontaine classification; however, a better but more elaborate way is according to Rutherford.(13) The major distinction is between patients which have complaints elicited by exercise (intermittent claudicaters) and those who have rest pain or in whom resting perfusion is inadequate for basic metabolic demands and that have ulcers. The underlying pathology in the former group is usually a discrete lesion in the iliac or femoral arteries, in contrast to patients with severe disease which usually have stenoses and obstructions at multiple levels or severe, distal (i.e. lower leg) disease. The diagnostic accuracy of peripheral CE-MRA in patients with intermittent claudication has been established as highly reliable in a number of publications.(2,14) However, the utility and efficacy of CE-MRA of the entire peripheral vascular tree in patients with critical ischemia has not been established firmly. In the aforementioned meta-analyses less than 30 patients in three publications were examined (15) so no firm conclusions can be made.(16,17) Although promising reports have appeared about non-contrast enhanced MRA techniques

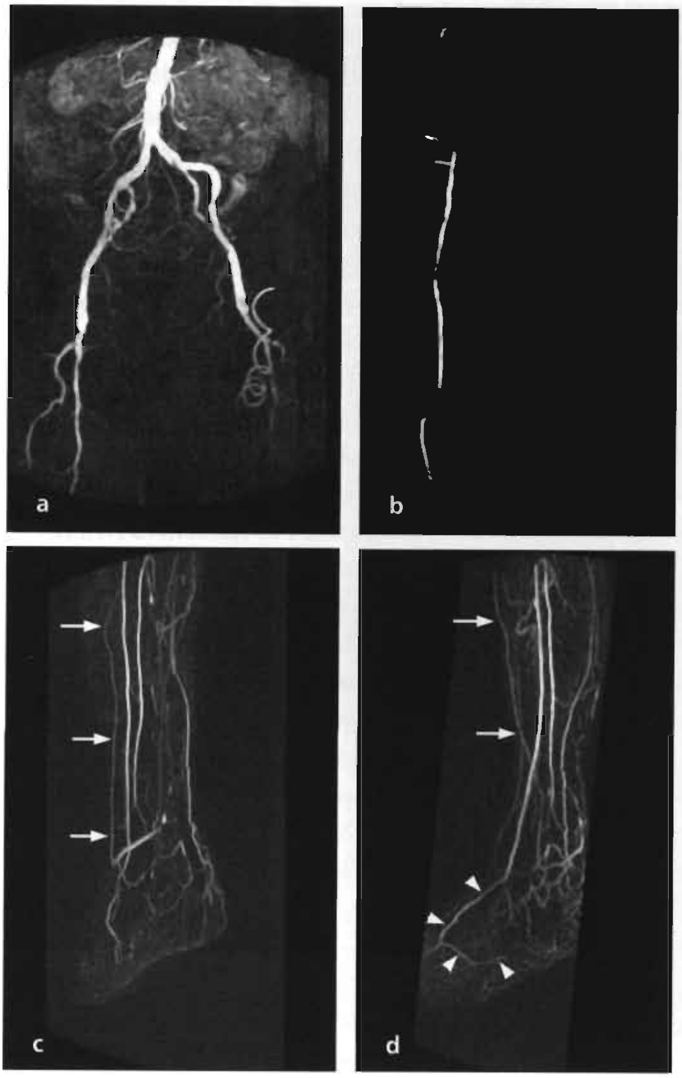

Figure 4 a,b,c,d Total outflow CE-MRA examination in 76-year old male patient with Fontaine IV (Rutherford grade III) peripheral arterial disease (chronic critical ischemia with tissue loss). This patient had already undergone an above-knee amputation of the left lower extremity and was now evaluated for a non-healing ulcer on the right foot. On the coronal images the aortoiliac (a), femoropopliteal (b) and tibiopedal (c) arteries are clearly depicted. The patient has an occlusion of the proximal part of the superficial femoral artery, the popliteal trifurcation and the posterior tibial artery. In the lower leg station there is slight venous enhancement (arrows), however, this is not disturbing image interpretation. On the coronal (c) and sagittal (d) images of the lower leg the entire pedal arch can be evaluated (arrowheads). Acquisition times and acquired resolutions were 17 s / 6 mm^3 (iliac), 11s / 5 mm^3 (upper leg) and 62 s / 1.5 mm^3 (lower leg).

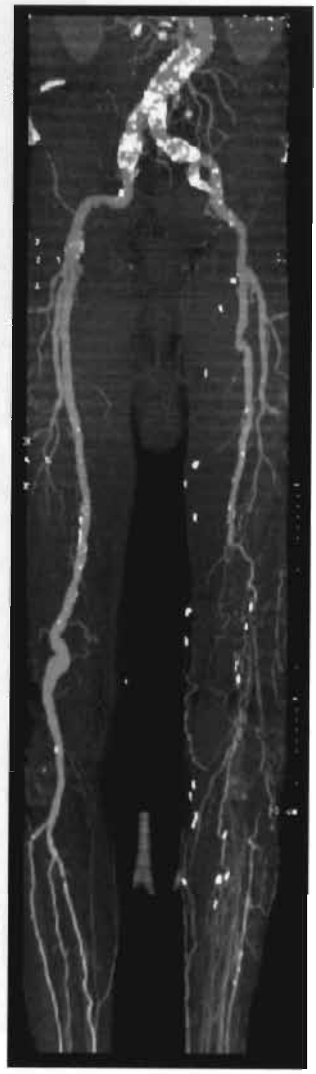

Figure 5 Multi-detector spiral CT angiogram (CTA) in a 67-year old male patient with a popliteal aneurysm on the right side and occlusion of the left distal superficial femoral artery, the popliteal artery and proximal lower leg arteries. The CTA is able to demonstrate distal runoff arteries to the level of the ankles. Note the extensive calcifications in the distal abdominal aorta and proximal iliac arteries, making interpretation of these vessels difficult. Image courtesy of Dr. Jean-Louis Sablayrolles, Centre Cardiologique du Nord, Saint Denis, France

(18) or single station contrast-enhanced imaging (19), multistation CE-MRA has not proven its efficacy yet in patients with severe PAOD. It is this group of patients, however, which potentially may benefit the most from the technique. The reasons for this are that conventional IA-DSA is often difficult in these patients because in extensive PAOD groin access may be compromised and often concerns of X-ray contrast medium nephrotoxicity in the presence of reduced renal function limits the total dose that can be given safely.(20) The detection of additional patent vessels with flow dependent MRA techniques, dedicated contrast-enhanced single station acquisitions, intra-operative X-ray angiography and surgical exploration in comparison with IA–DSA indicate the potential of multistation CE-MRA in this patient category (figure 4).(18,19) In chapter 7, we have shown that multistation CE-MRA is indeed able to detect more patent and graftable arteries in comparison to selective and non-selective IA-DSA in patients with chronic critical ischemia and tissue loss (Fontaine IV / Rutherford III). It remains to be determined if the implementation of CE-MRA in the diagnostic workup of these patients will lead to additional limb salvage.

The diagnostic accuracy of peripheral CE-MRA compared to other imaging techniques is excellent. In chapter 8 we have shown that the sensitivity of CE-MRA for detection of angiographically hemodynamic stenoses is significantly better than duplex ultrasonography, the most widely used non-invasive imaging tool for detection and grading of stenoses in patients with PAOD. Our findings are corroborated by a recent meta-analysis by Visser et al in which they have shown that CE-MRA has better discriminatory power than duplex ultrasonography for detection of hemodynamically significant (≥ 50% luminal reduction) stenoses.(21) Also, the limited anatomical coverage with duplex ultrasonography within a reasonable amount of time and inherent limitations of this technique in patients with obesity, calcified arteries and bowel gas make CE-MRA a compelling alternative for endovascular and surgical treatment planning as we have shown in chapter 9. Compared with diagnostic IA-DSA, CE-MRA has been shown to be a reliable alternative in the vast majority of cases.(2,21) Reported sensitivities and specificities for detection of PAOD are almost all above 90%, making the use of an invasive method with potentially serious complications for diagnostic reasons only questionable. However, the in-plane spatial resolution that can be obtained with X-ray angiography (pixels in the order of 0.2 x 0.2 mm) is still far superior to that of CE-MRA.

The imaging modality that most closely resembles peripheral CE-MRA is CT angiography (CTA) (figure 5). With the advent of multidetector spiral CT-scanners, imaging the complete outflow arteries is also feasible.(22,23) At the present time experience with the technique is limited but sensitivity and specificity will likely turn out to be similar to the values reported for CE-MRA. However, as with IA-DSA concerns still remain about X-ray exposure and the use of nephrotoxic contrast-media, making the technique less suited for repeated

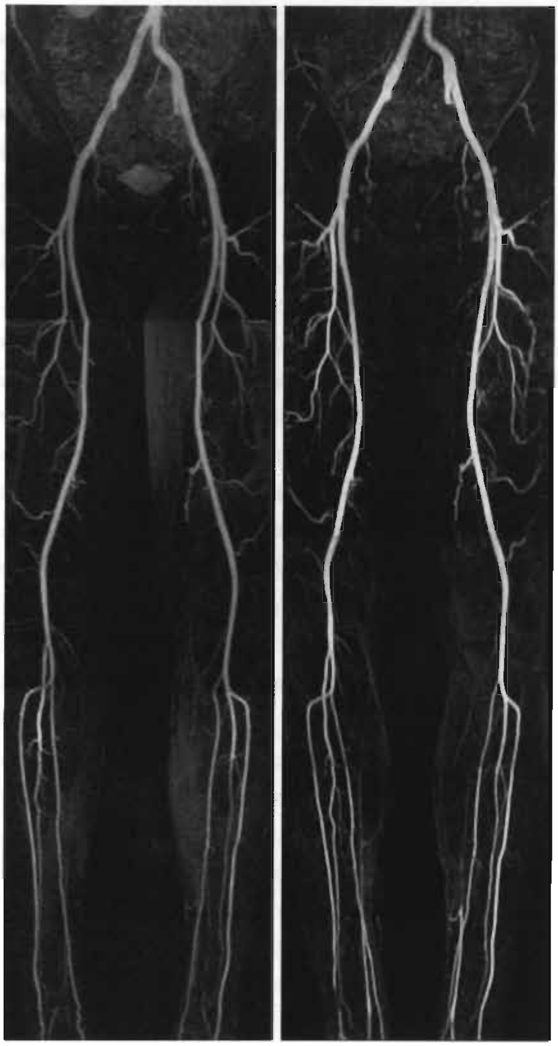

Figure 6 a,b
Coronal MIPs of CE peripheral MRAs at 1.5T (a) and 3.0T (b) in a healthy volunteer. Note that arteries are more intensely enhanced at 3.0T and that smaller braches are less noisy and better visible at 3.0T. The images of the lower legs at 1.5T were acquired with a dedicated lower extremity coil. The images acquired at 3.0T were made using the standard system built-in quadrature body coil.

imaging. From an acquisition point of view CTA may be easier to perform though since less parameters have to be considered before imaging a patient. Postprocessing CTA datasets can be more cumbersome than CE-MRA because of calcifications in the vessel wall which may obscure stenoses and obstructions. As with CE-MRA the definitive diagnosis should be made on original (axial) CTA partitions, which can easily number 700-1000 images per patient, compared to 200-300 (mostly coronal) images for CE-MRA.

Future directions

The main challenges for the succesfull application of peripheral CE-MRA in everyday radiological practice are dependent on the patient group one wants to image. In patients with intermittent claudication the success of CE-MRA exam will depend on the availability of a routine acquisition protocol and the facile and expeditious reading and reporting of results. In patients with severe PAOD the challenges are to obtain a technically succesfull exam in uncooperative patients and to prevent deep venous enhancement in those patients which are able to undergo the examination. Reliable detection and grading of disease in the lower legs together with depiction of the arterial arch in the foot across a variety of imaging platforms remains one the most important focal points for improvement of peripheral CE-MRA. The short term solution to overcome these limitations is the development of commercially available software which will enable acquisition of high resolution tailor made 3D volumes for each station with dedicated peripheral vascular reception coils or alternatively, to use time-resolved two dimensional (2D) projectional sequences.(6,24) The long term solution to overcome these problems is the reduction of scantimes to several seconds per station to prevent venous enhancement while maintaining the 3D character of current acquisitons. This may be achieved through parallel scanning techniques such as SENSE or SMASH (25), segmented K-space acquisition strategies (26,27) and improvements in field and gradient strength. Currently, first experience is emerging with the use of 3T whole body magnets (figure 6). These magnets offer a significant increase in signal-to-noise which has already shown to be beneficial for MRA.(28) Another important improvement will be stronger T1 reducing contrast agents such as iron oxide compounds, protein binding gadolinium compounds or 1.0 molar gadolinium chelates.(29) Besides all these technical considerations, there is no published data concerning the cost-effectiveness of contrast enhanced MRA for the diagnosis of and preinterventional workup of PAOD. Future studies will definitely need to address this point.

A further challenge for the diagnosis of PAOD with magnetic resonance imaging techniques will be to transcend the purely morphological and macroanatomical 'luminography' and to develop clinically usefull techniques that are prognostic for, correlate with and allow for follow up of PAOD. Efforts have been made in imaging of plaque morphology and stability (30-32), and collection of hemodynamic and physiological data about bloodstream and pulse wave velocities (33,34), wall shear stress (35-37), vessel distensibility (38), perfusion (39) and tissue metabolism.(40) Important advances can also be made with improved postprocessing of the acquired datasets. Currently, CE-MRA datasets are evaluated in much the same way as X-ray images are: assuming that luminal reduction ≥50% correlates with clinical symptoms. However, since CE-MRA is a 3D technique the acquired data allow for additional and perhaps better ways of predicting the hemodynamic significance of a stenosis, such as cross-sectional or volumetric analysis of stenoses. Preliminary data from our group in 34 patients with an iliac artery stenosis that underwent duplex ultrasonography, CE-MRA and IA-DSA suggest that cross-sectional analysis is the most sensitive technique (97%) when intra-arterial pressure measurement are used as the standard of reference. This technique was more sensitive than the currently considered standard of reference for imaging of PAOD, IA-DSA (sensitivity 78%).

Conclusions

In conclusion, the introduction of the moving-bed concept in peripheral CE-MRA has been very successful and has been implemented across a wide range of imaging systems in only three-four years. The diagnostic accuracy of imaging the most distal station, the lower legs and feet, has greatly benefited from station-optimized acquisitions with dedicated coils and the introduction of new scanning techniques. As for the clinical utility, CE-MRA has shown to be a useful tool for imaging runoff arteries in severely diseased patients and in addition, we have shown CE-MRA to be a more sensitive tool than DU for detection and grading PAOD. Because of these technical improvements and it's superior diagnostic accuracy, CE-MRA will probably become the imaging modality of first choice in the full spectrum of patients with PAOD.

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Summary and conclusions

Contrast-enhanced magnetic resonance angiography (CE-MRA) has met with widespread enthousiasm from the radiological community in the past few years. Since 4 years it is possible to depict the entire peripheral arterial tree using a moving bed concept that was first published by our institution. All major MR vendors have since implemented software packages on their scanners for this purpose and in many institutions this technique has replaced X-ray angiography for diagnostic purposes. Despite these developments many questions regarding the diagnostic accuracy, applicability and place of this technique in the diagnostic workup of patients with peripheral arterial disease remain. With the research done in this thesis, we have sought to answer some of those questions. The aims of this thesis were to summarize the diagnostic performance of magnetic resonance angiography, to optimize current CE-MRA protocols and to assess the clinical utility of CE-MRA, specifically in comparison to duplex ultrasonography.

The diagnostic accuracy of magnetic resonance angiography

In *chapter 2*, the overall diagnostic performance of magnetic resonance angiography in the evaluation of peripheral arterial occlusive disease is investigated and the most important sources of variation in diagnostic accuracy between studies are analyzed using summary receiver operator characteristic (SROC) analysis. We investigated the diagnostic accuracy of 23 published studies that used X-ray angiography as the standard of reference and found CE-MRA to be diagnostically superior over non-enhanced MRA. In addition we found that the diagnostic accuracy increased when source images were reviewed in addition to standard maximum intensity projections.

The optimization of contrast-enhanced peripheral MRA

In *chapter 3*, we introduce a new technique for the optimization of moving bed CE-MRA that is based on using different imaging parameters to image the three different vascular territories of peripheral arteries: the aortoiliac region, the upper legs and the lower legs. The single bolus techniques described to date all use the same imaging parameters for the separate fields-of-view which leads to suboptimal images, mainly for the lower legs in a large percentage of patients. The technique we describe is entirely flexible concerning number of partitions, resolution, K-space filling, size of the field-of-view or any other scanning parameter and can be tailored to the patients specific vascular anatomy. In five volunteers and six patients it is demonstrated that applying the new technique yields higher signal-and contrast-to-noise, better subjective image interpretability and less venous enhancement. We conclude that improvements have been realized for important aspects that determine clinical acceptance of peripheral CE-MRA images.

In *chapter 4*, the issue of background suppression is addressed. A potential drawback of subtracted, multi-station peripheral CE-MRA is subtraction misregistration artefacts. To avoid this, carefull patient repositioning and prolonged examination times are necessary. However, the advantage of background suppression is that small vessel branches are better visualized which may facilitate better treatment planning. In order to determine if background suppression is beneficial for peripheral CE-MRA we performed a study on 10 patients with peripheral arterial occlusive disease that underwent non-subtracted, subtracted and fat-saturated CE-MRA. Signal- and contrast-to-noise ratios as well as venous enhancement and subjective interpretability were determined in a station-by-station fashion for each technique and were found to be significantly higher for fat-saturated versus the other two techniques. Subjective interpretability was best for subtracted datasets in the lower leg station. In the iliac station fat-saturated datasets were considered to have significantly lower interpretability than subtracted datasets. Venous enhancement occurred significantly more often in the lower leg station with the fat-saturated technique. We conclude that subtraction is a usefull tool if dedicated surface coils are used and that background suppression by means of subtraction is necessary to ensure the best lower leg image interpretability.

In *chapter 5*, a dedicated 129 cm long phased array reception coil was evaluated for the optimization of single injection, multi-station peripheral MRA in 19 patients suffering from peripheral arterial occlusive disease. The specific aim of this study was to optimize the protocol in such a way that imaging of the pedal vasculature as part of a multi-station exam also becomes possible. Use of the coil enabled acquisition of high resolution peripheral vasculature images in all cases. In all requested cases the entire pedal arch was depicted and we conclude that a three-station dedicated peripheral vascular coil substantially improves CE-MRA quality.

In *chapter 6*, we tested the safety and efficacy of a representative of the class of intravascular or 'bloodpool' contrast media for peripheral MR angiography in a multicenter phase II trial. In four study centers, 33 patients underwent bloodpool enhanced MR angiography; MR angiograms were compared with intra-arterial digital subtraction angiography as the standard of reference. We conclude that bloodpool-enhanced high-resolution steady-state MR angiography can be performed safely and is feasible for the detection of peripheral arterial hemodynamically significant stenoses in large and medium sized arteries. Arterial-venous separation in small arteries such as those in the lower legs is still very challenging using currently available techniques.

The clinical utility of contrast-enhanced peripheral MRA

In *chapter 7*, we assessed the value of contrast-enhanced magnetic resonance angiography for demonstration of arterial anatomy and potential suitability for distal bypass surgery in 23 patients with chronic critical ischemia and tissue loss (Fontaine IV / Rutherford III). We also assessed the potential impact of the technique on clinical management of these patients. We found that CE-MRA detected more patent and graftable arterial segments in patients with chronic critical ischemia and tissue loss compared to IA-DSA and changed treatment planning in an experimental setting in 35% of these patients. On the basis of these finding we conclude that CE-MRA is a very usefull addition to conventional catheter-based intra-arterial angiographic techniques in the decision making process in patients with chronic critical ischemia.

In *chapter 8*, we prospectively compared the diagnostic accuracy of two minimally invasive procedures, color duplex ultrasonography (DU) and CE-MRA, for the diagnosis of the peripheral arterial occlusive disease in a large cohort of 302 patients. The results of this comparison indicate that CE-MRA is a more sensitive technique (85% sensitivity) than DU (71% sensitivity) for the detection of angiographically hemodynamically significant stenosis in the diagnostic workup of patients with intermittent claudication. We found that the higher sensitivity of CE-MRA is combined with slightly superior specificity compared to DU (97 versus 94%) which means that the improved detection of stenoses with CE-MRA does not come at the cost of more patients diagnosed with lesions false positively. We conclude that CE-MRA is a compelling alternative for DU and has the potential to replace it as the diagnostic procedure of choice for the diagnostic workup of peripheral arterial occlusive disease.

Because comparing treatment plans based on different diagnostic tests for PAOD may be more clinically relevant than simply comparing how well severity of disease in different vessel segments corresponds, we investigated the effect of substituting total outflow contrast-enhanced magnetic resonance angiography (CE-MRA) for color duplex ultrasonography (DU) on treatment planning in the diagnostic workup of 100 patients with suspected or known peripheral arterial occlusive disease (PAOD) in *chapter 9*. Three vascular surgeons formulated treatment plans based on standardized clinical information and either DU or

CE-MRA. We found that based on CE-MRA surgeons were able to formulate treatment plans on a mean of 91 patients compared to a mean of 62 patients with DU. It is concluded that compared to aortoiliac and femoropopliteal DU, multi-station total outflow CE-MRA is a more effective tool for treatment planning in most patients with known or suspected PAOD, especially those presenting for the first time or patients that underwent previous vascular surgery.

In *chapter 10*, the findings of this thesis are discussed in the light of current literature and key points for succesful implementation of contrast-enhanced MRA are discussed. We conclude chapter 10 with an outlook towards future developments for the use of magnetic resonance angiography and magnetic resonance imaging in patients with peripheral arterial occlusive disease.

Conclusions

The conclusions of this thesis are:

1 Contrast-enhanced magnetic resonance angiography is a highly accurate imaging modality for the diagnostic and preinterventional workup of patients with peripheral arterial occlusive disease compared to the standard of reference, X-ray arteriography

2 The image quality of contrast-enhanced MR angiography studies has improved substantially over the past few years because of the technical optimizations as described in this thesis and be considered equal or superior to X-ray angiography in a large majority of patients

3 Contrast-enhanced magnetic resonance angiography is a more valuable tool in the diagnostic workup of patients with chronic critical ischemia and tissue loss than X-ray angiography because the technique is able to better detect residual arteries considered suitable for bypass grafting and it is better able to define the extent of compromised inflow.

4 Contrast-enhanced magnetic resonance angiography is a more sensitive imaging modality than duplex ultrasonography for the detection of hemodynamically signifcant stenoses in the diagnostic workup of patients with peripheral arterial occlusive disease

5 Because of the superior sensitivity and the possibility of CE-MRA to provide inflow and outflow information similar to that obtained with X-ray angiography, we believe that CE-MRA should become the diagnostic procedure of first choice for investigating suspected peripheral arterial disease.

Samenvatting en conclusies

De afgelopen jaren is contrast-versterkte magnetische resonantie angiografie (CV-MRA) van de perifere vaten door radiologen en verwijzende clinici enthousiast ontvangen. Sinds 4 jaar is het mogelijk om de gehele perifere vaatboom af te beelden door gebruik te maken van een schuivende tafel, zoals voor het eerst gepubliceerd door ons instituut. Alle grote MRI fabrikanten hebben sindsdien software pakketten voor dit doel op de markt gebracht en in vele ziekenhuizen heeft de techniek diagnostische röntgenarteriografie vervangen. Ondanks deze ontwikkelingen zijn er veel onbeantwoorde vragen over de diagnostische betrouwbaarheid, de toepasbaarheid en plaats van perifere CV-MRA in het diagnostisch traject van patiënten met perifeer vaatlijden. Met het onderzoek zoals beschreven in dit proefschrift is getracht enkele van deze vragen te beantwoorden. Het doel van het proefschrift was het onderzoeken van de diagnostische betrouwbaarheid van perifere CV-MRA, het optimaliseren van bestaande perifere CV-MRA protocollen en de klinische waarde van perifere CV-MRA, in het bijzonder in vergelijking met duplex ultrageluid.

De diagnostische betrouwbaarheid van magnetische resonantie angiografie

In *hoofdstuk 2* wordt de diagnostische betrouwbaarheid van MRA bij patiënten met perifeer vaatlijden en de belangrijkste oorzaken van variatie in betrouwbaarheid tussen studies onderzocht door middel van summary receiver operating characteristic (SROC) analyses. Na analyse van de diagnostische betrouwbaarheid van 23 gepubliceerde studies waarbij röntgenangiografie als gouden standaard werd gebruikt, werd CV-MRA superieur bevonden aan niet CV-MRA. Daarnaast werd gevonden dat de diagnostische betrouwbaarheid verder toenam als, naast maximum intensity projections (maximale intensiteits projecties; MIP), ook de bronbeelden werden geanalyseerd.

Optimalisatie van contrast-versterkte perifere MRA

In *hoofdstuk 3*, wordt een nieuwe techniek voor optimalisatie van perifere MRA beschreven. Deze techniek is gebaseerd op het gebruik van optimale acquisitie scanparameters voor de drie overlappende metingen in bekken, boven- en onderbenen. De tot nu toe beschreven afbeeldingstechnieken, waarbij de volledige dosis contrastmiddel in een enkele injectie wordt toegediend, maken gebruik van identieke scanparameters voor bekken, boven- en onderbenen. Deze strategie leidt in een substantieel aantal gevallen echter tot suboptimale afbeelding van met name de onderbenen. Met de nieuwe techniek is het mogelijk om scanparameters per meting geheel naar wens te kiezen en aan te passen aan de patiënt voor wat betreft het aantal partities, de resolutie, K-ruimte vulling, afmetingen van het meetveld, of enig andere willekeurige scanparameter. Bij vijf gezonde vrijwilligers en zes patiënten werd na toepassing van de nieuwe techniek een hogere signaal- en contrast-ruis verhouding gevonden, evenals een betere subjectieve beoordeelbaarheid van de beelden en minder potentiëel verstorende veneuze aankleuring. Er wordt geconcludeerd dat met de nieuwe techniek belangrijke verbeteringen zijn gerealiseerd voor wat betreft klinische acceptatie van CV-MRA beelden.

In *hoofdstuk 4*, wordt achtergrond onderdrukking onderzocht. Bij achtergrond onderdrukking worden niet contrast-verstrekte beelden van identieke contrastversterkte beelden afgetrokken om arteriën beter te visualiseren. Een potentieel nadeel van subtractie zijn zogenaamde subtractieartefacten. Deze kunnen ontstaat als de patiënt beweegt tussen acquisitie van de 'masker' metingen en de metingen tijdens injectie van contrastmiddel. Subtractieartefacten kunnen de beoordeelbaarheid van de beelden nadelig beïnvloeden. Ter voorkoming van deze artefacten moet de patiënt nauwkeurig in de scanner gepositioneerd worden; echter dit verlengt de onderzoeksduur. Het potentiële voordeel van subtractie is dat kleine en distale arteriën beter in beeld gebracht worden (met name indien oppervlakte ontvangstspoelen worden gebruikt) en derhalve de uitgebreidheid van vaatlijden en beter gevisualeerd kan worden. Dit leidt ertoe dat een eventuele behandeling beter gepland kan worden. Een andere methode voor achtergrond onderdrukking is selectieve vetsaturatie. Dit is een techniek waarbij de signaalintensiteit van vet, het weefsel dat de meeste verstoring van de beelden oplevert bij de gebruikte afbeeldingsmethode, selectief onderdrukt wordt zodat de bekken- en beenarteriën beter zichtbaar worden. Om te zien of achtergrond onderdrukking daadwerkelijk de beeldkwaliteit positief beïnvloedt werd een studie bij 10 patiënten met perifeer vaatlijden verricht. In deze studie werden beelden verkregen met subtractie en selectieve vetsaturatie vergeleken met beelden zonder achtergrond onderdrukking. Als eindpunten werden signaal- en contrast ruisverhouding, de mate van veneuze aankleuring en de subjectieve beoordeelbaarheid van de beelden in bekken, boven- en onderbenen genomen. De signaal- en contrast-ruis verhouding was het hoogst voor de beelden met selectieve vetonderdrukking, terwijl veneuze aankleuring bij deze techniek significant vaker voorkwam in de onderbenen. Subjectieve interpreteerbaarheid was met name voor de onderbenen het best voor gesubtraheerde beelden. Concluderend wordt gesteld dat gesubtraheerde beelden de beste beeldkwaliteit opleveren.

In *hoofdstuk 5* wordt een 129 cm lange oppervlakte ontvangstspoel getest ten behoeve van de optimalisatie van perifere CV-MRA bij 19 patiënten met perifeer vaatlijden. Het specifieke doel van deze studie was de zodanige optimalisatie van het scanprotocol dat de beeldkwaliteit van de onderbenen zou verbeteren en dat de arteriële voetboog afgebeeld kon worden. Gebruik van de spoel maakte het in alle 19 gevallen mogelijk hoge-resolutie beelden van de gehele perifere vaatboom te verkrijgen. In alle gevallen waarin dit gevraagd werd, is de arteriële voetboog in zijn geheel afgebeeld. Wij concluderen dat de nieuwe oppervlaktespoel het mogelijk maakt om met name in de onderbenen belangrijke verbeteringen in beeldkwaliteit te realiseren.

In *hoofdstuk 6* worden de resultaten van een multicentrische fase II studie gerapporteerd voor wat betreft veiligheid en bruikbaarheid van een nieuw intravasculair contrastmiddel voor perifere MRA. Intravasculaire contrastmiddelen hebben als voordeel dat zij langer in de bloedvaten aanwezig blijven dan conventionele extracellulaire contrastmiddelen. Het gebruik van deze middelen biedt de mogelijkheid om langer te scannen en zo beelden met een hogere spatiële resolutie te verkrijgen, wat de diagnostische nauwkeurigheid mogelijk ten goede komt. Voor deze studie werden in 4 centra 33 patiënten geïncludeerd. De verkregen beelden van de perifere vaten werden vergeleken met röntgenarteriografie dat als referentiestandaard gebruikt werd. Er wordt geconcludeerd dat intravasculaire CV-MRA veilig kan worden uitgevoerd en gebruikt kan worden voor detectie en gradering van perifeer arteriëel vaatlijden in grote en middelgrote arteriën. Echter, het onderscheid tussen kleine arteriën en venen zoals aanwezig in de onderbenen is zeer moeilijk te maken met de huidige technieken waardoor deze contrastmiddelen nog voorlopig nog niet klinisch toepasbaar zijn.

De klinische bruikbaarheid van contrast-versterkte MRA

In *hoofdstuk 7* wordt de waarde van perifere CV-MRA onderzocht voor het aantonen van de arteriële anatomie en de potentiële bruikbaarheid van deze techniek voor distale bypass chirurgie. Drieëntwintig patiënten met chronische kritieke ischemie en weefselverlies (Fontaine IV / Rutherford III; de meest ernstige vorm van perifeer arteriëel vaatlijden) participeerden in dit onderzoek. Met CV-MRA werden in deze studie meer open vaten gevonden, en werden meer vaten geschikt bevonden voor een distale bypass-anastomose, in vergelijking met röntgenarteriografie. Het initiële behandelplan werd in 35% van deze patiënten ten voordele veranderd door het gebruik van CV-MRA. Op basis van deze bevindingen concluderen wij dat CV-MRA een zeer bruikbare toevoeging is op conventionele intra-arteriële catheter technieken in het behandeltraject van patiënten met chronische kritieke ischemie en weefselverlies, met name als dit onderzoek vóór het röntgenonderzoek plaatsvindt.

In *hoofdstuk 8* wordt prospectief de diagnostische betrouwbaarheid van twee niet- of minimaal invasieve procedures, namelijk kleuren ultrageluidsonderzoek en CV-MRA, voor de diagnostiek van perifeer arteriëel vaatlijden in 302 patiënten onderzocht. Intra-arteriële röntgenarteriografie werd hierbij gebruikt als de referentiestandaard. De resultaten beschreven in dit proefschrift laten zien dat CV-MRA een meer gevoelige techniek is (85% sensitiviteit) dan kleuren duplex ultrageluid (71% sensitiviteit) voor het aantonen van luminale vernauwingen 50% ('hemodynamisch significante stenosen'). Tevens werd voor CV-MRA ook een hogere specificiteit gevonden, wat inhoudt dat de techniek ondanks de hogere gevoeligheid niet meer patiënten ten onrechte ziek verklaart (d.w.z. niet bij meer patiënten ten onrechte een stenose ≥ 50% ziet). Wij concluderen dat CV-MRA een betere diagnostische modaliteit is dan duplex ultrageluid voor de evaluatie en behandeling van patiënten met perifeer vaatlijden en derhalve in de toekomst de methode van eerste keus kan worden.

In plaats van het vergelijken van de ernst van vernauwing in verschillende vaatsegmenten met verschillende modaliteiten in relatie tot een derde modaliteit kan het ook nuttig zijn om te kijken naar het effect van het gebruik van verschillende modaliteiten op het behandelplan bij patiënten met perifeer arteriëel vaatlijden. Om dit effect te quantificeren onderzoeken wij in *hoofdstuk 9* bij 100 patiënten met perifeer vaatlijden of het vervangen van kleuren duplex ultrageluid door CV-MRA tot andere behandelplannen leidde. Drie vaatchirurgen stelden hiertoe behandelplannen op die gebaseerd waren op gestandaardiseerde klinische informatie en de uitslag van, ofwel kleuren duplex ultrageluidonderzoek, ofwel CV-MRA onderzoek. Wij vonden dat indien CV-MRA werd gebruikt als beeldvormende modaliteit de chirurgen in gemiddeld 91 gevallen een behandelplan konden formuleren, in vergelijking met gemiddeld 62 gevallen voor duplex ultrageluid. Op basis van deze resultaten concluderen wij dat CV-MRA een effectievere modaliteit is dan duplex ultrageluid voor het formuleren van een behandelplan bij de meeste patiënten. Dit verschil is zowel groot voor patiënten die zich voor het eerst presenteren of patiënten die in het verleden reeds vaatchirurgie ondergingen en nu opnieuw klachten hebben.

In *hoofdstuk 10* worden de bevindingen in dit proefschrift in perspectief geplaatst van de huidige literatuur en worden de belangrijkste punten voor successvolle implementatie van perifere CV-MRA besproken. Het hoofdstuk wordt afgesloten met een discussie over toekomstige ontwikkelingen m.b.t. het gebruik van MRA en MRI voor het afbeelden van patiënten met perifeer arteriëel vaatlijden.

Conclusies

De conclusies van dit proefschrift zijn:

1 Contrast-versterkte MR angiografie is een zeer betrouwbare beeldvormende modaliteit voor de diagnostische en preïnterventionele evaluatie van patiënten met perifeer vaatlijden in vergelijking met de referentiestandaard, intra-arteriële röntgenarteriografie.
2 De beeldkwaliteit van contrast-versterkte MR studies is aanzienlijk verbeterd in de afgelopen jaren door technische optimalisatie zoals beschreven in dit proefschrift en de huidige beeldkwaliteit van MR angiografie is gelijkwaardig of beter dan intra-arteriële röntgenarteriografie bij de meeste patiënten.
3 Contrast-versterkte MR angiografie is een waardevol diagnosticum voor de diagnostische en preinterventionele evaluatie van patiënten met chronische kritieke ischemie en weefselverlies, omdat met MR angiografie meer bloedvaten gedetecteerd worden die geschikt worden geacht voor bypass chirurgie. Met MR angiografie is tevens de status van de inflow vaten beter te evalueren.
4 Contrast-versterkte MR angiografie is een meer sensitieve techniek dan duplex ultrageluid voor de detectie van haemodynamisch significante stenosen in de diagnostische evaluatie van patiënten met perifeer vaatlijden.
5 Vanwege de hoge sensitiviteit van contrast-versterkte MR angiografie en de mogelijk om informatie over proximale en distale bekken- en beenarteriën te verkrijgen gelijkwaardig aan invasieve intra-arteriële röntgenarteriografie, vinden wij dat contrast-versterkte MR angiografie de beeldvormende procedure van eerste keuze moet worden bij patiënten met de verdenking op perifeer vaatlijden.

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About the author

The author of this thesis was born on April 27, 1973 in Geleen, The Netherlands. He obtained his highschool diploma (magna cum laude) at Robbinsdale Armstrong Highschool in Plymouth, Minnesota, USA and subsequently completed the first year of Biomedical Engineering at the Institute of Technology at the University of Minnesota (magna cum laude). In 1990 he returned to The Netherlands and finished his secondary education at the Schöndeln College, Roermond in 1992. After leaving Roermond he attended the first year of Medical School at Leuven Catholic University in Leuven, Belgium. In 1993 he enrolled in the Medical School at Maastricht University where he participated in research alongside his medical studies at the departments of Immunology (1994/5), Anatomy & Embryology (1995/6) and Radiology (1996/7) and was founding vice-president and treasurer of the first Maastricht Medical Students Research Conference (1996). He obtained his MSc degree in 1997 (cum laude). In September 1997 he started internships and, from June 1998 enrolled in the MD-PhD program where the present line of research was established. In September 2000 he received his MD degree (cum laude) in the meantime working on the research projects which resulted in this thesis. For part of this work he was nominated for the Annual Ernst Schering Prize of the Dutch Radiological Society (1998). He has presented original research and invited papers at many international conferences. The author has been awarded the Niels Stensen Stipend and will continue research as a postdoctoral research fellow at the Angiogenesis Research Center at Dartmouth Medical School and Dartmouth Hitchcock Medical Center in Hanover, New Hampshire, USA.

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