MR angiography after coiling of intracranial aneurysms

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MR angiography after coiling of intracranial aneurysms

MR angiografie na coiling van intracraniële aneurysmata

(met een samenvatting in het Nederlands)

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General introduction

Introduction

The prevalence of unruptured intracranial aneurysms ("ανεύρυσμα" (Greek), meaning "dilatation") in the general population is approximately 3%.[1] The impact of rupture of these aneurysms is enormous because this often occurs on a relatively young age and has a high mortality and morbidity. Aneurysmal subarachnoid hemorrhage therefore accounts for a loss of productive life years similar to that of ischemic stroke.[2]

As from the early nineties, endovascular occlusion of intracranial aneurysms with detachable coils has been gradually introduced as an alternative treatment to neurosurgical clipping.[3,4] Its minimal invasiveness is the most important advantage of this treatment compared to clipping. The disadvantage of occlusion with coils is an approximately 20% risk of reopening of the aneurysm as a result of coil impaction, dissolution of thrombus, or growth of the aneurysm. Around 10% of coiled patients need additional treatment.[5] As a consequence, patients need to be followed up after coiling to detect and treat reopening and thereby prevent rupture of a reopened aneurysm. The standard technique to follow up coiled patients is intra-arterial digital subtraction angiography (IA-DSA). Mainly because of its complication risk, we would prefer an alternative non-invasive imaging technique. CT angiography cannot be used because the coils produce large artifacts but magnetic resonance angiography (MRA) is promising.[6] Besides its lower complication risk, MRA has more advantages over IA-DSA, such as absence of radiation, the outpatient setting, more comfort and convenience for patients, and lower costs.

Objective of this thesis

The aim of this thesis is to assess whether the diagnostic performance of MRA in coiled patients is sufficient to replace IA-DSA as the first-choice follow-up modality for this patient group. Specific questions are: 1) should we scan patients at 1.5 Tesla or at 3.0 Tesla; 2) is contrast enhancement necessary; 3) how can coil-induced artifacts be reduced; 4) can policy decisions be made on MRA; and 5) is MRA cost-effective compared to IA-DSA.

Outline of the thesis

In chapter 2 of this thesis we focus on the methodology of diagnostic research. In the chapters thereafter we show how we applied this methodology to our research question. In chapter 3, we describe the test characteristics of MRA; in chapter 4 and 5, we focus on the induction of coil artifacts; in chapter 6, we compare test characteristics of MRA with and without contrast

agent; in chapter 7, policy decisions on MRA and IA-DSA are compared; and in chapter 8, the cost-effectiveness of MRA related to IA-DSA is assessed. In the last two chapters, we aim to address a start for a tailored approach to follow up coiled patients. In chapter 9, we investigated whether geometry of intracranial arteries forms a risk factor for reopening, and in chapter 10, we assessed the long-term bleeding risk from adequately coiled aneurysms.

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2

Decision analysis to complete diagnostic research by closing the gap between test characteristics and cost-effectiveness

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Abstract

Objective: The lack of a standard methodology in diagnostic research impedes adequate evaluation before implementation of constantly developing diagnostic techniques. We discuss the methodology of diagnostic research and underscore the relevance of decision analysis in the process of evaluation of diagnostic tests.

Study design and setting: Overview and conceptual discussion.

Results: Diagnostic research requires a stepwise approach comprising assessment of test characteristics followed by evaluation of added value, clinical outcome, and cost-effectiveness. These multiple goals are generally incompatible with a randomized design. Decision-analytic models provide an important alternative through integration of the best available evidence. Thus critical assessment of clinical value and efficient use of resources can be achieved.

Conclusion: Decision-analytic models should be considered part of the standard methodology in diagnostic research. They can serve as a valid alternative to diagnostic randomized clinical trials.

Introduction

To date, consensus on the methodology to evaluate new diagnostic tests is lacking.[1] Moreover, with rapid technical advances, especially in the field of imaging, diagnostic techniques undergoing evaluation may be already outdated before diagnostic and clinical value have been established.[2,3]

Similar to therapeutic research a hierarchy can be discerned within diagnostic research.[1,2,4-7] A first step is assessment of test characteristics of a new test. The next step is evaluation of its added value.[8] A third step is assessment of the effect on clinical outcome, and the final step comprises a cost-effectiveness analysis.[7] For evaluation of clinical outcome and cost-effectiveness of tests, randomized clinical trials are often not feasible.

We will shortly review each step of diagnostic research and discuss decision analysis as a useful alternative methodology for critical assessment of clinical value and efficient use of resources.

The hierarchy in diagnostic research

We will illustrate the different phases of diagnostic research following the example of carotid artery stenosis, a well-known risk factor for stroke. Carotid endarterectomy reduces this risk in selected patients.[9,10] The standard technique for grading stenosis used to be intra-arterial angiography (IA-DSA), an invasive imaging modality. Later on, magnetic resonance angiography (MRA) and duplex ultrasound (DUS) were introduced as noninvasive alternatives.[11]

Step 1: Test characteristics

Test characteristics of a diagnostic tool provide information on the ability to discriminate between absence and presence of disease. They are expressed in terms of sensitivity, specificity, predictive values, and likelihood ratios. Sensitivity and specificity are useful in selecting tests, while predictive values provide information on the probability of disease given a certain test result.[1] Likelihood ratios characterize the change in the probability of disease after completing the test compared with the probability of disease before completing the test.

Test characteristics should be evaluated in a blinded cross-sectional study. Each test including a reference test needs to be performed in all study subjects to enable direct comparisons of the tests. Furthermore, the study participants ought to be representative of the target population.[12,13] In diagnostic tools that require interpretation, intra- and inter observer variability should also be assessed. In carotid artery stenosis test characteristics of MRA and DUS have been established in a blinded cross-sectional study with IA-DSA as the reference test.[14]

A limitation of assessing test characteristics is dichotomization of test results, whereas only few tests yield just "presence" or "absence" of disease as test results. For continuous and ordinal test results, a threshold needs to be established to determine whether a result is positive or negative. Ideally, this positivity criterion should reflect the clinical impact of false-positive and false-negative results. In case of carotid stenosis the consequences of false-positive results such as complications of unnecessary treatment, should be weighed against the consequences of missing severe stenosis. Dichotomization generally leads to loss of information. To avoid this, likelihood ratios can be used. They represent the ratio between the likelihood of a particular test result in patients with a certain disease status and the likelihood of the same test result in patients without this disease status. In case of multiple test results, the likelihood ratio can be calculated for each test result. Subsequently, the probability of the presence of disease, given a certain test result, can be calculated starting from the probability of disease before the test result was known and the likelihood ratio of the pertaining test result.[15,16]

A further limitation of test characteristics is the use of a "gold" standard to establish a "true" disease status. Within this framework, a new test can never outperform its reference test, which in daily practice has frequently happened. For example, computed tomography (CT) scanning was clearly better than skull radiography for assessing intracranial pathology.

Moreover, test characteristics are not constant, but are influenced by factors, such as prevalence of disease, disease severity, gender, age, and comorbidity. The higher the prevalence of disease, the higher the predictive value of a positive test result and the lower the predictive value of a negative test result. Apart from the predictive values, sensitivity and specificity may also be influenced by disease prevalence. However, the latter effect is indirect through prevalence varying with disease severity or disease spectrum. The probability of disease changes when information is obtained from the history, physical examination, and prior tests, because this information is used to select patients with a higher probability of disease for further diagnostic testing.[17] Within a specific selection of patients, the prevalence of disease and disease severity may be higher. In case of a more advanced stage of disease, the sensitivity will increase when abnormalities are easier detected. The relation between prevalence and clinical setting is illustrated by the comparison between a hospitalized bedridden patient who develops sudden dyspnea and hypoxia accompanied by an elevated level of d-dimers, and an otherwise healthy person who presents with acute dyspnea in an outpatient setting. Clearly, the first patient has a higher probability of pulmonary embolism than the second. Since the first patient was bedridden, more extensive pulmonary embolism could have been developed than in the second patient, which may increase the likelihood that embolism is detected on subsequent pulmonary CT angiography, thus increasing sensitivity. Conversely, in a screening setting, the prevalence

of disease is low and disease stages are likely to be less advanced, which may increase the specificity. Hence, test characteristics can vary with the population in which the test is applied. The influence of other factors, such as age, sex, and comorbidity on test characteristics can be evaluated by multivariate regression analysis.[18,19]

Although seemingly straightforward, a considerable variation in study design in test research has been observed. To overcome inconsistent methodology and reporting on test research the STARD initiative (STandards for Reporting of Diagnostic Accuracy) was launched.[20]

Step 2: Added value of a test

In clinical practice, tests are generally used in sequence. For each subsequent test, its added value must be considered. The added value in this phase of evaluation is expressed in terms of increase in proportion of patients correctly categorized as diseased or nondiseased, which is represented by an increased area under the receiver-operating characteristic (AUROC) curve.

Added value of a new test can be estimated using multivariate regression analysis.[3,8]

In addition, a statistically significant increase in the AUROC curve does not necessarily represent clinical improvement, because this also depends on the positivity criterion. In patients with clinically suspected carotid artery stenosis, the added value of imaging will not inform us whether clinical outcome will improve in terms of strokes avoided. If MRA enables detecting smaller grade stenosis than DUS, more patients will have a positive test result. When patients with carotid artery stenosis benefit from treatment of severe stenosis only, which could already be accurately detected by DUS, detection of smaller grade stenosis by MRA will not improve outcome. Thus, added value in terms of a statistically significant increase in AUROC curve may not always have actual clinical value.

Step 3: Clinical outcome

The eventual goal of a new diagnostic test is to improve clinical outcome.[3-5,8] Clinical outcome after implementation of a new diagnostic test can be assessed by an RCT.[2-4,7]

RCTs in diagnostic research, however, have several limitations. Firstly, RCTs generally require a long follow-up before consequences of false-positive and false-negative test results become apparent. During this long period of follow-up, new diagnostic techniques may emerge, which may outdate the results of the trial before it is completed. Secondly, large groups of participants are often needed. When the new and the reference tests do not differ much in their ability to detect disease, only the limited subset of subjects with discordant test results carries relevant

information. Dependent on the expected difference in disease course after diagnosis and ensuing treatment, the overall difference in outcome between randomized groups may be further diluted. Therefore, a straightforward comparison of two diagnostic tests may already require many participants. Importantly, often more than two diagnostic tests require simultaneous evaluation. Additionally, various cutoff criteria, including multiple test results, the order of tests, and specific combinations of tests, will increase the number of diagnostic strategies to be evaluated. Representing all diagnostic strategies implies that the number of participants required increases exponentially. In the example of carotid stenosis, test characteristics of DUS, MRA, and IA-DSA show little difference. An RCT should include ample participants to represent all relevant diagnostic strategies and to attain sufficiently large groups with discordant test results. Finally, a diagnostic RCT including an already established treatment strategy is inefficient. If outcome of treatment has already been established by therapeutic research, follow-up of treated patients would be redundant. In carotid stenosis, the effect on clinical outcome after carotid endarterectomy had already been assessed in therapeutic trials.[9,10] Therefore, follow-up after treatment was deemed unnecessary for the evaluation of diagnostic strategies. An RCT would be a viable option only if the new diagnostic tool has consequences for treatment that has not been previously evaluated.

Decision-analytic models present an important alternative to an RCT.[2,5] Through modeling, clinical outcome after application of a new test can be predicted by integrating the available evidence. A decision tree gives an overview of all diagnostic strategies with probabilities for each event. A decision tree will not suffice when events tend to recur or when events occur after a long and variable time span, such as in chronic diseases.[21,22] For more complex diagnostic and disease processes, such as in carotid artery stenosis, Markov models are useful. These are typically based on probabilities of transitions between pre-defined health states for all possible scenarios. Time-dependent risks and instantaneous risks for each scenario can be included. The distribution of patients among the different health states after a specified time span, for example, one year, is calculated. This can repeatedly be performed depending on the defined duration of follow-up. Uncertainty regarding the estimates of the input parameters of the model can be explored using Monte Carlo simulation. Through Monte Carlo simulation, multivariable sensitivity analysis is conducted to predict clinical outcome of a hypothetical group of subjects after a defined period of time, including uncertainty regarding the predicted outcome.[22-24] Decision-type models are flexible and can be designed to reflect an infinite number of diagnostic strategies. Furthermore, models can simulate a long follow-up period for a large group of subjects while recording all relevant outcomes and time frames simultaneously. Because there is no need to perform a lengthy RCT, the duration of uncertainty regarding the

best diagnostic strategy is considerably shortened. Moreover, although decision models may appear complex and modeler driven, they do not obscure clinical evidence. All assumptions and estimates can be verified.

The level of decision uncertainty with regard to the appropriate diagnostic strategy is mostly reduced by an RCT. Decision modeling forms the only alternative where a proper RCT is unfeasible. Uncertainty remaining after a modeling study may be reduced by further research on the parameter that introduces most uncertainty. Whether investment of additional resources to reduce uncertainty is worthwhile can be formally assessed.[25]

There are some limitations to decision models. Sufficient information should be available to create the model. Furthermore, diagnostic processes may be too complex to summarize in a decision tree. In addition, decision models may never comprise all subtle associations and interactions of clinical reality. For instance, test characteristics are generally assumed to be constant and independent of other test results acquired previously. In reality, these previous test results can influence the interpretation of the subsequent test as being discussed before, but the actual change in test characteristics is rarely known. The influence of change in test characteristics on the eventual outcome can be assessed by sensitivity analysis.

Step 4: Cost-effectiveness

Decision models can also keep track resource use in relation to clinical outcome. The costs of the tests applied, the transitions, and events occurring can be integrated in the model. Subsequently, the incremental costs per additional unit of health, for example, extra costs per quality-adjusted life-year (QALY) gained, can be calculated for all diagnostic strategies. By comparing these results, the strategy with the best trade-off between costs and effects can be identified.

A study comparing 62 diagnostic strategies for carotid artery stenosis was performed. Using a Markov model, long-term outcome of the diagnostic work-up and following treatments in terms of life-years, QALYs, and costs were predicted and compared across strategies. DUS alone resulted in an optimal balance between costs and effects. The addition of MRA led to a slightly better outcome with a disproportionate increase in costs. Because of its complication risk, any strategy comprising IA-DSA was proven inferior.[26]

This demonstrates that Markov modeling not only allows for assessment of cost-effectiveness, but also for evaluation of clinical outcome. Hence, this example covers step three and step four.

Evaluation of decision models

Examples of validated decision-analytic models showed that the results of decision modeling were consistent with observed data from cohort follow-up studies.[27-29] For two of these studies, the input parameters of the Markov model originated from a cohort different from that with which the results were compared.[27,28] Another study used the short-term follow-up data of an observational study cohort for a Markov model. The expected value of the model was compared with the long-term follow-up data of the same cohort and with data from the literature.[29]

A few aspects are important for the evaluation of Markov models. First, the model should reflect clinical reality in sufficient detail such that critical evaluation by expert peers remains possible. Furthermore, all model components, that is, the parameters describing each state transition, the health state value judgments, and cost estimates, need to be discussed in a multidisciplinary setting. Finally, because Markov models will be increasingly used, guidelines for its evaluation need to be developed.[30,31]

We strongly recommend using decision models to evaluate diagnostic tests, provided reliable model parameters can be obtained, particularly, estimates of key variables. Notably, a reference standard is required to evaluate any diagnostic approach because it remains essential for the diagnosis of any disease. This reference standard does not necessarily have to be a "gold" standard. Even though imperfection of a reference standard impairs perfect labeling of "false"-positive and "false"-negative test results, the impact of uncertainty of test characteristics on clinical outcome can be evaluated by Monte Carlo simulation. Finally, a standard treatment and pertaining outcome should be established. This can range from supportive treatment to causal treatment. For the majority of diseases, a certain treatment can be recognized. Hence, we believe that, in most cases, a decision model has major advantages compared to diagnostic RCTs because it saves time and resources, and allows cost-effectiveness analysis.

Conclusions

Evaluation of a diagnostic strategy requires a phased approach. Frequently, an RCT is neither feasible nor warranted for assessment of outcome in addition to test characteristics. Decision-analytic models can integrate the best available evidence, including economical data, and should be part of the standard methodology in diagnostic research.

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3

Test characteristics of follow-up MR angiography in patients with coiled intracranial aneurysms

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Abstract

Background and purpose: To determine the test characteristics of magnetic resonance angiography (MRA) in the assessment of occlusion of aneurysms treated with coil placement.

Methods: This was an ethics committee-approved multicenter study. Written informed consent was obtained in 311 patients with 343 aneurysms, who had been treated with coil placement and who were scheduled for routine follow-up with intra-arterial digital subtraction angiography (IA-DSA). Thirty-five patients participated two or three times. Either 3.0-Tesla or 1.5-Tesla time-of-flight (TOF) and contrast-enhanced (CE) MRA were performed in addition to IA-DSA. Aneurysm occlusion was evaluated by independent readers on IA-DSA and MRA. The test characteristics of MRA were assessed by using IA-DSA as the reference standard. The area under the receiver operating characteristic curve (AUROC) was calculated for 3.0-Tesla versus 1.5-Tesla MRA and for TOF-MRA versus CE-MRA. Factors associated with discrepancies between MRA and IA-DSA were assessed with logistic regression.

Results: Aneurysm assessments (n=381) on IA-DSA and MRA were compared. Incomplete occlusion was seen on IA-DSA in 88 aneurysms (23%). The negative predictive value of MRA was 94% (95% CI, 91 to 97), the positive predictive value 69% (95% CI, 60 to 78), sensitivity 82% (95% CI, 72 to 89), and specificity 89% (95% CI, 85 to 93). AUROCs were similar for 3.0-Tesla (0.90 [95% CI, 0.86 to 0.94]) and 1.5-Tesla MRA (0.87 [95% CI, 0.78 to 0.95]), and for TOF-MRA (0.86 [95% CI, 0.81 to 0.91]) and CE-MRA (0.85 [95% CI, 0.80 to 0.91]). A small residual lumen (odds ratio, 2.1 [95% CI, 1.1 to 4.3]) and suboptimal projection on IA-DSA (odds ratio, 5.5 [95% CI, 1.5 to 21.0]) were independently associated with discordance between IA-DSA and MRA.

Conclusion: Documentation of good diagnostic performance of TOF-MRA at both 1.5 Tesla and 3.0 Tesla in the current study represents an important step towards replacing IA-DSA by MRA in the follow-up of patients treated with coils.

Introduction

Currently, endovascular occlusion with coils is the first-line treatment for intracranial aneurysms.[1,2] A disadvantage of coil placement is the substantial risk for reopening of the aneurysm, which occurs in approximately 20% of patients.[3-7] Additional treatment is required in around 10% of patients treated with coils,[4-8] and follow-up imaging of coiled aneurysms to detect reopening is therefore recommended. The standard follow-up modality is intra-arterial digital subtraction angiography (IA-DSA), but this diagnostic procedure is invasive, exposes patients to vascular complications and to ionizing radiation, and requires angiography suite facilities and personnel.[9,10]

Magnetic resonance angiography (MRA) is a noninvasive, nonirradiating alternative method for assessing the degree of occlusion of coiled intracranial aneurysms and can be performed in an outpatient setting. Small single-center studies on the diagnostic performance of MRA have shown promising, but not yet conclusive, results.[11-20] Other unresolved issues are the additional value of contrast-enhanced (CE) MRA over time-of-flight (TOF) MRA and the comparison between 1.5- and 3.0-Tesla MRA in patients treated with coil placement.

The purpose of our study was to determine the test characteristics of MRA in the assessment of occlusion of aneurysms treated with coil placement.

Materials and methods

The institutional review boards of the participating centers approved this study. All participants provided written informed consent. No indirect or direct financial support was provided by an industry. The authors had control over the data submitted for publication.

Participants

In four university hospitals (University Medical Center Utrecht, Academic Medical Center Amsterdam, Vrije Universiteit Medical Center Amsterdam, and University Medical Center Leiden) in which treatment of aneurysms with coils had been performed for more than five years at time of onset of the study, we prospectively approached consecutive patients with coiled intracranial aneurysms who were eligible for follow-up IA-DSA. In these centers, follow-up IA-DSA is considered appropriate when patients have regained independence in activities of daily living after subarachnoid hemorrhage, and in patients with unruptured aneurysms. IA-DSA is usually performed twice in the first two years after coiling. Within the inclusion period, patients could be recurrently recruited after additional coiling or for the second follow-up IA-DSA

examination. Patients were excluded for the following reasons: (a) additional aneurysms treated with neurosurgical clips that either contained ferromagnetic material or were located less than 20 mm from the coiled aneurysm, (b) claustrophobia, (c) presence of a cardiac pacemaker, or (d) age younger than 18 years (Figure 3.1). For included patients (Table 3.1), we planned the MRA examination on the same day as the IA-DSA examination. On the basis of available data prior to the study, a 25% reopening rate and a range of less than 5% around the point estimate of the false-negative rate, would require 350 aneurysm comparisons on MRA and IA-DSA.

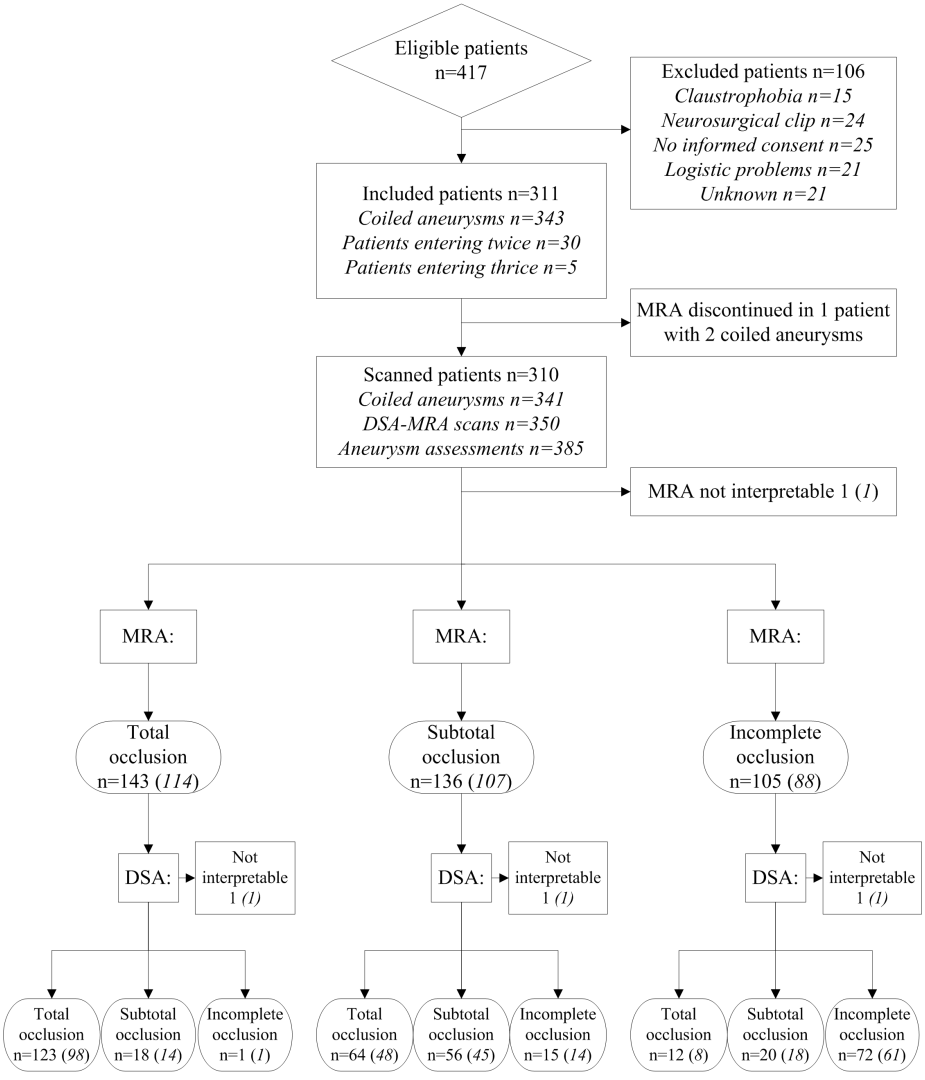

Figure 3.1 Flow diagram shows recruitment of patients, as well as test results. The boxes and ovals for test results report the number of aneurysm assessments, with the number of patients in parentheses.

Table 3.1 Baseline characteristics of 311 patients

Characteristic	
Center	
1	69 (22)
2	119 (38)
3	69 (22)
4	54 (17)
No. of women	219 (70)
Age (y)*	51 ± 12 (19-79)
No. of patients with multiple coiled aneurysms	28 (9)
No. of coiled aneurysms	343
No. of ruptured aneurysms	264 (77)
Location of coiled aneurysms	
Carotid artery†	128 (37)
Anterior communicating artery‡	129 (38)
Middle cerebral artery	34 (10)
Posterior circulation	52 (15)
Size of coiled aneurysms (mm)*	7 ± 5 (1-50)
Total no. of IA-DSA examinations	350
Interval between coiling and imaging (mo)	
3 months	38 (11)
6 months	202 (58)
18 months	83 (24)
>18 months	27 (8)

Unless otherwise specified, data are numbers of patients or aneurysms, with percentages in parentheses.
* Data are means ± standard deviations, with the range in parentheses.
† Including the posterior communicating and ophthalmic arteries.
‡ Including the anterior cerebral and pericallosal arteries.

Imaging technique for IA-DSA

IA-DSA was performed with an angiographic unit (Integris BN5000/Allura Neuro, Philips Medical Systems, Best, the Netherlands; Infinix Bi-plane, Toshiba Medical Systems, Otawara, Japan; or Axiom Artis, Siemens Medical Systems, Erlangen, Germany) by means of transfemoral catheterization. The following standard projections were obtained: (a) an anterior-posterior view; (b) a lateral view; and (c) the optimal projection used at coil embolization. A maximum of 8 mL of nonionic contrast agent (iodixanol, Visipaque; GE Healthcare, Oslo Norway) (300 mmol/mL) was injected with a velocity of 4 mL/s. We recorded the occurrence of any complications, defined as symptomatic or asymptomatic thromboembolic events, arterial perforation or dissection, and allergic reactions to the contrast agent.

Imaging techniques for MRA

Three centers (University Medical Center Utrecht, Academic Medical Center Amsterdam, University Medical Center Leiden) performed MRA with a 3.0-Tesla MR imaging unit (Achieva, Philips Medical Systems), but in the presence of neurosurgical clips made of cobalt or titanium, patients were imaged at a 1.5-Tesla unit (Achieva, Philips Medical Systems) instead of a 3.0-Tesla unit. One center (Vrije Universiteit Medical Center Amsterdam) performed all MR imaging studies at a 1.5-Tesla unit (Sonata, Siemens). We used phased-array head coils equipped for parallel imaging as receive coils. The protocol consisted of transverse T1-weighted spin echo and T2-weighted fast spin echo sequences, three-dimensional TOF-MRA, and CE-MRA sequences with bolus-timing for each patient (See Appendix for imaging parameters). Total imaging time was 20 minutes. We recorded allergic reactions to the contrast agent.

Evaluation of IA-DSA images

The method of image evaluation was discussed during research meetings prior to the data collection. In each center two neuroradiologists, of whom at least one was an interventional neuroradiologist, independently evaluated IA-DSA images. They were unaware of the parallel MRA results. The observers recorded whether the projection of the aneurysm was optimal. They subsequently assessed the degree of aneurysm occlusion according to the following classification: class 1 indicated total occlusion, when the aneurysm was completely obliterated; class 2, subtotal occlusion, when residual filling was restricted to the neck of the aneurysm; and class 3, incomplete occlusion, when there was residual flow in the aneurysm sack.[21] The maximum diameter of the residual lumen was measured in relation to the caliber of the carotid artery (4 mm) or of the basilar artery (3 mm). Discordant test results were solved by joint reassessment.

Evaluation of MRA images

MRA images were also independently evaluated in each center by two neuroradiologists, of whom at least one was an interventional neuroradiologist, who were unaware of the parallel IA-DSA results. T1- and T2-weighted images were used to evaluate the presence of thrombus because thrombus usually appears as an area of high signal intensity on TOF-MRA, similar to residual flow. Source images, three-dimensional maximum intensity projections, and three-dimensional volume-rendered reconstructions were available for the assessment. The occlusion level was first scored on TOF-MRA, then on CE-MRA with a final judgment based on both sequences. The observers indicated preference for TOF- or CE-MRA and reported whether coil artifacts impaired the assessment. The maximum diameter of the residual lumen was measured. Discordant test results were solved by joint reassessment.

Statistical analysis

We assessed interobserver agreement for all ratings on IA-DSA and for all ratings on MRA by kappa-statistics with linear weighting for the occlusion categories. We additionally computed interobserver agreement between two interventional neuroradiologists and between an interventional and a noninterventional neuroradiologist. The interpretation of kappa was as follows: $\kappa < 0$ indicated no agreement; κ 0-0.19, poor agreement; κ 0.2-0.39, fair agreement; κ 0.4-0.59, moderate agreement; κ 0.6-0.79, substantial agreement; and κ 0.8-1.00, almost perfect agreement.[22]

Using IA-DSA as a reference test, we first calculated test characteristics of MRA with corresponding 95% confidence intervals (CIs) for all assessments after dichotomization between incomplete occlusion, for which repeated treatment is considered, and subtotal and total occlusion. We subsequently calculated test characteristics on the basis of the first participation without assessments for additional coiled aneurysms. In addition, we computed test characteristics for dichotomization between total occlusion and subtotal and incomplete occlusion.

We compared the areas under the receiver operating characteristic curves (AUROCs) of 1.5-Tesla and 3.0-Tesla MRA. We also compared the AUROCs for TOF-MRA and CE-MRA to assess the added value of CE-MRA over TOF-MRA. These subgroup analyses were planned before assessment of the overall test characteristics.

We additionally analyzed potential explanatory factors for discrepancies between IA-DSA and MRA results by using univariate and multivariate logistic regression analysis.[23,24] We assessed the effect on test discrepancy of the following determinants: more than one follow-up IA-DSA examination, multiple coiled aneurysms, center, interobserver variability, small residual lumen (defined as 1-3mm[25,26]), impeding coil artifacts on MRA, and suboptimal projection of the coiled aneurysm on IA-DSA.

Our results are reported according to the "standards for reporting of diagnostic accuracy" (STARD).[27]

Results

Participants

Of 417 patients who were eligible for the study between May 2005 and November 2007, 311 patients with 343 aneurysms were included. We excluded 106 patients (Figure 3.1, Table 3.1).

Thirty patients participated in two follow-up procedures, and five participated in three follow-up procedures. One patient with two coiled aneurysms was excluded from the analysis after MRA was discontinued because of claustrophobia. No allergic reactions to the contrast agent occurred during MRA (0% [95% CI, 0 to 1%]). Adverse events occurred during 11 (3.1% [95% CI, 1.6 to 5.6%]) IA-DSA procedures: four thromboembolic events with temporary neurological deficit, a rash as an allergic reaction to the contrast agent in six patients, and a femoral artery dissection in one patient.

Image evaluation

Images from both TOF- and CE-MRA in one patient treated with platinum-iridium alloy coils containing a nitinol core were not interpretable because of coil artifacts and were excluded from the analysis. Two aneurysms (0.6% [95% CI, 0.0 to 2.1%]) could not be evaluated on TOF-MRA. One of these aneurysms was filled with thrombus that could not be distinguished from residual flow, despite comparison with T1-weighted images. The second aneurysm was imaged in the sagittal plane, which caused in-plane saturation. For these aneurysms, we used only CE-MRA for the analysis. Six other aneurysms (1.8% [95% CI, 0.7 to 3.8%]) could not be interpreted on CE-MRA. In two instances the aneurysm was not located in the coronal field of view; in two CE-MRA examinations, the timing of contrast bolus failed; and in two patients no CE-MRA was performed. In these cases, we only used TOF-MRA for the analysis. Movement artifacts were visible on TOF-MRA in three patients but did not impede the assessment. IA-DSA images were not interpretable for three aneurysms (0.9% [95% CI, 0.2 to 2.6%]) in two patients because the aneurysm was inadequately depicted. Thus, one aneurysm on MRA and three on IA-DSA could not be evaluated and were excluded from the analysis.

With 75 additional assessments for either additional investigations or for additional aneurysms in 310 patients, the total number of assessments was 385. Because four aneurysms were not interpretable on either MRA or IA-DSA, the total number of assessments available for the analysis was 381 (Figure 3.1). Aneurysms were incompletely occluded on 88 (23% [95% CI, 19 to 27%]) IA-DSA examinations in 76 patients (25% [95% CI, 20 to 29%]). The mean size of the residual lumen was 5 mm.

Interobserver agreement was substantial for both IA-DSA (κ 0.62 [95% CI, 0.56 to 0.69]) and MRA (κ 0.64 [95% CI, 0.57 to 0.70]). The interobserver agreement between two interventional neuroradiologists (κ 0.61 [95% CI, 0.54 to 0.68]) was similar to the interobserver agreement between an interventional and a noninterventional neuroradiologist (κ 0.65 [95% CI, 0.60 to 0.71]).

Test discrepancies and test characteristics

Sixteen incompletely occluded aneurysms on IA-DSA in 16 patients were not identified as such on MRA. One aneurysm was classified on MRA as totally occluded but the assessment was influenced by coil artifacts. The remaining aneurysms were considered subtotally occluded on MRA (Figure 3.2). These 16 incompletely occluded aneurysms did not require repeat treatment.

Thirty-two aneurysms in 32 patients were classified as incompletely occluded on MRA whereas on IA-DSA, 20 of these aneurysms were classified as subtotally occluded with a mean residual lumen of 3 mm and 12 as totally occluded (Figure 3.3, 3.4).

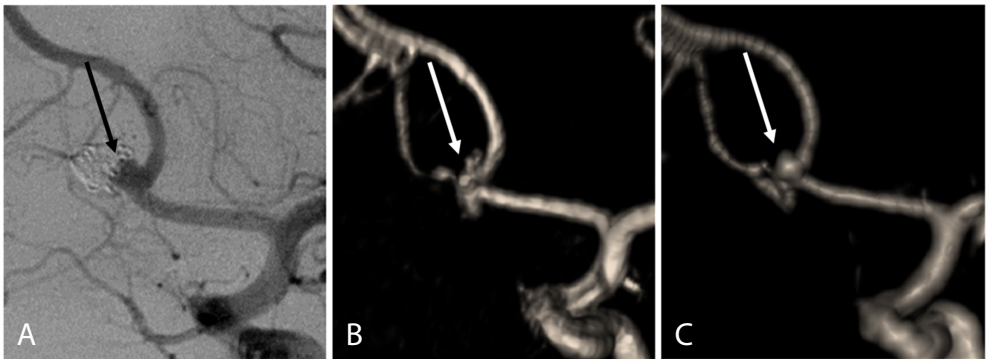

Figure 3.2 False-negative MRA result in a 52-year-old woman with a coiled anterior communicating artery aneurysm that was classified as incompletely occluded on **(a)** IA-DSA (optimal projection at coil embolization), and subtotally occluded on both **(b)** TOF-MRA (embolization view) and **(c)** CE-MRA (embolization view).

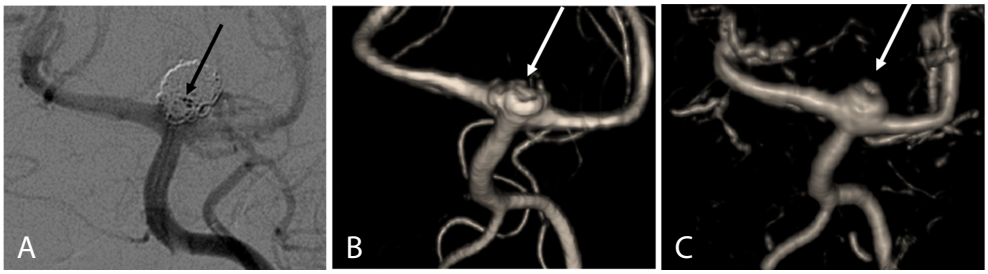

Figure 3.3 False-positive MRA result in a 33-year-old woman with a coiled basilar tip aneurysm that was classified as subtotally occluded on **(a)** IA-DSA (optimal projection at coil embolization), and incompletely occluded on both **(b)** TOF-MRA (embolization view) and **(c)** CE-MRA (embolization view).

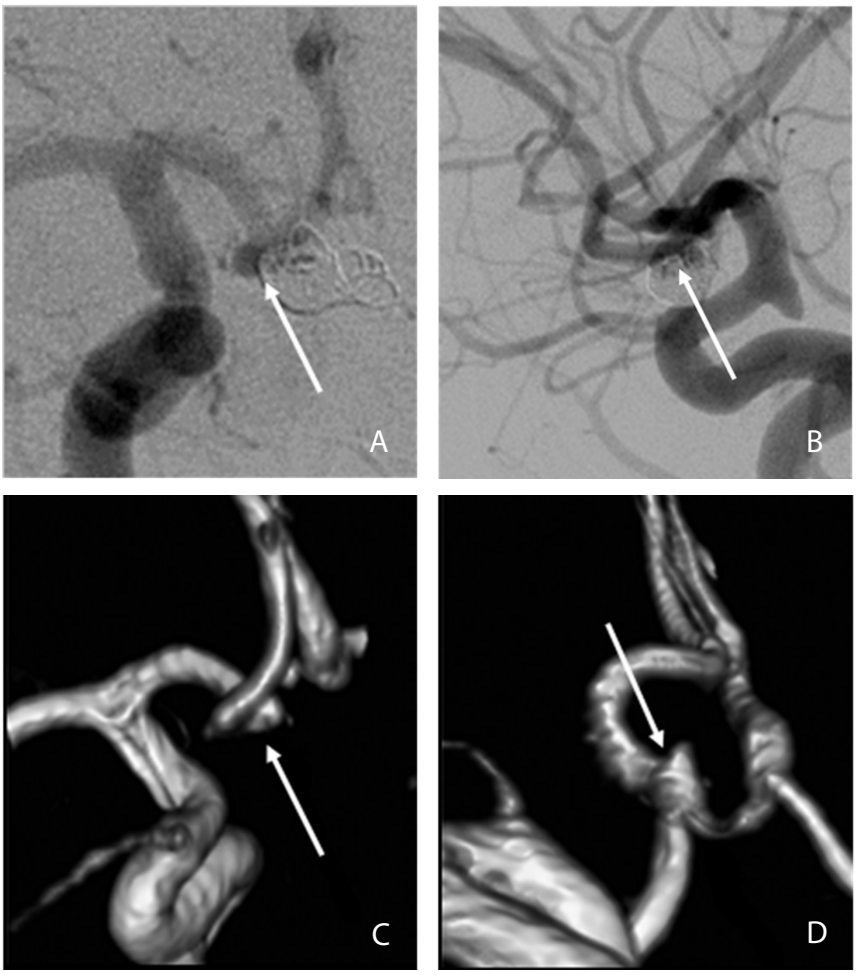

Figure 3.4 MRA provided additional information to IA-DSA in a 35-year-old man with a coiled anterior communicating artery aneurysm (arrow). **(a)** Anteroposterior view and **(b)** lateral view on IA-DSA. **(c)** Anteroposterior view on TOF-MRA. **(d)** By rotating the TOF-MRA images, we were able to improve depiction of the residual lumen.

The negative predictive value for the absence of incomplete occlusion on MRA with the use of IA-DSA as a reference, was 94%; the positive predictive value for the presence of incomplete occlusion was 69%; the sensitivity of MRA for detecting incomplete occlusion was 82%; the specificity for excluding incomplete occlusion was 89%; and the AUROC was 0.89 (Table 3.2). Test characteristics and AUROCs for 1.5-Tesla and 3.0-Tesla MRA were comparable (Table 3.2, Figure 3.5A).

Table 3.2 Test characteristics of MRA

Test characteristic*	Overall (381 assessments)			1.5-Tesla (74 assessments)			3.0-Tesla (307 assessments)		
NPV	261/277	(94)	[91, 97]	44/47	(94)	[82, 99]	217/230	(94)	[90, 97]
PPV	72/104	(69)	[60, 78]	17/27	(63)	[42, 81]	55/77	(71)	[60, 81]
Sensitivity	72/88	(82)	[72, 89]	17/20	(85)	[62, 97]	55/68	(81)	[70, 89]
Specificity	261/293	(89)	[85, 93]	44/54	(81)	[68, 91]	217/239	(91)	[86, 94]
AUROC†	0.89		[0.86, 0.93]	0.87		[0.78, 0.95]	0.90		[0.86, 0.94]

Unless otherwise specified, data are numbers of assessments, with percentages in parentheses and 95% CIs in brackets.
* NPV = negative predictive value, PPV = positive predictive value, AUROC = area under the ROC curve.
† Data are fractions.

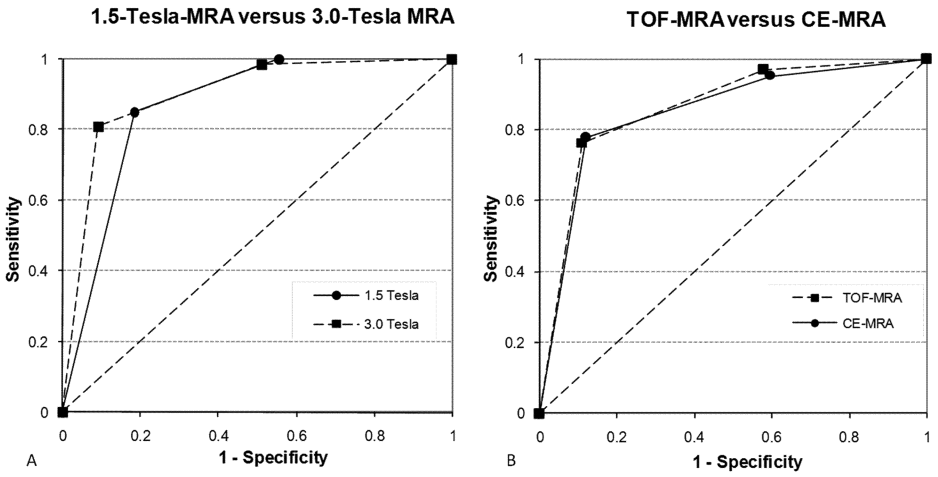

Figure 3.5 Receiver operating characteristic curves for **(a)** 3.0-Tesla versus 1.5-Tesla MRA and **(b)** TOF-MRA versus CE-MRA.

The test characteristics of the first MRA examination without assessments for additional coiled aneurysms, were similar: the negative predictive value was 93% (95% CI, 89 to 96%), the positive predictive value was 70% (95% CI, 59 to 80%), sensitivity was 80% (95% CI, 70 to 89%), and specificity was 89% (95% CI, 85 to 93%).

After dichotomization between total occlusion versus subtotal and incomplete occlusion, sensitivity increased (90% [95% CI, 85 to 94%]), the positive predictive value remained similar (68% [95% CI, 62 to 74%]), and the negative predictive value (87% [95% CI, 81 to 92%]) and specificity (62% [95% CI, 55 to 69%]) decreased.

Added value of CE-MRA

Review of the CE-MRAs led observers to change the classification of the aneurysm for 21 (6% [95% CI, 4 to 8%]) assessments. For nine aneurysms, the adjusted classification corresponded with the assessment on IA-DSA; for one aneurysm, the adjusted classification corresponded with a higher degree of occlusion; and for 11 aneurysms, the adjusted classification corresponded with a lower degree of occlusion than on IA-DSA. The AUROCs were similar for TOF-MRA (0.86 [95% CI, 0.81 to 0.91]) and for CE-MRA (0.85 [95% CI, 0.80 to 0.91]) (Figure 3.5B).

In 51% (95% CI, 48 to 55%) of the assessments, observers had no preference for CE-MRA over TOF-MRA. For 23% (95% CI, 20 to 26%) of the assessments, TOF-MRA was preferred, mostly because of a more detailed visualization of the vessels of interest. For the remaining 26% (95% CI, 23 to 29%) of the assessments, CE-MRA was preferred because of fewer artifacts or a better depiction of the residual lumen than on TOF-MRA.

Coil artifacts

Besides the excluded assessment of the aneurysm treated with platinum-iridium coils containing a nitinol core, coil-related artifacts impeded 29 (8%, [95% CI, 5 to 11%]) aneurysm assessments for both observers: 22 on TOF-MRA, one on CE-MRA, and six on both TOF-MRA and CE-MRA. Despite the artifacts, the observers could record a degree of occlusion. One aneurysm was classified on MRA as totally occluded and on IA-DSA as incompletely occluded after consensus reading. Eight other aneurysms were classified as subtotally occluded on MRA and as totally occluded on IA-DSA. The remaining aneurysms were similarly classified on MRA and IA-DSA.

Factors associated with discrepancy between IA-DSA and MRA

A small residual lumen (odds ratio, 2.1 [95% CI, 1.1 to 4.3]) and suboptimal projection of the coiled aneurysm on IA-DSA (odds ratio, 5.5 [95% CI, 1.5 to 21.0]) were independently associated with discrepancy between IA-DSA and MRA. Disagreement between two observers on both IA-DSA and MRA, and the presence of multiple coiled aneurysms tended to be associated with discrepancy, but not independently. Test discrepancy was not associated with a certain center or centers. We also found no association between discordant results and the other determinants (Table 3.3).

Table 3.3 Factors of influence on discrepancy between IA-DSA and MRA

	Regression analysis	
Factor	Univariate	Multivariate
Patients with multiple IA-DSA procedures (n=35)	1.1 (0.4, 2.8)	NA
Patients with multiple coiled aneurysms (n=28)	0.3 (0.1, 0.97)	0.3 (0.1, 1.0)
Center		NA
1 (77 assessments)	1.0	
2 (164 assessments)	1.1 (0.5, 2.6)	
3 (79 assessments)	0.4 (0.1, 1.4)	
4 (61 assessments)	2.1 (0.8, 5.3)	
Interobserver disagreement on IA-DSA (n=108)	2.0 (1.1, 3.8)	1.6 (0.8, 3.1)
Interobserver disagreement on MRA (n=115)	2.0 (1.1, 3.7)	1.9 (1.0, 3.5)
Small (1-3mm) residual lumen on IA-DSA (n=75)	3.1 (1.7, 5.8)	2.1 (1.1, 4.3)
Impeding coil artifacts on MRA (n=29)	0.2 (0.3, 1.7)	NA
Suboptimal projection on IA-DSA (n=12)	6.3 (2.0, 21.7)	5.5 (1.5, 21.0)

Data are odds ratios, with 95% CIs in parentheses. Discrepancy is defined as a rating of incomplete occlusion on IA-DSA with (sub) total occlusion on MRA or vice versa. NA = not applicable (variables that did not significantly contribute to discordant results in the univariate analysis were not evaluated in the multivariate logistic regression analysis).

Discussion

In the current study we demonstrated that TOF- and CE-MRA at both 1.5 and 3.0 Tesla had a high negative predictive value for aneurysm recurrence. Hence, there is only a very small probability of finding incomplete occlusion of an aneurysm on IA-DSA when MRA shows total or subtotal occlusion. Moreover, in our series, MRA depicted all incompletely occluded aneurysms that required repeat treatment. The lower positive predictive value of MRA implies that IA-DSA will not always help confirm a suspected incomplete occlusion on MRA, suggesting that recurrences identified on MRA might reasonably be confirmed with IA-DSA.

Previous smaller, single-center studies on the diagnostic performance of MRA after coiling found a wide range of test characteristics.[11,13-16,18] A meta-analysis showed test characteristics similar to those found in our study, but that analysis was limited by substantial methodologic heterogeneity of the individual studies.[15] These previous studies were predominantly performed at 1.5 Tesla rather than at 3.0 Tesla. Despite concerns about increased coil artifacts at 3.0 Tesla compared with 1.5 Tesla,[28] a previous study found no differences in 18 patients who were imaged at both 1.5 and 3.0 Tesla.[11]

The design of our study precluded direct comparison between TOF-MRA and CE-MRA. In one of the four centers, the aneurysm occlusion level was independently reassessed on CE-MRA and TOF-MRA. There was no difference in test characteristics between the two techniques.[29] Previous studies have also not identified a clear additional value of CE-MRA over TOF-MRA.[15] TOF-MRA may not depict slow residual flow due to spin saturation and may therefore underestimate the residual lumen.[30] Conversely, in our study, CE-MRA had a lower spatial resolution than TOF-MRA; this is inherent to the contrast-enhanced technique.

We aimed to attain a representative study population by including a consecutive series of patients who were being followed up routinely. We do not expect the reasons for exclusion to have been factors of influence on test characteristics. The mean aneurysm size and the proportion of patients with incomplete occlusion in our study were similar to those in other series of patients,[3-7] which underlines the idea that our study population was representative and that our results are generally applicable for patients treated with coils. Other factors supporting the external validity of our results are the use of MR imaging units from different companies, two field strengths, and the involvement of multiple observers.

The assessment of the occlusion status was to some extent limited by the use of a classification that does not take into account subtle differences in the degree of occlusion. This is illustrated by the greater discrepancy between IA-DSA and MRA results in coiled aneurysms with a small residual lumen than in those with a large or absent residual lumen. Apparently, in cases of a small residual lumen, it is more difficult to decide between subtotal and incomplete occlusion. We partly compensated for this loss of information by reporting the test characteristics after changing the cutoff value for a positive test result from incomplete to subtotal occlusion.

Variation in interpretation of the classification was also reflected in the interobserver agreement, which was substantial and similar for MRA and IA-DSA. The interobserver agreements were comparable to those found in a previous study on this classification.[31] The involvement of noninterventional neuroradiologists in the aneurysm assessments did not markedly influence the interobserver agreement.

Although IA-DSA is considered the standard of reference for identifying aneurysm recurrence after coiling, it is not a perfect method. Aneurysm assessment on IA-DSA can be limited by superimposition of arteries or by an impenetrable radiodense "helmet" around the remnant.[32] We found that suboptimal projection of the coiled aneurysm on IA-DSA was associated with discordant test results. Because we regard IA-DSA as the reference investigation, incomplete occlusion on MRA and not on IA-DSA was counted as a false-positive result, whereas in case of suboptimal projection of the aneurysm on IA-DSA, the residual flow detected on MRA is

probably real. The use of an imperfect reference test can therefore lead to underestimation of the diagnostic performance of MRA. Although three-dimensional rotational angiography is of proved value in untreated aneurysms,[33,34] at the time of this study it was of limited use in patients treated with coils because of pulsation artifacts caused by the coils. Improvement of the quality of three-dimensional rotational angiography may provide additional information to suboptimal two-dimensional IA-DSA projection.

Study limitations included the unequal proportions of patients imaged at 1.5 Tesla and those imaged at 3.0 Tesla. Moreover, some patients were included multiple times or had multiple coiled aneurysms, but test characteristics were similar in analyses confined to the first time assessments only.

These results favor the use of MRA at either 1.5 or 3.0 Tesla instead of IA-DSA for the follow-up of coiled aneurysms. Because CE-MRA carries a small but definite risk of nephrogenic systemic fibrosis[35,36] and its additional value to TOF-MRA is limited, TOF-MRA is preferred. The high negative predictive value in our study suggests that when a total or subtotal occlusion is observed on MRA, no further IA-DSA is required. As a result of the somewhat lower positive predictive value, additional diagnostic IA-DSA may be performed in case of incomplete occlusion on MRA to evaluate whether repeat treatment is necessary. Nevertheless, because the consequences of (re)bleeding are severe, the effects of incomplete occlusions that are not classified as such on MRA and remain undetected if IA-DSA is no longer performed should be accurately weighed against the risk of complications of performing IA-DSA in all patients treated with coils. Only on the basis of a risk–benefit balance can we conclude if MRA, and no longer IA-DSA, should be the first-line investigation in the follow-up of patients with coiled aneurysms.

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4

Artifacts induced by coiled intracranial aneurysms on 3.0-Tesla versus 1.5-Tesla MR angiography – an *in vivo* and *in vitro* study

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Abstract

Background and purpose: To compare metal-induced artifacts from coiled intracranial aneurysms on 3.0-Tesla and 1.5-Tesla magnetic resonance angiography (MRA), since concerns persist on artifact enlargement at 3.0 Tesla.

Methods: We scanned 19 patients (mean age 53; 16 women) with 20 saccular aneurysms treated with coils only, at 1.5 and 3.0 Tesla according to standard clinical 3D TOF-MRA protocols containing a shorter echo time but weaker read-out gradient at 3.0 Tesla in addition to intra-arterial digital subtraction angiography (IA-DSA). Per modality two neuroradiologists assessed the occlusion status, measured residual flow, and indicated whether coil artifacts disturbed this assessment on MRA. We assessed relative risks for disturbance by coil artifacts, weighted kappa's for agreement on occlusion levels, and we compared remnant sizes. For artifact measurements, a coil model was created and scanned with the same protocols followed by 2D MR scans with variation of echo-time and read-out gradient strength.

Results: Coil artifacts disturbed assessments less frequently at 3.0 Tesla than at 1.5 Tesla (RR: 0.3 [95% CI 0.1 to 0.8]). On 3.0-Tesla MRA, remnants were larger than on 1.5-Tesla MRA (difference: 0.7 mm [95% CI 0.3 to 1.1]) and larger than on IA-DSA (difference: 1.0 mm [95% CI 0.6 to 1.5]) with similar agreement on occlusion levels with IA-DSA for both field strengths (κ: 0.53 [95% CI 0.23 to 0.84] for 1.5-Tesla MRA and IA-DSA; κ: 0.47 [95% CI 0.19 to 0.76] for 3.0-Tesla MRA and IA-DSA). Coil model artifacts were smaller at 3.0 Tesla than at 1.5 Tesla. The echo time influenced artifact size more than the read-out gradient.

Conclusions: Artifacts were not larger, but smaller at 3.0 Tesla because a shorter echo time at 3.0 Tesla negated artifact enlargement. Despite smaller artifacts and larger remnants at 3.0 Tesla, occlusion levels were similar for both field strengths.

Introduction

Endovascular occlusion with coils has become an established method of treating intracranial aneurysms.[1] Because flow may reappear in the coiled aneurysm, patients need to be followed up to prevent rupture. Even though intra-arterial digital subtraction angiography (IA-DSA) is the standard imaging modality for follow-up, magnetic resonance angiography (MRA) is a valid non-invasive alternative technique.[2]

A drawback of MRA is that coils create artifacts that may conceal recurrent flow. In most centers, 1.5-Tesla scanners are used for MRA but 3.0-Tesla scanners are increasingly available. The main advantage of using higher field strength is the increased intrinsic MR signal that allows the use of a higher spatial resolution while maintaining acceptable signal-to-noise-ratio (SNR) levels and scan duration. Conversely, metal-induced field disturbances proportionally increase with increasing field strength for metals below magnetic saturation and in absence of permanent magnetisation.[3] Such field disturbances contribute to imaging artifacts in several ways. For single echo gradient echo scans, as used for TOF-MRA, the most important mechanisms for artifact formation are 1) interference of field disturbances with the read-out gradient resulting in geometric distortion of tissue in the metal's vicinity, and 2) intra-voxel dephasing leading to signal loss in regions of strong local magnetic field gradients around the metallic implant. The degree of geometric distortion decreases when a stronger read-out gradient is used. However, using a stronger read-out gradient increases the bandwidth of the receiver and thereby the noise level in the images. The degree of intra voxel dephasing is determined by the voxel size and the echo time. Smaller voxels and a shorter echo time result in less dephasing and thereby to smaller regions of signal loss.

Since it has been suggested that 3.0-Tesla MRA should be avoided in coiled patients because of artifact enlargement,[4,5] we compared aneurysm assessments and coil artifacts on 3.0-Tesla MRA with 1.5-Tesla MRA.

Materials and methods

Patient recruitment

This was an ethical-committee approved study and all participants provided written informed consent. We prospectively and consecutively recruited 19 patients (mean age 53; 16 women) with 20 saccular intracranial aneurysms occluded with platinum/tungsten alloy coils (GDC™, Stryker Neurovascular, Fremont, USA) who were eligible for follow-up IA-DSA after treatment.

In all patients, the aneurysm had only been treated by coils without placement of stents or flow-diverters. None of the patients had contraindications for MRA. Three-Tesla 3D time-of-flight (TOF) MRA was performed for each patient on the same day as their scheduled follow-up IA-DSA, followed by 1.5-Tesla TOF-MRA with a mean interval of 15 days (range 0 to 21 days). The mean interval between the coiling procedure and these examinations was 11 months (range 3 to 19 months, median 7 months).

Image acquisition

Patients were scanned on a 1.5-Tesla and on a 3.0-Tesla magnetic resonance system (both Achieva, Philips Healthcare, Best, the Netherlands). An 8-channel phased-array head coil equipped for parallel imaging was used as a receive coil.

We used TOF-MRA, since contrast-enhanced MRA has not been proven to provide additional information to TOF-MRA and may cause adverse reactions to the contrast agent.[2]

MR scan parameters were based on standard clinical 3D TOF protocols used in our hospital for evaluation of coiled intracranial aneurysms at 1.5 Tesla and 3.0 Tesla. (See appendix for scan parameters of 3D TOF-MRA at 1.5 Tesla and 3.0 Tesla)

IA-DSA was performed on an angiographic unit (Integris BV5000, Philips Medical Systems, Best, the Netherlands). The following standard projections were made: 1) anterior-posterior view; 2) lateral view; and 3) the optimal projection used at coil-embolization. A maximum of 8mL of non-ionic contrast agent (300mmol/mL) was injected per view with a velocity of 4 ml/s.

Evaluation of images

A neuroradiologist and an interventional neuroradiologist evaluated the TOF-MRA images separately and additionally in consensus for discrepant readings. They were unaware of the field strength and of the IA-DSA results. Source images and volume renderings of 3D TOF images were used for the assessment. The observers assessed the occlusion status of the treated aneurysm according to the following classification: 1) total occlusion (complete obliteration), 2) subtotal occlusion (residual filling of the aneurysm neck), or 3) incomplete occlusion (residual filling of the aneurysm sack).[6] They indicated whether they were unsure about this rating because coil artifacts disturbed the assessment. This uncertainty was expressed in a level of confidence (LOC) of 1 (certain, no disturbance by artifacts) or 0 (uncertain, disturbance by artifacts). The maximum diameter of the residual lumen was measured.

IA-DSA images were evaluated by two other neuroradiologists of whom one was an interventional neuroradiologist. They were unaware of the TOF-MRA results and used the same scale for occlusion of coiled aneurysms. The maximum diameter of a residual lumen was measured in the optimal projection. Consensus reading followed for discrepant results. We recorded whether patients were recoiled.

Data analysis

We calculated the relative risk (RR) with 95% confidence interval (CI) for the presence of disturbing artifacts at 3.0 Tesla versus 1.5 Tesla. We subsequently assessed the relative risk for discrepancy with IA-DSA for 3.0-Tesla MRA related to 1.5-Tesla MRA. In addition, we used weighted kappa-statistics to assess agreement between 3.0-Tesla MRA and IA-DSA and between 1.5-Tesla MRA and IA-DSA. The interpretation of kappa was: <0 no agreement, 0-0.19 poor agreement, 0.2-0.39 fair agreement, 0.4-0.59 moderate agreement, 0.6-0.79 substantial agreement, and 0.8-1.00 almost perfect agreement.[7] We used dependent samples t-tests to compare the mean size of remnants at 1.5-Tesla MRA, 3.0-Tesla MRA, and IA-DSA.

Construction of a coil model

On the clinical TOF-MRAs, the coil artifact could not be discriminated from the subarachnoid space because both have a low signal intensity, and could therefore not be reliably measured. So we created a coil phantom of platinum/tungsten alloy coils (GDC™, Stryker, Neurovascular, Fremont, USA). We used a thin-walled, minimally compliant, cellulose dialysis tube (Visking, Medicell, London, UK) with a diameter of 6.3 mm and a wall thickness of 0.1 mm.[8] When submerged in an aqueous blood mimicking fluid, the wall material absorbs water, which minimizes artifacts produced by the tube itself, allowing us to accurately evaluate the extent of the coil artifacts. From this tube, we created a cylinder of 5.5 mm in height that served as aneurysm model. An interventional neuroradiologist subsequently positioned coils in the model until no more coils could be inserted and a representative packing density was achieved on 3D rotational angiography. The coil model was suspended in a solution of manganese chloride ([MnCl2•4H2O] = 19.2 mg/L) to obtain a fluid with relaxation times close to those of blood,[8] so a pack of coils was created in a homogeneous static background fluid with relaxation properties mimicking blood. The coil mesh diameter was 6.6 mm due to the slightly compliant 6.3-mm dialysis tube.

Image acquisition

The coil model was scanned according to the same 1.5-Tesla and 3.0-Tesla 3D TOF-MRA protocols as used for the patients (see Appendix). To investigate the contribution to artifact formation of geometrical distortion and of signal void through dephasing, additional 2D gradient echo scans were acquired with 5-mm slices, in which we varied echo time and the chosen value for the water-fat-shift (expressed in pixels) as a measure for read-out gradient strength.

Artifact measurement

For volumetric artifact measurements, we segmented artifacts on 3D TOF-MRA using in-house developed image post-processing software (ImageXplorer) that has been previously validated for semi-automatic tuber segmentation in tuberous sclerosis.[9] We adapted the software to segment regions with low signal intensity compared to the background signal. First, the artifact was identified by a single mouse click inside the artifact. Then, the local lowest intensity value surrounding the click point was automatically determined. From this point a region growing procedure was started. The threshold for inclusion of voxels with higher intensity values in the segmentation was stepwise increased until the artifact was completely segmented. The corresponding artifact volume was then automatically computed (Figure 4.1A).

In the transverse 2D MR images the artifact had a circular shape. The diameter of the artifact was measured where the signal dropped to half of its maximum intensity ("full width at half maximum") (Figure 4.1B).

All artifacts were repeatedly measured while being unaware of the field strength and scan parameters. The standard error and repeatability of this method were assessed.[10]

Results

Occlusion level of the aneurysms

On 3.0-Tesla MRA, 3 of 20 aneurysm classifications were uncertain because of disturbance by coil artifacts (LOC 0) versus 12 of 20 assessments on 1.5-Tesla MRA (RR: 0.3 [95% CI 0.1 to 0.8]) (Figure 4.2). The risk of discrepancy between MRA and IA-DSA was similar for assessments at 1.5 Tesla and 3.0 Tesla (RR: 1.1 [95% CI 0.5 to 2.6]). The agreement on occlusion level between 1.5-Tesla MRA and IA-DSA (weighted kappa: 0.53 [95% CI 0.23 to 0.84]), and between 3.0-Tesla MRA and IA-DSA (weighted kappa: 0.47 [95% CI 0.19 to 0.76]) were both moderate.

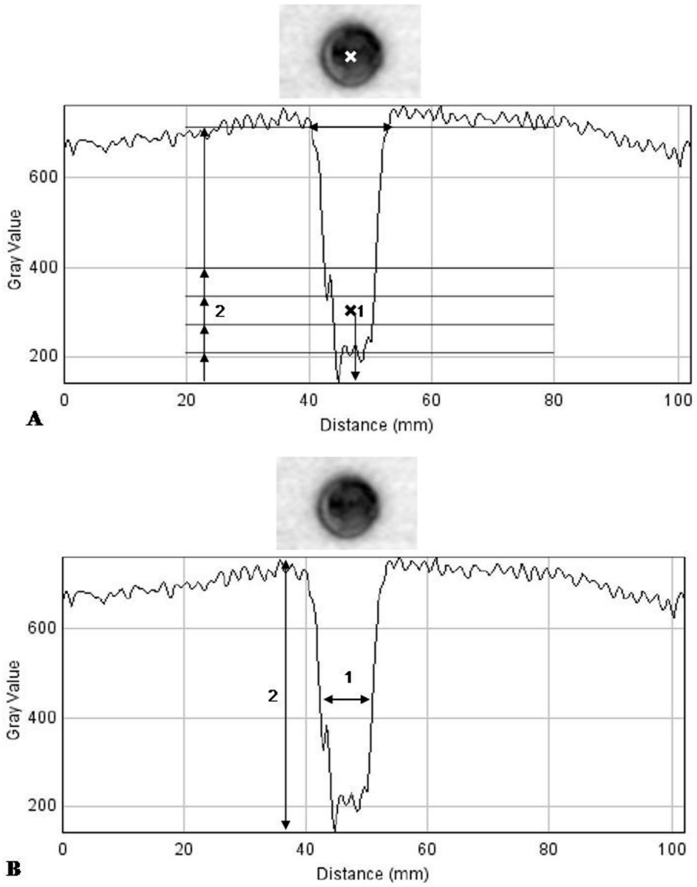

Figure 4.1 1D-image profiles for artifact measurements. Artifact volume measurement **(A)**: identification of the artifact by a mouse click inside the artifact (X). Local lowest intensity value (**arrow 1**) as a starting point for region growing. Stepwise increase of intensity value threshold (**arrow 2**) for complete segmentation of the artifact. Artifact diameter measurement **(B)**: artifact diameter (**arrow 1**) at 50% drop of the global maximal signal intensity (**arrow 2**).

Two patients were recoiled. Both patients had an incompletely occluded aneurysm on all image modalities. MRA underestimated the occlusion level in two patients. One of these patients had incomplete occlusion on IA-DSA but subtotal occlusion on MRA at 1.5 Tesla and 3.0-Tesla (Figure 4.3, Table 4.1) and the second patient had incomplete occlusion on IA-DSA and 3.0-Tesla MRA with subtotal occlusion on 1.5-Tesla MRA (Table 4.1). The remnant diameter in these patients was similar or larger on MRA than on IA-DSA, though, and these two patients did not need further treatment, because the interventional neuroradiologist considered the remnant too small for additional coiling.

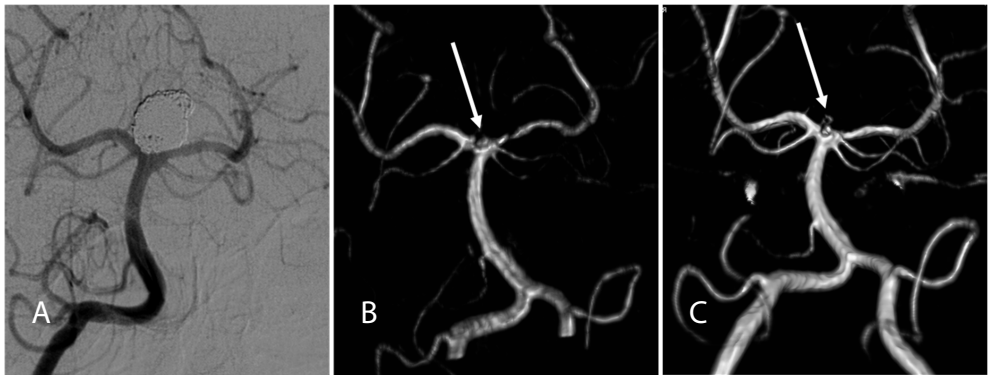

Figure 4.2 IA-DSA **(A)**, 1.5-Tesla **(B)** and 3.0-Tesla **(C)** TOF-MRA in a 67-year-old woman with a coiled basilar tip aneurysm. The MRA assessment was disturbed by artifacts at 1.5 Tesla, but not at 3.0 Tesla (patient number 12 in Table 4.1).

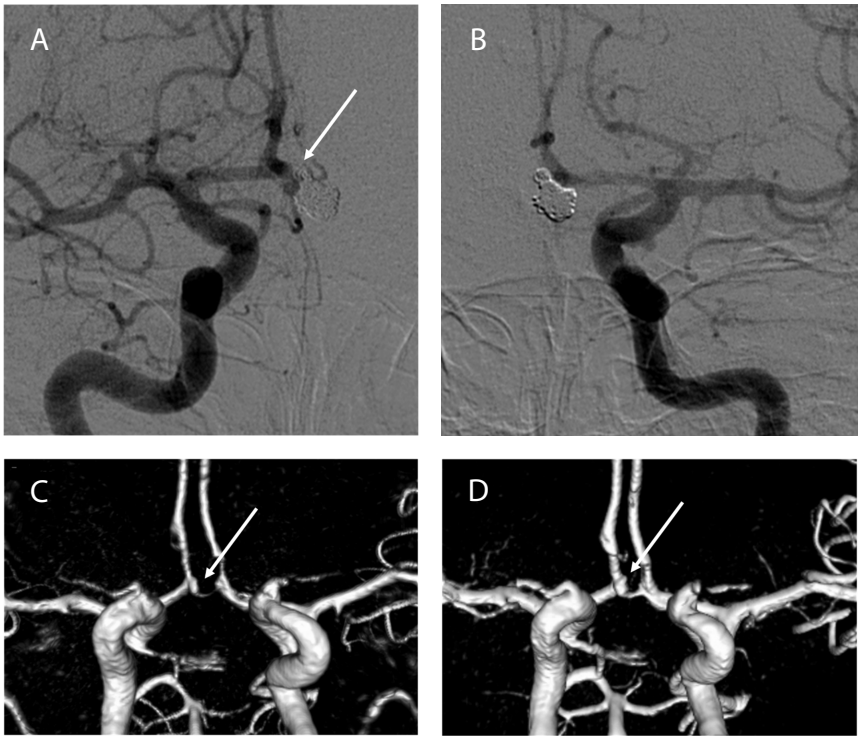

Figure 4.3 IA-DSA, filling from the right internal carotid artery **(A)** and left internal carotid artery **(B)**, 1.5-Tesla **(C)** and 3.0-Tesla **(D)** TOF-MRA in a 56-year-old woman with a coiled anterior communicating artery aneurysm. The aneurysm was classified as sub-totally occluded on MRA at both field strengths and as incompletely occluded on IA-DSA (patient number 3 in Table 4.1).

Table 4.1 Occlusion status and influence by artifacts for each patient

#[a]	Aneurysm location	Aneurysm diameter (mm)	1.5-Tesla MRA			3.0-Tesla MRA			IA-DSA	
			OS[b]	Size[c] (mm)	LOC[d]	OS[b]	Size[c] (mm)	LOC[d]	OS[b]	Size[c] (mm)
1	AcomA[e]	6	1	0.0	1	2	2.0	0	1	0.0
2	AcomA[e]	5	1	0.0	0	2	1.5	1	1	0.0
3	AcomA[e]	8	2	1.0	1	2	2.7	1	3	2.0
4	PcomA[f]	6	2	3.3	1	3	3.0	1	1	0.0
5	AcomA[e]	4	1	0.0	0	1	0.0	0	1	0.0
6	MCA[g]	2	2	1.0	1	2	1.5	1	1	0.0
7	AcomA[e]	7	1	0.0	1	1	0.0	1	1	0.0
8	AcomA[e]	6	3	5.0	1	3	5.5	1	3	4.0
9	AcomA[e]	5	1	0.0	0	2	1.2	1	1	0.0
10	PcomA[f]	8	2	1.1	0	1	0.0	1	1	0.0
	ICA[h]	3	1	0.0	0	1	0.0	1	1	0.0
11	SCA[i]	4	2	1.5	0	2	1.9	1	2	1.0
12	Bas tip[j]	14	3	2.0	0	3	3.0	1	1	0.0
13	PcomA[f]	8	1	0.0	0	2	1.9	1	2	1.0
14	ICA[h]	6	1	0.0	0	2	1.3	1	1	0.0
15	AcomA[e]	6	3	3.3	1	3	4.0	1	3	3.0
16	AcomA[e]	8	2	2.0	0	3	3.1	1	3	2.0
17	AcomA[e]	6	3	3.0	0	3	3.9	1	3	4.0
18	PcomA[f]	8	1	0.0	0	1	0.0	0	1	0.0
19	AcomA[e]	4	2	2.0	1	2	3.0	1	2	2.0

[a]patient number; [b]occlusion status: 1 = total occlusion, 2 = subtotal occlusion, 3 = incomplete occlusion; [c]largest remnant diameter; [d]level of confidence: 0 = disturbance by artifacts, 1= no disturbance by artifacts; [e]anterior communicating artery; [f]posterior communicating artery; [g]middle cerebral artery; [h]internal carotid artery; [i]superior cerebellar artery; [j]basilar tip. Patient number 8 and 17 were recoiled.

Remnant size

The mean size of remnants on 3.0-Tesla MRA was 2.0 mm (±1.6 mm), on 1.5-Tesla MRA 1.3 mm (±1.5 mm), and on IA-DSA 1.0 mm (±1.4 mm). At 3.0 Tesla, remnants were significantly larger than at 1.5 Tesla (difference: 0.7 mm [95% CI 0.3 to 1.1]), and significantly larger than on IA-DSA (difference: 1.0 mm [95% CI 0.6 to 1.5]). On 1.5-Tesla MRA, remnant sizes were similar to those on IA-DSA (difference: 0.3 mm [95% CI -0.2 to 0.8]) (Figure 4.4).

Artifact size

The coil model artifact was 970 mm3 (±40 mm^3) on 1.5-Tesla and 660 mm^3 (±46 mm^3) on 3.0-Tesla 3D TOF-MRA. On the 2D images, the echo time influenced the artifact more than the read-out gradient strength (Table 4.2). The coefficient of repeatability was 58 mm^3 for the volume measurements and 0.33 mm for the diameter measurements.

Table 4.2 Coil artifact diameter related to echo time and determined water fat shift for the coil model at 1.5 Tesla

Scan parameters	Coil model (mm)	Artifact (mm±SE[a])	DOE[b] (mm)
TE[c] =2.3 ms / WFS[d] =2 pixels	6.6	7.0±0.2	0.4
TE[c] =6.9 ms / WFS[d] =2 pixels	6.6	9.2±0.2	2.6
TE[c] =6.9 ms / WFS[d] =4 pixels	6.6	9.4±0.2	2.8
TE[c] =15 ms / WFS[d] =2 pixels	6.6	12.5±0.2	5.9

[a] Standard error. [b] Diameter overestimation (artifact - coil model). [c] Echo time. [d] Water fat shift (determines read-out gradient strength).

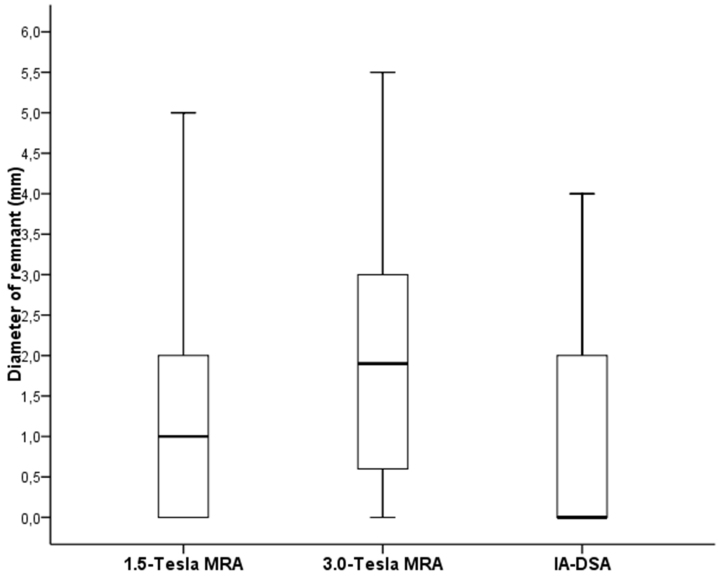

Figure 4.4 Box plots describing the diameter of residual flow measured on 1.5-Tesla MRA, 3.0-Tesla MRA, and IA-DSA.

Discussion

Coil artifacts disturbed aneurysm evaluation more frequently on 1.5-Tesla MRA than on 3.0-Tesla MRA with the clinical 3D TOF-MRA protocols because artifacts were larger at 1.5 Tesla than at 3.0 Tesla. Remnants were furthermore larger on 3.0-Tesla MRA than on 1.5-Tesla MRA and IA-DSA, but agreement on the occlusion status with IA-DSA was similar for both field strengths. Finally, the echo time influenced artifact size more than the read-out gradient strength.

At higher field strength, the evaluation of coiled intracranial aneurysms may benefit from the higher intrinsic SNR. Not only the signal strength is higher at 3.0 Tesla, also the longer longitudinal relaxation times at 3.0 Tesla results in better suppression of the background tissue. The higher signal strength allows for echo time shortening while keeping acceptable SNR. The *in vitro* experiments showed that the echo time largely influenced the size of coil-related artifacts. This indicates that signal loss due to intra-voxel dephasing is the dominant mechanism in coil artifact formation in the gradient echo scans used for TOF-MRA. Because of the absence of the refocusing pulse in gradient echo imaging, a longer echo time allows increased spin dephasing that produces larger signal voids.[5,8,11-14] Primarily, the longer echo time in the 1.5-Tesla TOF-MRA protocol explained larger artifacts at 1.5 Tesla compared to 3.0 Tesla. Apparently, using a short echo time can even negate the effect of stronger field disturbances at higher field strengths.

The influence of the read-out gradient strength on geometrical distortion was small. On spin-echo sequences geometrical distortion has more influence on image quality than on gradient echo sequences since the effect of dephasing is stronger on gradient echo.[12,15] This was also reflected in the volumetric measurements. Despite the stronger read-out gradient in the 1.5-Tesla scan protocol, artifacts were still larger at 1.5 Tesla. As for other differences between the 1.5-Tesla and 3.0-Tesla scan parameters, only the slightly larger acquired voxel size at 1.5 Tesla may have contributed to artifact enlargement through dephasing.

MRA underestimated the occlusion classification of two aneurysms. This was probably the result of different interpretation of the classification by the observers in those cases because the remnant size was similar or larger on MRA compared to IA-DSA. There was overall not more discrepancy in the occlusion classification between MRA and IA-DSA for either field strength. Our study may be underpowered to show a statistically significant difference in occlusion classification. Although, in a large cohort on the diagnostic accuracy of MRA versus IA-DSA where 60 patients were scanned at 1.5 Tesla and 250 patients at 3.0 Tesla, results were not different for both field strengths.[2] This indirect comparison between 1.5 and 3.0 Tesla supports our current findings in a direct comparison. Also other studies that compared occlusion levels

on 1.5-Tesla and 3.0-Tesla MRA after coiling did not show a statistically significant benefit for 3.0-Tesla MRA.[16-19]

Remnants were overall similar to IA-DSA on 1.5-Tesla MRA and larger on 3.0-Tesla MRA. So artifacts did not substantially obscure residual flow. The appearance of remnants on MRA seemed realistic and it suggests that 3.0-Tesla MRA offers more information than IA-DSA. A previous study also found larger remnants on 3.0-Tesla MRA than on IA-DSA.[20] The three dimensional MRA images as opposed to the two dimensional IA-DSA images probably explain this. Three-dimensional rotational angiography may depict coiled aneurysms better than standard IA-DSA, but pulsation artifacts and superimposition of the coil mesh often impede image evaluation. This procedure also exposes patients to more radiation and contrast agent.

The phantom set-up in addition to the clinical study allowed us to measure coil artifacts independently from the inflow signal and from the subarachnoid space. We could furthermore relate several factors that contribute to coil artifact formation. Despite these advantages, we faced some limitations. Because of the small study group we could not reliably calculate measures of diagnostic accuracy, such as sensitivity, specificity, and predictive values, of 1.5-Tesla and 3.0-Tesla MRA with IA-DSA as the reference test. We could also not relate our findings to aneurysm location because of this reason. As a result, the confidence intervals around the point estimates for weighted kappas were wide. The observers could furthermore notice differences in image quality between 1.5-Tesla and 3.0-Tesla MRA, which may have introduced bias. To reduce recognition of the individual patients, the MRAs were randomly assessed over a period of three months.

In conclusion, the occlusion level of coiled aneurysms was similar on 1.5-Tesla and 3.0-Tesla TOF-MRA, even though at 3.0 Tesla, remnants were larger and assessments were less frequently disturbed by artifacts. Coil artifacts were even smaller at 3.0 Tesla than at 1.5 Tesla, because the higher SNR allowed echo time shortening that could compensate for artifact enlargement at higher field strength. So 3.0-Tesla TOF-MRA should certainly not be avoided in coiled patients.

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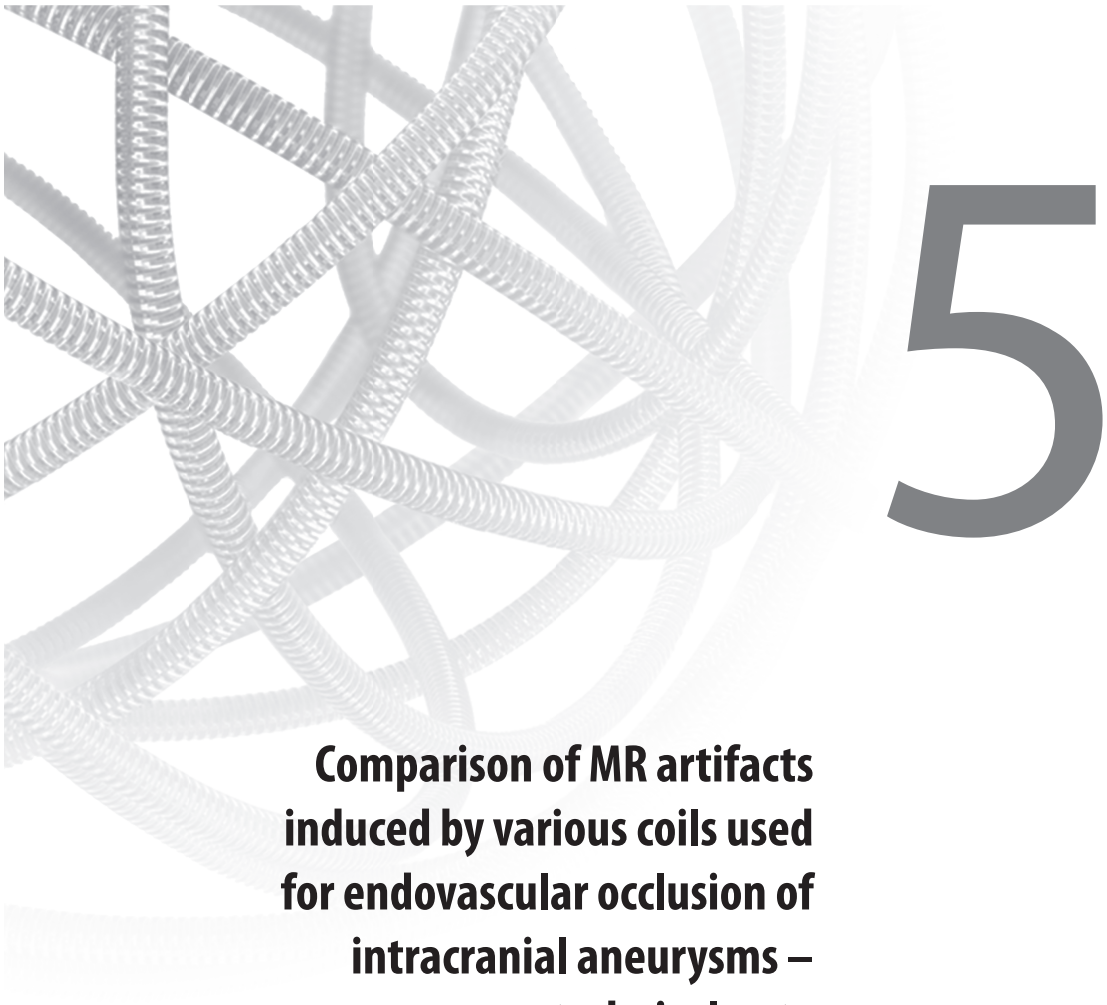

5

Comparison of MR artifacts induced by various coils used for endovascular occlusion of intracranial aneurysms – a technical note

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Abstract

Background and purpose: To assess the contribution of coil types to artifact production in magnetic resonance angiography (MRA) that is used to follow up patients with coiled intracranial aneurysms.

Methods: We created four coil models of GDC (bare platinum/tungsten alloy), Matrix (covered platinum/tungsten alloy), Nexus (covered platinum/iridium alloy with nitinol), and Axium (bare platinum/tungsten alloy) for artifact measurements. They were scanned according to clinical 3D time-of-flight (TOF) MRA protocols at 3.0 Tesla.

Results: Nexus coils induced substantially larger artifacts than the other coils. Coil artifacts from other coils were similar with slightly smaller artifacts from Matrix coils.

Conclusions: TOF-MRA in patients treated with Nexus coils should be avoided because of induction of large artifacts that can impede detection of reopening.

Introduction

Patients with coiled intracranial aneurysms are increasingly followed up by magnetic resonance angiography (MRA) to detect reopening.[1,2] Time-of-flight (TOF) MRA is preferred over contrast-enhanced MRA, since contrast-enhanced MRA does not provide a clear additional value to TOF-MRA.[1-3]

A drawback of vessels containing metallic implants is its susceptibility to metal-induced artifacts on MRA that may impede clinical evaluation. Various types of coils are used for occlusion of intracranial aneurysms, but the extent of artifacts induced by different coil types is unknown, which is important for the feasibility of MRA in the follow-up of coiled patients. We therefore compared the size of coil artifacts in 3.0-Tesla MR induced by a subset of coils that are commonly used in clinical practice.

Materials and methods

Construction of coil models

To study metal-induced artifacts independently from inflow effects we used a phantom set-up. We constructed four aneurysm models from different types of coils that are frequently used for occlusion of intracranial aneurysms: bare platinum/tungsten alloy coils from different producers (GDC, Stryker Neurovascular, Fremont, CA, USA, and Axium coils, EV3 Irvine, CA, USA), platinum/tungsten coils covered with polyglycolic/polylactic acid (PGLA) (Matrix, Stryker Neurovascular, Fremont, CA, USA), and platinum/iridium alloy coils with a nitinol core and PGLA cover (Nexus, EV3, Irvine, CA, USA).

We used a thin-walled, minimally compliant, cellulose dialysis tube (Visking, Medicell, London, UK) with a diameter of 6.3 mm and a wall thickness of 0.1 mm.[4] When submerged in an aqueous blood mimicking fluid, the wall material absorbs water, which minimizes artifacts produced by the tube itself, allowing us to accurately evaluate the extent of the artifacts. From this tube, we created four closed cylinders of 5.5 mm in height that served as aneurysm models. An interventional neuroradiologist subsequently positioned coils in each model until no more coils could be inserted and a representative packing density was achieved on 3D rotational angiography (Integris BV5000, Philips Medical Systems, Best, the Netherlands). For calculation of the packing density, the total coil volume, as provided by the coil manufacturer, was divided by the cylinder volume. The coil models were suspended in a solution of manganese chloride ($[MnCl_2 \bullet 4H_2O]$ = 19.2 mg/L) to obtain a fluid with relaxation times close to those of blood,[4]

so four packs of coils were created in a homogeneous static background fluid with relaxation properties mimicking blood. The coil mesh diameter of each model was 6.6 mm due to the slightly compliant 6.3-mm dialysis tube.

Image acquisition

Three-dimensional rotational angiography datasets were acquired for measurement of the coil model volumes. The four models were then imaged in a 3.0-Tesla MR scanner (Philips Medical Systems, Best, the Netherlands) according to the 3D MOTSA TOF-MRA protocol as used in our hospital for patients with coiled aneurysms. An 8-channels phased-array head coil equipped for parallel imaging was used as a receive coil (see Appendix for scan parameters of 3D TOF-MRA at 3.0 Tesla).

Artifact measurements

Coil artifacts present as signal voids on TOF-MRA. To measure the artifact volumes, we segmented the artifacts in the 3D data using in house developed image post-processing software (ImageXplorer) that has been previously validated for semi-automatic tuber segmentation in tuberous sclerosis.[5] We adapted the software to segment regions with low signal intensity compared to the background signal. First, the artifact was identified by a single mouse click inside the artifact. Then, the local lowest intensity value surrounding the click point was automatically determined. From this point a region growing procedure was started. The threshold for inclusion of voxels with higher intensity values in the segmentation was stepwise increased until the artifact was completely segmented. The corresponding artifact volume was then automatically computed (Figure 5.1). The volume of each coil model was similarly measured on 3DRA images to reach an accurate estimate of the actual volume filled by coils. All artifacts and coil models were repeatedly measured while being unaware of the type of coil and the repeatability of this method was assessed.[6]

The artifact measures were subsequently related to the actual size of the coil models. We calculated the proportional overestimation by dividing the artifact size by the coil model size.

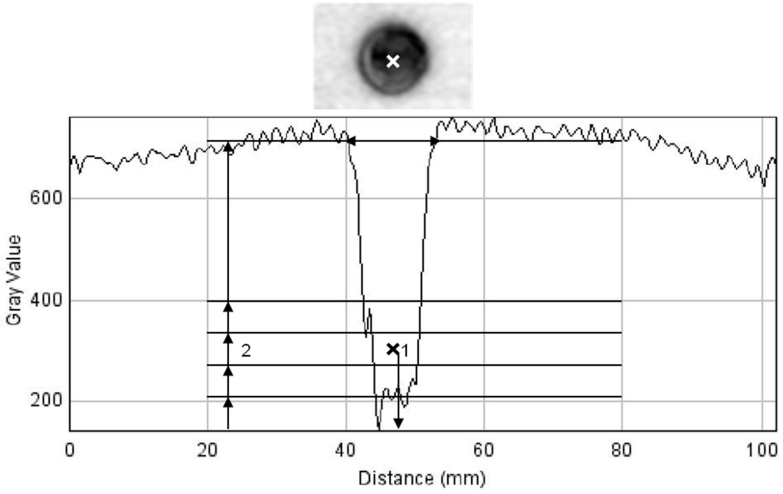

Figure 5.1 1D-image profiles for artifact measurements. Identification of the artifact by a mouse click inside the artifact (X). Local lowest intensity value (**arrow 1**) as a starting point for region growing. Stepwise increase of intensity value threshold (**arrow 2**) for complete segmentation of the artifact.

Results

The packing density was 18% for GDC, 28% for Matrix, 19% for Nexus, and 28% for Axium coils (Table 5.1).

The Nexus coils induced the largest coil artifact, whereas the volume and packing density of the Nexus model was smaller than those of Matrix and Axium models, and comparable to those of the GDC model (Table 5.1, Figure 5.2). The artifact volume related to the coil model volume was similar for the other coil types with slightly smaller artifacts for Matrix coils (Table 5.1). The coefficient of repeatability was 58 mm^3.

Table 5.1 Coil model and artifact volumes at 3.0 Tesla for the four coil materials

Coil Type	PD[a]	Coil model (mm^3±SE[b])	Coil artifact (mm^3±SE[b])	POE[c]
GDC	18%	154±5	660±46	4.29
Matrix	28%	202±7	647±22	3.20
Nexus	19%	172±7	1,787±187	10.39
Axium	28%	212±4	773±17	3.65

[a] Packing density. [b] Standard error. [c] Proportional overestimation (volume of artifact divided by volume of coil model).

Figure 5.2 Artifacts induced by the four coil models in the transverse plane. GDC coils **(A)**, Nexus coils **(B)**, Matrix coils **(C)**, and Axium coils **(D)**.

Discussion

These *in vitro* experiments showed that Nexus coils induce substantially larger artifacts than GDC, Axium, and Matrix coils.

Nexus coils are composed of platinum/iridium alloy with a nitinol core in contrast to the other coil models that are made of platinum/tungsten alloy. The magnetic volume susceptibility of the individual metals is as follows: platinum 279 ppm, tungsten 78 ppm, iridium 47 ppm, and nitinol 245 ppm.[7,8] Because the magnetic susceptibility of iridium and nitinol is lower than the magnetic susceptibility of platinum, the increased artifact size provoked by Nexus coils is probably the result of a larger total metallic mass. This is supported by the slightly smaller artifacts induced by Matrix coils that contain relatively less platinum than the other coils.[9]

The phantom set-up allowed us to study coil artifact production independently from the inflow signal in clinical TOF-MRA and this facilitated comparison of the different coil types. On the other hand, the coil phantoms were not completely identical in size and packing density, which limited to some extent the comparison between the coils. The packing densities ranged from 18% to 28%, which is still representative for the packing achieved in clinical practice.[10] Nevertheless, the artifacts induced by Nexus coils were clearly larger than the other coil types.

In conclusion, Nexus coils induce large artifacts on TOF-MRA that are likely to impede image evaluation. For GDCs, Axium, and Matrix coils there is no substantial difference in artifact size. So far, follow-up TOF-MRA to detect reopening in patients treated with Nexus coils should be avoided.

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6

Evaluation of the occlusion status of coiled intracranial aneurysms with MR angiography at 3T: is contrast enhancement necessary?

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Abstract

Background and purpose: MR angiography (MRA) is increasingly used as a noninvasive imaging technique for the follow-up of coiled intracranial aneurysms. However, the need for contrast enhancement has not yet been elucidated. We compared 3D time-of-flight MRA (TOF-MRA) and contrast-enhanced MRA (CE-MRA) at 3T with intra-arterial digital subtraction angiography (IA-DSA).

Methods: Sixty-seven patients with 72 aneurysms underwent TOF-MRA, CE-MRA, and IA-DSA after coiling. Occlusion status on MRA and IA-DSA was classified as adequate (complete and neck remnant) or incomplete by two independent observers. The interobserver agreement on MRA and the agreement between the three imaging techniques were assessed by κ-statistics. Test characteristics and areas under the receiver operating characteristic curves (AUROC) of TOF-MRA and CE-MRA were also assessed with IA-DSA as the reference test.

Results: IA-DSA revealed incomplete occlusion in 12 (17%) of the 69 aneurysms; 3 aneurysms were excluded due to MR imaging artifacts. All 5 incompletely occluded aneurysms that were additionally treated, were correctly identified with both MRA techniques. Interobserver agreement was substantial for CE-MRA (κ = 0.77; 95% confidence interval [CI], 0.55-0.98) and almost perfect for TOF-MRA (κ = 0.89; 95% CI 0.75-1.00). Agreement between TOF-MRA and IA-DSA (κ = 0.78; 95% CI 0.58-0.99) and between CE-MRA and IA-DSA (κ = 0.74; 95% CI 0.52-0.96) were both substantial. Agreement between TOF-MRA and CE-MRA was almost perfect (κ = 0.83; 95% CI 0.65-1.00). The area under the receiver operating characteristic curve was 0.90 (95% CI 0.79-1.02) for TOF-MRA and 0.91(95% CI 0.79-1.02) for CE-MRA.

Conclusion: In this study, TOF-MRA and CE-MRA at 3T were equivalent in evaluating the occlusion status of coiled intracranial aneurysms after coiling. Because TOF-MRA does not involve contrast administration, this method is preferred over CE-MRA.

Introduction

Endovascular occlusion with coils is an established method to occlude intracranial aneurysms.[1] A shortcoming of coiling is a risk for reopening of the aneurysm, which occurs in about 20% of coiled aneurysms.[2-4] Because patients with reopened aneurysms are at risk for hemorrhage, additional treatment is advocated. Follow-up imaging is therefore highly recommended. The standard follow-up imaging modality after coiling is intra-arterial digital subtraction angiography (IA-DSA) but this diagnostic procedure is invasive, uses ionizing radiation, and exposes the patient to a small risk of serious complications.[5,6]

MR angiography (MRA) has been used as an alternative noninvasive imaging technique to assess the occlusion of coiled intracranial aneurysms with promising but not yet conclusive results.[7] MRA can be performed without contrast enhancement with 3D time-of-flight (TOF-MRA) or with contrast enhancement (CE-MRA). Contrast administration has several disadvantages such as patient discomfort, risk of renal damage,[8] risk of allergic reaction, and higher costs. From published data it is unclear which of the two MRA techniques provides better diagnostic accuracy. The purpose of our study was to compare the diagnostic performance of TOF-MRA with CE-MRA at 3T with IA-DSA as a reference.

Materials and methods

Patients

The study was approved by the institutional review board. Written informed consent was obtained from all patients.

Between May 2005 and November 2007, all patients with coiled intracranial aneurysms scheduled for follow-up IA-DSA were selected to participate in this study. Patients were requested to undergo TOF-MRA and CE-MRA at 3T on the same day as their standard follow-up IA-DSA. Patients were not considered eligible when they were younger than 18 years old, when additional aneurysms were treated with neurosurgical clips, when they had claustrophobia, or when a pacemaker was implanted. Complications of IA-DSA and CE-MRA were recorded.

Imaging technique: IA-DSA

Follow-up IA-DSA was performed on a single-plane angiographic unit (Integris Allura Neuro; Philips Medical Systems, Best, The Netherlands). Six to 8 ml of nonionic contrast material (iodixanol, Visipaque 320 mgI/mL; Amersham Health, Cork, Ireland) was injected into the

internal carotid or vertebral artery with a power injector at 4–6 mL/s. Three views were acquired in each patient, including the working projection of the endovascular treatment.

Imaging techniques: MRA

MR imaging examinations were performed on a 3T system (Intera R10; Philips Medical Systems, Best, the Netherlands) by using the sensitivity encoding (SENSE) 8-channel phased-array head coil. The protocol included transversal T1-weighted spin-echo and T2-weighted fast spin-echo sequences, phase contrast survey MRA as a preparation for MRA, 3D TOF-MRA with multiple overlapping thin slab acquisition (MOTSA), and CE-MRA sequences. (See Appendix for scan parameters of MOTSA 3D TOF-MRA and CE-MRA at 3.0 Tesla).

Image evaluation

Aneurysm occlusion status on follow-up IA-DSA was assessed by two experienced interventional neuroradiologists, who were blinded to parallel MRA results. The occlusion status of the coiled aneurysms was classified both on a 3-tier scale as complete occlusion, neck remnant, and incomplete occlusion, and on a 2-tier scale as adequate occlusion (complete occlusion and neck remnant) and incomplete occlusion. We dichotomized this occlusion scale, because only incomplete occlusion is important in clinical decision making for additional treatment.

All TOF-MRA and CE-MRA images were evaluated independently and in random order by two experienced interventional neuroradiologists, who were unaware of the parallel IA-DSA results. Source images, 3D maximum-intensity projections, and 3D volume-rendered reconstructions were available on a 3D Vitrea workstation (Vital Images Inc, Minnetonka, Minn). Occlusion status of the coiled aneurysms was classified in the same way as for IA-DSA. Consensus reading followed after discordant results among observers.

Data analysis

Kappa-statistics were applied to assess interobserver agreement for TOF-MRA and CE-MRA, and to assess agreement between the three imaging techniques. We calculated weighted kappas for the 3-tier occlusion scale and unweighted kappas for the 2-tier occlusion scale. The interpretation of kappa was: <0.20 poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 almost perfect agreement.[9]

Test characteristics with 95% confidence intervals (CI) of TOF-MRA and CE-MRA with IA-DSA as a reference test, were calculated for the 2-tier occlusion scale. We compared the areas under the receiver operating characteristic curve (AUROC) for TOF-MRA and CE-MRA.

Results

Patients

Sixty-seven patients (46 women; mean age, 49 ± 12 years) with 72 coiled aneurysms agreed to participate in the study. Of 72 coiled aneurysms, 60 had ruptured. Mean aneurysm size was 7 ± 5 mm. Twenty-nine aneurysms were located on the carotid artery; 28 on the anterior cerebral artery; 8 on the middle cerebral artery; and 7 in the posterior circulation.

On CE-MRA, 3 aneurysms could not be assessed due to coil artifacts and venous overlap and were excluded, leaving 69 aneurysms evaluated with CE-MRA. On TOF-MRA, 1 aneurysm could not be assessed due to coil artifacts; this aneurysm showed similar coil artifacts on CE-MRA and had already been excluded, leaving 71 aneurysms evaluated with TOF-MRA. As a result, 69 aneurysm assessments in 64 patients could be used to compare TOF- with CE-MRA (Figure 6.1). There were no complications, neither from IA-DSA, nor from MRA.

IA-DSA

On follow-up IA-DSA, 57 coiled aneurysms were adequately occluded and 12 aneurysms were incompletely occluded (Figure 6.1). Of the 12 incompletely occluded aneurysms, 5 were additionally treated.

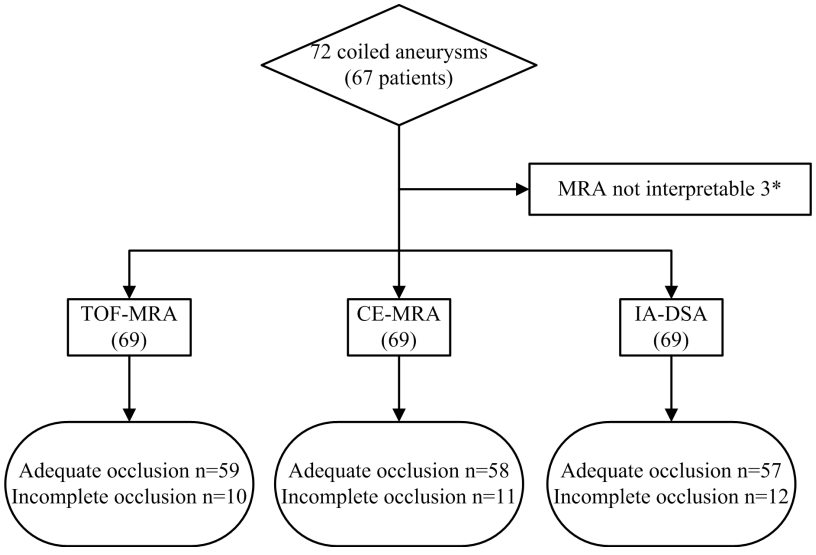

Figure 6.1 Flowchart of all coiled aneurysms at follow-up. * Three aneurysms were excluded due to coil artifacts and venous over projection on CE-MRA. One of these aneurysms was also excluded due to coil artifacts on TOF-MRA.

Interobserver agreement

Interobserver agreement on TOF-MRA for the 3-tier classification was substantial (weighted κ = 0.74; 95% CI 0.60-0.88) with full agreement in 58 (82%) of the 71 aneurysms that could be evaluated. For the 2-tier classification, interobserver agreement was almost perfect (κ = 0.89; 95% CI 0.75-1.00), with full agreement in 69 (97%) of 71 aneurysms.

Interobserver agreement on CE-MRA for the 3-tier classification was also substantial (weighted κ = 0.67; 95% CI 0.51-0.82), with full agreement in 53 (77%) of 69 aneurysms. For the 2-tier classification, interobserver agreement was again substantial (κ = 0.77; 95% CI 0.55-0.98) with full agreement in 65 (94%) of 69 aneurysms.

TOF-MRA compared to IA-DSA

Agreement between TOF-MRA and IA-DSA for the 3-tier classification was moderate (weighted κ = 0.57; 95% CI 0.40-0.74), with full agreement in 47 (68%) of 69 aneurysms. For the 2-tier classification, agreement between TOF-MRA and IA-DSA was substantial (κ = 0.78; 95% CI 0.58-0.99), with full agreement in 65 (94%) of 69 aneurysms (Table 6.1). TOF-MRA misclassified 3 of the 12 incompletely occluded aneurysms as adequately occluded: a ruptured 4-mm carotid tip aneurysm (Figure 6.2), a ruptured 4-mm middle cerebral artery aneurysm (Figure 6.3), and a ruptured 7-mm carotid artery aneurysm (Figure 6.4). In none of these 3 aneurysms additional treatment was indicated. All 5 incompletely occluded aneurysms that were additionally treated were correctly identified with TOF-MRA as incompletely occluded (Figure 6.5). One ruptured 6-mm basilar tip aneurysm that was completely occluded on IA-DSA, was incorrectly classified by TOF-MRA as incompletely occluded. Test characteristics of TOF-MRA and the AUROC are provided in Table 6.2.

Table 6.1 TOF-MRA and IA-DSA results

	IA-DSA			
		Adequate occlusion		
TOF-MRA	Incomplete occlusion	Neck remnant	Complete occlusion	Total
Incomplete occlusion	9	0	1	10
Adequate occlusion				
Neck remnant	3	14	5	22
Complete occlusion	0	13	24	37
Total	12	27	30	69

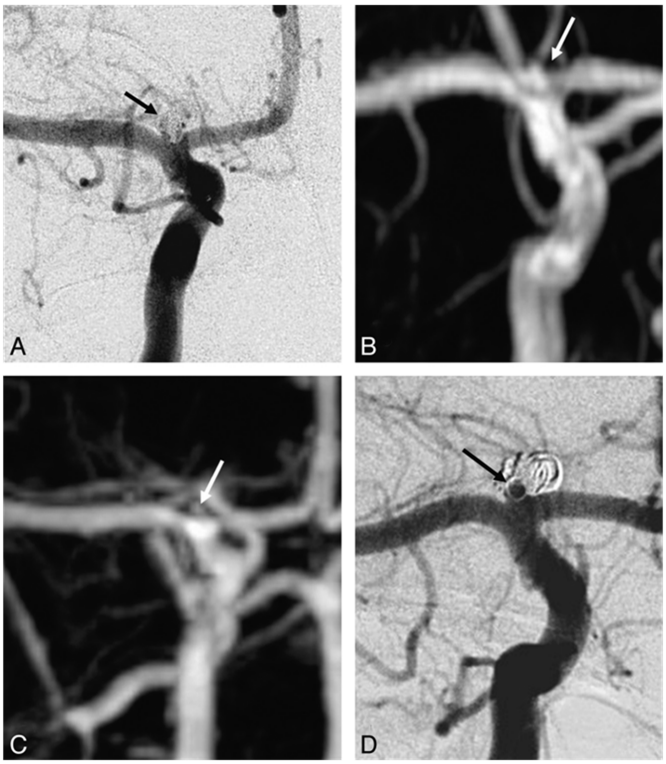

Figure 6.2 Disagreement between both TOF-MRA and CE-MRA with IA-DSA on the occlusion of a carotid tip aneurysm. **(A)** IA-DSA obtained immediately after coiling shows adequate occlusion with a small neck remnant (**arrow**). **(B)** Follow-up TOF-MRA at 6 months shows complete occlusion (**arrow**). **(C)** Follow-up CE-MRA at 6 months shows a small neck remnant (**arrow**). **(D)** Follow-up IA-DSA at 6 months shows incomplete occlusion (**arrow**). Because the geometry of the reopened aneurysm was unfavorable, this patient was not retreated but subjected to extended follow-up.

CE-MRA compared with IA-DSA

Agreement between CE-MRA and IA-DSA for the 3-tier classification was moderate (weighted $\kappa = 0.52$; 95% CI 0.35-0.69), with full agreement in 44 (64%) of 69 aneurysms. For the 2-tier classification, correlation between CE-MRA and IA-DSA was substantial ($\kappa = 0.74$; 95% CI 0.52-0.96), with full agreement in 64 (93%) of 69 aneurysms (Table 6.3). CE-MRA misclassified 3 of the 12 incompletely occluded aneurysms as adequately occluded. These were the same 3 aneurysms that were not correctly classified as incompletely occluded with TOF-MRA (Figure 6.2-6.4).

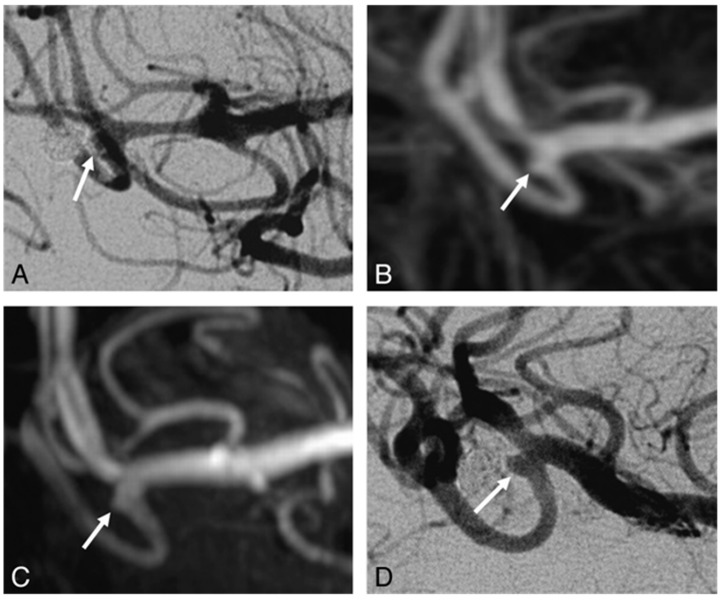

Figure 6.3 Disagreement between both TOF-MRA and CE-MRA with IA-DSA on the occlusion of a middle cerebral artery aneurysm. **(A)** IA-DSA obtained immediately after coiling shows a small neck remnant (**arrow**). **(B)** Follow-up TOF-MRA at 6 months shows a small neck remnant (**arrow**). **(C)** Follow-up CE-MRA at 6 months shows a small neck remnant (**arrow**). **(D)** Follow-up IA-DSA shows incomplete occlusion (**arrow**). Because the geometry of the reopened aneurysm was unfavorable, this patient was not retreated but was subjected to extended follow-up.

All 5 incompletely occluded aneurysms that were additionally treated were correctly identified with CE-MRA as incompletely occluded (Figure 6.5).

CE-MRA misclassified 2 adequately occluded aneurysms as incompletely occluded: a ruptured 3-mm anterior communicating artery aneurysm and a ruptured 6-mm pericallosal artery aneurysm. Test characteristics of CE-MRA and the AUROC are provided in Table 6.2.

TOF-MRA compared with CE-MRA

Agreement between TOF-MRA and CE-MRA for the 3-tier classification was substantial (weighted = 0.71; 95% CI 0.57-0.85) with full agreement in 54 (78%) of the 69 aneurysms (Table 6.4). Agreement between both MR imaging techniques for the 2-tier classification was almost perfect (κ = 0.83; 95% CI 0.65-1.00) with full agreement in 66 (96%) of the 69 aneurysms (Table 6.4).

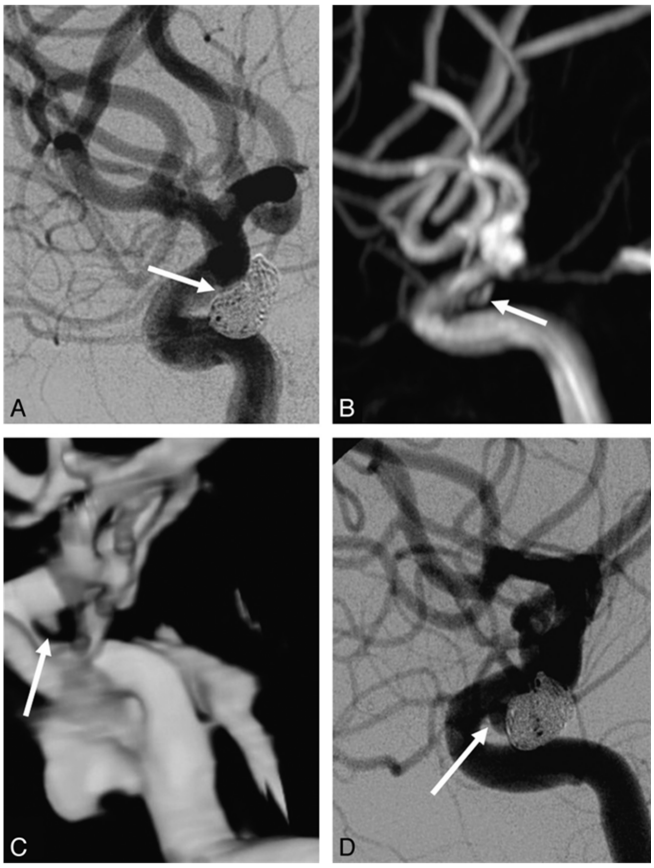

Figure 6.4 Disagreement between both TOF-MRA and CE-MRA with IA-DSA on the occlusion of a carotid artery aneurysm. **(A)** IA-DSA obtained immediately after coiling shows a small neck remnant (**arrow**). **(B)** Follow-up TOF-MRA at 6 months shows a small neck remnant (**arrow**). **(C)** Follow-up CE-MRA at 6 months shows a small neck remnant (**arrow**). **(D)** Follow-up IA-DSA at 6 months shows incomplete occlusion (**arrow**). Because the geometry of the reopened aneurysm was unfavorable, this patient was not retreated but was subjected to extended follow-up.

Discussion

In the evaluation of aneurysm-occlusion status after coiling, diagnostic performance of TOF-MRA equaled that of CE-MRA. Interobserver agreement of both MRA techniques was substantial and also agreement with IA-DSA as reference standard was similar and good for both techniques. The negative predictive value for adequate occlusion was exactly the same for

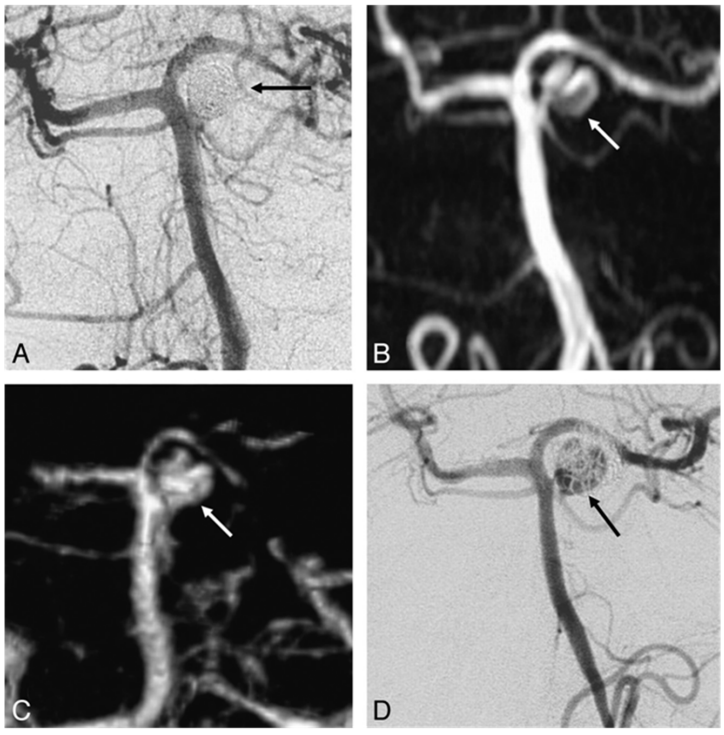

Figure 6.5 Agreement between TOF-MRA, CE-MRA, and IA-DSA on the occlusion of a partially thrombosed superior cerebellar artery aneurysm. **(A)** IA-DSA obtained immediately after coiling shows complete occlusion (**arrow**). **(B)** Follow-up TOF-MRA at 6 months shows incomplete occlusion (**arrow**). **(C)** Follow-up CE-MRA at 6 month shows incomplete occlusion (**arrow**). **(D)** Follow-up IA-DSA at 6 month shows incomplete occlusion (**arrow**). The aneurysm was additionally coiled without complications, and complete occlusion was achieved.

Table 6.2 Test characteristics of TOF-MRA and CE-MRA compared with IA-DSA

	TOF-MRA (95% CI)	CE-MRA (95% CI)
Sensitivity	75% (43-95%)	75% (43-95%)
Specificity	98% (91-100%)	96% (88-100%)
PPV	90% (56-100%)	82% (48-98%)
NPV	95% (86-99%)	95% (86-99%)
AUROC	0.90 (0.79-1.02)	0.91 (0.79-1.02)

PPV indicates positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Table 6.3 CE-MRA and IA-DSA results

	IA-DSA			
		Adequate occlusion		
CE-MRA	Incomplete occlusion	Neck remnant	Complete occlusion	Total
Incomplete occlusion	9	2	0	11
Adequate occlusion				
Neck remnant	2	10	5	17
Complete occlusion	1	15	25	41
Total	12	27	30	69

Table 6.4 TOF-MRA and CE-MRA results

	CE-MRA			
		Adequate occlusion		
TOF-MRA	Incomplete occlusion	Neck remnant	Complete occlusion	Total
Incomplete occlusion	9	2	0	11
Adequate occlusion				
Neck remnant	1	12	4	17
Complete occlusion	0	8	33	41
Total	10	22	37	69

TOF-MRA and CE-MRA. This implies that contrast enhancement does not have additional value in excluding incomplete occlusion when TOF-MRA shows adequate occlusion. The positive predictive value of CE-MRA was somewhat lower than that of TOF-MRA. Thus, in our study group, contrast enhancement had no additional value for ruling in incompletely occluded aneurysms either.

Despite favorable test characteristics, 3 of 12 incompletely occluded aneurysms were misclassified as adequately occluded on MRA. Both TOF-MRA and CE-MRA failed to identify the same incompletely occluded aneurysms. However, in none of these 3 aneurysms was additional treatment judged indicated. The assessment of the occlusion status was to some extent limited by the use of a classification that allowed room for subjective differences. Apparently, it was

sometimes difficult to classify a small residual lumen as borderline adequate- or borderline incomplete occlusion.[10] All 5 incompletely occluded aneurysms that were additionally treated, were correctly identified with both MRA techniques.

Another 3 adequately occluded aneurysms were misclassified as incompletely occluded, 1 with TOF MRA and 2 with CE-MRA. So for incomplete occlusions on MRA, additional IA-DSA may be considered before deciding whether the aneurysm should be retreated.

Three aneurysms were excluded from assessment due to artifacts on CE-MRA, compared with 1 aneurysm on TOF-MRA.

Most previous studies have evaluated either TOF-MRA or CE-MRA for coiled aneurysms, but a few evaluated both techniques with IA-DSA as a reference.[11-16] Some reported better diagnostic performance of CE-MRA.[12,14] All these studies, however, were performed at 1.5T without independent evaluation of the two MR imaging techniques, except for one study that did not find a difference between TOF- and CE-MRA.[15] A recent study at 3T but without IA-DSA as a reference, showed a similar classification of aneurysm occlusion on TOF-MRA and CE-MRA, although visualization of residual flow was considered better on CE-MRA.[17] A meta-analysis of 16 studies on the diagnostic performance of MRA in patients with coiled aneurysms, found no difference between TOF-MRA and CE-MRA.[7] The findings of this meta-analysis should be interpreted with some caution, though, because the included studies were of moderate methodological quality and all pooled estimates were subject to heterogeneity.

Interobserver agreement and agreement between the imaging techniques were substantially better in the 2-tier scales which is in concordance with a study on aneurysm assessment scales.[10] Apparently, differentiation between a completely occluded aneurysm and a small neck remnant was more difficult on the 3-tier scale. Although the 2-tier scale may not identify these subgroups, this outcome has little clinical impact because additional treatment is considered only in incompletely occluded aneurysms.

A limitation of our study is the small sample size of 69 aneurysms, of which 12 (17%) were incompletely occluded, which precludes definitive conclusions on whether MRA can replace IA-DSA in the follow-up of coiled aneurysms. However, all patients underwent both TOF-MRA and CE-MRA, resulting in 138 MRA datasets for comparison with IA-DSA, which was sufficient to draw conclusions about the additional value of contrast enhancement in MRA.

Although in a few previous studies CE-MRA was considered superior to TOF-MRA, this could not be confirmed in our study. Our TOF-MRA technique was optimized by using a short echo time and the MOTSA technique instead of the single volume 3D-TOF sequence that is used by

others.[11] In the MOTSA-sequence, we used a section thickness of 1 mm, which may seem large for modern scanner technology. However, complete coverage within an acceptable timeframe with a good signal intensity-to-noise ratio, we used the overlapping slab technique. Halving the section thickness from 1 to 0.5 mm while maintaining the signal intensity-to-noise ratio would require a 4-fold increase in acquisition time. Because the parameters we used resulted in a relatively long acquisition time of 7 minutes, a substantially longer acquisition time was not considered an option. MOTSA minimizes signal-intensity loss due to spin saturation and maintains small voxels and short echo times to minimize intravoxel phase dispersion. Our MOTSA TOF technique resulted in a reconstructed voxel size of 0.2x0.2x0.5 mm, whereas for the CE-MRA sequence, the reconstructed voxel size was 0.49x0.49x0.5 mm. The problem of image degrading by venous over projection can be decreased by faster imaging with higher SENSE factors, at the expense of decreased signal-to-noise ratio.[11] Large aneurysm remnants may be better visualized by CE-MRA than by TOF-MRA, due to saturation effects and signal intensity loss with TOF.[11] Because in our study no large aneurysm remnants were present, this possible advantage of CE-MRA could not be substantiated.[18]

In summary, in this study, TOF-MRA and CE-MRA at 3T were equivalent in evaluating the occlusion status of coiled intracranial aneurysms. Because TOF-MRA does not involve contrast administration, this method is preferred over CE-MRA in most patients if MRA is used instead of IA-DSA for the follow-up of patients with coiled intracranial aneurysms.

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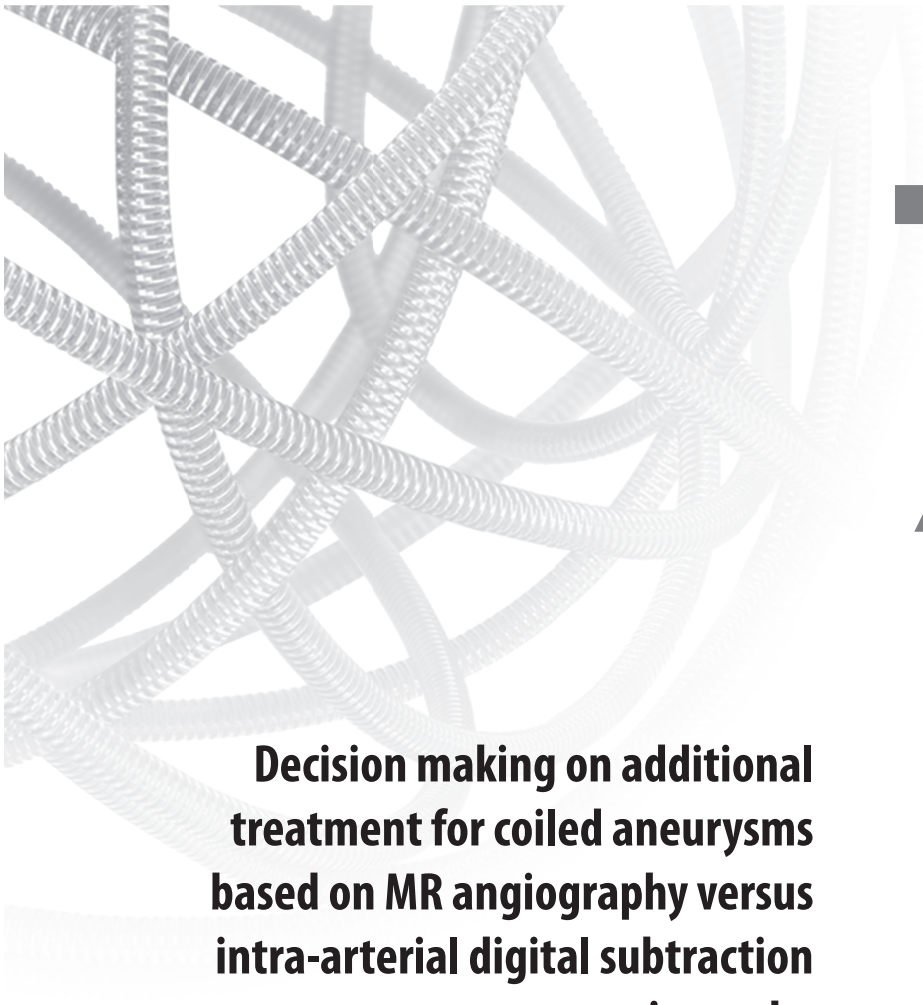

7

Decision making on additional treatment for coiled aneurysms based on MR angiography versus intra-arterial digital subtraction angiography

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Abstract

Background and purpose: To assess whether magnetic resonance angiography (MRA) can be used as a noninvasive alternative to intra-arterial digital subtraction angiography (IA-DSA) to indicate additional treatment in the follow-up of patients with coiled intracranial aneurysms.

Methods: This was an ethics committee-approved multicenter study. Consecutive patients who were scheduled for follow-up IA-DSA after coiling were invited for additional MRA after providing written informed consent. Interventional neuroradiologists gave a treatment advice (additional treatment, extended follow-up imaging, or discharge from follow-up) for each imaging modality. Agreement between treatment advices on IA-DSA and MRA and interobserver agreement were assessed with weighted kappa-statistics.

Results: Agreement between IA-DSA- and MRA-based advices was substantial (κ: 0.73 [95% CI, 0.66 to 0.80]). In 34 of the 310 patients (11%), additional treatment was recommended based on IA-DSA and MRA. In six patients (2%), the advice based on IA-DSA was additional treatment while that based on MRA was extended follow-up imaging. None of the patients with IA-DSA-based additional treatment advice was discharged from follow-up based on MRA. Interobserver agreement was substantial for IA-DSA (κ : 0.73 [95% CI, 0.64 to 0.82]) and moderate for MRA (κ: 0.53 [95% CI, 0.36 to 0.70]). In six other patients (2%), the advice based on MRA was additional treatment while that based on IA-DSA was extended follow-up imaging (four patients), discharge (one patient), and non-interpretable (one patient). Extended follow-up imaging was suggested for 37 patients (12%) after IA-DSA and for 49 patients (16%) after MRA (difference: 4% [95% CI, -0.6 to 8%]).

Conclusion: The overall proportion of patients advised to be additionally treated is similar based on IA-DSA and MRA, with only few individual discrepancies. MRA can therefore be used for therapeutic decision making in the follow-up of coiled patients.

Introduction

Endovascular treatment with coils is an established treatment for intracranial aneurysms, despite a risk of reopening of the coiled aneurysm after the treatment.[1] Approximately 10% of the patients need additional coiling at some time during follow-up due to reopening of the aneurysm.[2]

Magnetic resonance angiography (MRA) is increasingly used as a non-invasive alternative to the standard intra-arterial digital subtraction angiography (IA-DSA) to follow up patients with coiled aneurysms.[3] Besides its safety, MRA is performed in an outpatient setting and creates less discomfort for patients than IA-DSA. The test characteristics of MRA compared to IA-DSA are good,[4] but more insight in the subsequent image-based additional treatment decisions is desirable before MRA is implemented as a standard follow-up imaging technique.

We investigated whether therapeutic decision making can be solely based on MRA by comparing treatment decisions based on MRA and IA-DSA in the follow-up of patients with coiled aneurysms who were examined by both imaging techniques.

Materials and methods

The institutional review boards of the participating centers approved this study. All participants provided written informed consent. No indirect or direct financial support was provided by an industry. The authors had control over the data submitted for publication.

Patient inclusion

In four academic centers in which treatment of aneurysms with coils had been performed for more than five years at time of onset of the study, we prospectively approached consecutive patients who were scheduled for routine follow-up IA-DSA after coiling of intracranial aneurysms from May 2005 until November 2007. At the time of the study, coiled patients who were independent for daily activities, were generally followed-up by IA-DSA twice in the first two years after the treatment.

Eligible patients were invited for additional MRA on the same day as their regular follow-up IA-DSA. We excluded patients with contra-indications for MRI (pacemaker, ferromagnetic neurosurgical clip, or claustrophobia), patients younger than 18 years old, and patients who did not consent to the study.

Imaging

MRA consisted of three-dimensional unenhanced (time-of-flight (TOF)) as well as contrast enhanced (CE) images using gradient echo techniques. Three centers used a 3.0-Tesla and one center a 1.5-Tesla machine. (See appendix for MRA scan parameters)

IA-DSA was performed on single or biplane angiographic units with a trans-femoral approach using standard hospital specific protocols. Angiographic projections included an anteroposterior view, a lateral view, and a projection similar to the one used during coil embolization of the aneurysm.

Image evaluation

We previously reported about assessment of the occlusion status on MRA versus IA-DSA of this patient population.[4] A senior interventional neuroradiologist who was blinded to the parallel MRA results, evaluated the IA-DSA images. As in clinical practice, all previous IA-DSAs were available for assessment. The rater discriminated adequate occlusion (complete occlusion or small neck remnant) from incomplete occlusion (partial filling of the aneurysm sack).[5] For patients with incompletely occluded aneurysms, either additional treatment or further follow-up imaging was advised when the recurrence was considered too small for additional treatment. Patients with adequately occluded aneurysms would be discharged from further follow-up imaging.

The MRAs were assessed similarly to IA-DSA by another interventional neuroradiologist who was unaware of the parallel IA-DSA results. Source images, maximum intensity projections, and volume renderings of TOF-MRA as well as of CE-MRA were used for the assessment. TOF-MRA and CE-MRA were not evaluated separately.

In three centers, two interventional neuroradiologists were available for a double-reading of IA-DSA, MRA, or both. They first evaluated the aneurysm independently of each other and subsequently in consensus for discrepant readings on the imaging modality in question.

Data analysis

We used weighted kappa-statistics to calculate the intertechnique agreement for treatment decisions based on IA-DSA and MRA, and to calculate the interobserver agreement for double-readings. The categories for the analysis were additional treatment, extended follow-up imaging, and discharge from follow-up. We performed a preplanned subgroup analysis for patients scanned at 1.5 Tesla and patients scanned at 3.0 Tesla. The interpretation of kappa was: <0 no agreement, 0-0.19 poor agreement, 0.2-0.39 fair agreement, 0.4-0.59 moderate agreement, 0.6-0.79 substantial agreement, and 0.8-1.00 almost perfect agreement.[6]

Results

Patient inclusion

Of 417 eligible patients, 310 patients with 341 coiled aneurysms met the inclusion criteria. The other 107 patients were excluded because of claustrophobia (n=16), neurosurgical clips (n=24), participation in the study declined (n=25), logistic problems (n=21), or for unknown reasons (n=21). Age, sex, and aneurysm size were not different for participating and non-participating patients. The baseline characteristics of the 310 included patients are provided in Table 7.1.

Image quality

In two patients superimposing arteries precluded aneurysm assessments of three aneurysms on IA-DSA. In one of these patients, MRA showed incomplete occlusion for which additional coiling was recommended. In a third patient whose aneurysm was treated with Nexus coils (EV3, Irvine, CA, USA), MRA was not interpretable as a result of large coil artifacts. IA-DSA

Table 7.1 Baseline characteristics

	n (%)
Participants	310
Age yr ±SD	51 ±12
Women	218/310 (70%)
Coiled aneurysms	341
Location of coiled aneurysms	
Carotid artery	126/341 (37%)
Anterior cerebral artery	129/341 (38%)
Middle cerebral artery	34/341 (10%)
Posterior circulation	52/341 (15%)
Size of coiled aneurysms (mm±SD)	7±5
Interval of imaging after coiling	
3 months	37/310 (12%)
6 months	202/310 (65%)
18 months	45/310 (15%)
>18 months	26/310 (8%)
Patients scanned at 3.0 Tesla	250/310 (81%)
Patients scanned at 1.5 Tesla	60/310 (19%)

showed adequate occlusion in this patient. So a total of four aneurysms in three patients were not interpretable on either IA-DSA or MRA (Table 7.2). The ratings of these patients were not included for the kappa-statistics.

Intertechnique agreement

77 of 310 patients (25%) had an incompletely occluded aneurysm on IA-DSA and 89 of 310 patients (29%) on MRA. In four patients, the observer did not provide a treatment advice based on MRA and recommended IA-DSA instead.

The agreement between treatment decisions based on MRA and IA-DSA was substantial (weighted κ: 0.73 [95% CI, 0.66 to 0.80]). For the subgroups of patients scanned at either 1.5 Tesla or 3.0 Tesla the agreement between IA-DSA and MRA based advices was also substantial (weighted κ: 0.64 [95% CI, 0.47 to 0.81] for 1.5 Tesla and weighted κ: 0.75 [95% CI, 0.67 to 0.84] for 3.0 Tesla). The slightly lower agreement between IA-DSA and MRA at 1.5 Tesla was predominantly explained by more frequent recommendation of follow-up imaging after MRA at 1.5 Tesla than at 3.0 Tesla.

The observers recommended additional treatment based on both IA-DSA and MRA for 34 of 310 patients (11%) (Figure 7.1). Six patients (2%) with additional treatment advice based on IA-DSA, would get extended follow-up imaging after MRA. In six other patients (2%) additional treatment was suggested only based on MRA. Four of these six patients had an extended follow-up advice after IA-DSA, one patient was recommended to be discharged from further follow-up, and IA-DSA of one patient was not interpretable.

Follow-up imaging was suggested for 37 of 310 patients (12%) after IA-DSA and for 49 of 310 patients (16%) after MRA (difference: 4% [95% CI, -0.6 to 8%]). In 24 patients further follow-

Table 7.2 Treatment decisions for all patients based on IA-DSA and MRA

IA-DSA (n)	MRA (n)					
	Retreatment	Follow-up*	IA-DSA†	Discharge‡	Not interpretable	Total
Retreatment	34	6	0	0	0	40
Follow-up*	4	15	3	15	0	37
Discharge‡	1	24	1	204	1	231
Not interpretable	1	0	0	1	0	2
Total	40	45	4	220	1	310

n = number of patients; * Recurrence that is too small for additional treatment and needs extended follow-up imaging; † Incomplete occlusion that requires additional information from IA-DSA to decide between additional treatment and follow-up imaging; ‡ Adequate occlusion, so discharge from follow-up.

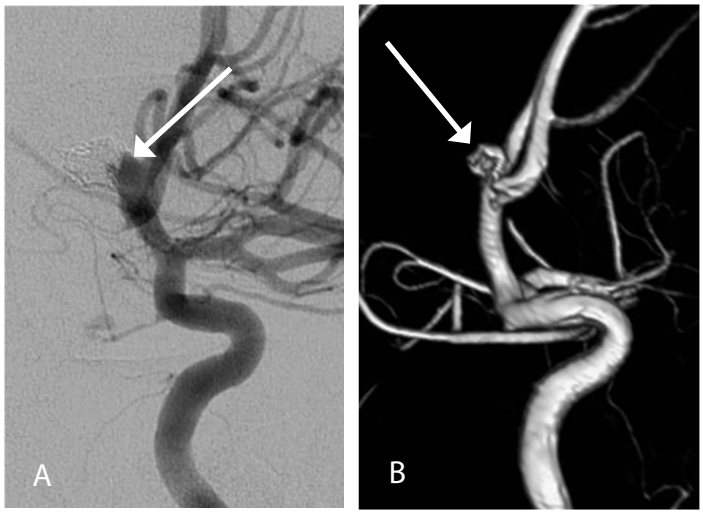

Figure 7.1 IA-DSA **(A)** and 3D TOF-MRA at 3.0 Tesla **(B)** of a 46-year old woman with a coiled anterior communicating artery aneurysm. The observers recommended additional coiling based on both IA-DSA and MRA.

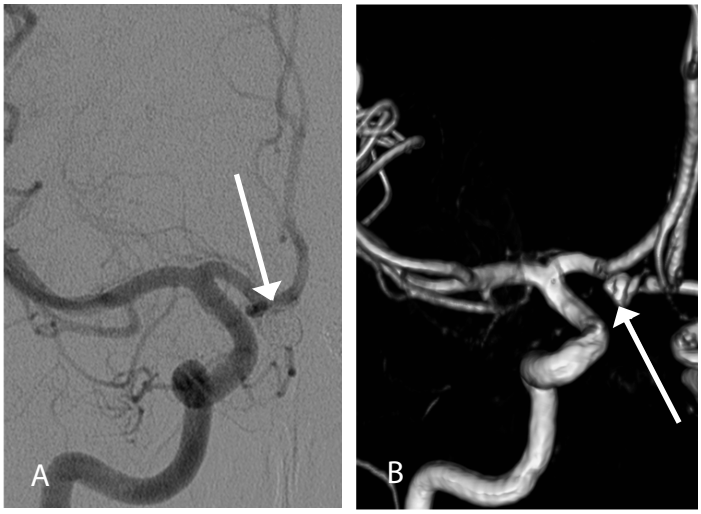

Figure 7.2 IA-DSA **(A)** and 3D TOF-MRA at 3.0 Tesla **(B)** of a 49-year old woman with a coiled anterior communicating artery aneurysm. Based on IA-DSA the observers recommended discharge from follow-up, while based on MRA the observers advised extended follow-up because of incomplete occlusion.

up imaging was recommended based on MRA, while based on IA-DSA they were discharged from follow-up since their aneurysms were adequately occluded (Figure 7.2). Conversely, 15 patients would undergo further follow-up based on IA-DSA while based on MRA these aneurysms seemed adequately occluded (Table 7.2).

Interobserver agreement

A double-reading by two interventional neuroradiologists was done on IA-DSA in 188 of 310 patients (61%) and on MRA in 106 of 310 patients (34%). The interobserver agreement on treatment decisions was substantial for IA-DSA (weighted κ: 0.73 [95% CI, 0.64 to 0.82) and moderate for MRA (weighted κ: 0.53 [95% CI, 0.36 to 0.70]).

Discussion

These results show that the decisions to additionally treat coiled patients were on group level comparable on IA-DSA and MRA. Moreover, none of the patients who needed additional treatment based on IA-DSA would be discharged from extended follow-up after MRA. There was a tendency to intensified follow-up imaging after MRA compared to IA-DSA.

Discrepant policy advices based on IA-DSA and MRA were partly the result of differences in aneurysm occlusion grades. This can be explained by the different information that is obtained by MRA and IA-DSA. MRA provides 3D images in contrast to IA-DSA, the coil mesh configuration is visible on IA-DSA and not on MRA, and coil induced artifacts may disturb evaluation of MRA.[4,7,8] Differences in occlusion grading on IA-DSA and MRA can also be explained by the to some extent subjective discrimination between neck remnant and residual aneurysm. By dichotomization of the occlusion level, information is lost on the exact degree of occlusion.

Besides a different occlusion grade, variability in treatment advices among interventional neuroradiologists may explain discrepancy in policy decisions based on IA-DSA and MRA. Therapeutic decision making is subjective and depends on the level of treatment experience as well as on familiarity with the imaging techniques. The interobserver agreement for IA-DSA was similar to, and for MRA lower than, the intertechnique agreement on treatment advices. This means that differences in treatment advices between IA-DSA and MRA can not only be attributed to differences in imaging technique, but also to different opinions of the observers. A previous study of 27 patients with incompletely occluded aneurysms, showed a substantial interobserver variability in whether or not and how to additionally treat the aneurysm based on IA-DSA.[9]

The interobserver agreement for MRA was lower than for IA-DSA. This may be explained by unfamiliarity with decision making based on MRA. Through implementation of an existing technique in a new setting, in this case MRA for patients after coiling, diagnostic and therapeutic decision-making is expected to improve with time.[10]

Previous studies focused on detection of reopened aneurysms on MRA versus IA-DSA, and not on the clinically important subsequent treatment decisions.[3,4,7] A limitation of our study is that we still did not fully reflect clinical practice. Treatment options are often discussed in multi-disciplinary meetings together with neurologists and neurosurgeons. We could not carry out blinded MRA- and IA-DSA-assessments in such a setting but whenever it was possible, two interventional neuroradiologists did a double-reading. We furthermore focused on treatment decisions only based on imaging characteristics and not on patient characteristics. Patient characteristics may influence the decision to follow up with IA-DSA in a different way than the decision to follow up with MRA, because IA-DSA implies another invasive procedure with a small but definite complication risk.[11] Moreover, follow-up schedules differ in each clinic. For the purpose of our study the policy for patients with adequately occluded aneurysms was discharge from further imaging follow-up, while these patients might get another routine follow-up investigation later on depending on the follow-up schedule in that particular clinic. This would not change the interpretation of our study results though, because these routine follow-up schedules are irrespective of previous imaging results. Furthermore, at the time when our study was performed stents were rarely used to treat aneurysms. Therefore, our results apply only to patients who had straightforward coiling of aneurysms and not to patients who are treated by stents only or by stent-assisted coiling. Finally, although there was a relatively large number of excluded patients (25.6%), with claustrophobia and non-titanium neurovascular clips being the reason for excluding 10% of the patients, age, sex, and aneurysm size were not different for participating and non-participating patients.

We did not compare therapeutic advices based on TOF-MRA and CE-MRA, because we previously described similar test characteristics for both techniques in this patient population, so we did not expect a difference in therapeutic decisions.[4,12]

Our results show that in clinical practice decisions for additional treatment during follow-up of coiled intracranial aneurysms can be made on MRA alone. Follow-up with MRA is also expected to reduce costs compared to follow-up with IA-DSA.[13] The tendency of a slightly increased number of follow-up investigations after MRA may diminish but not negate the cost-effectiveness. Future studies could focus on possible advantages of baseline MRA obtained immediately after coiling. This might aid the detection of a change in occlusion grade of the coiled aneurysm on the next follow-up MRA, which can facilitate therapeutic decision making

during follow-up. We conclude that the comparable therapeutic decisions based on MRA and IA-DSA as found in our study in addition to the high diagnostic performance, safety, and convenience of MRA, support the use of MRA instead of IA-DSA in the follow-up of patients with coiled intracranial aneurysms.

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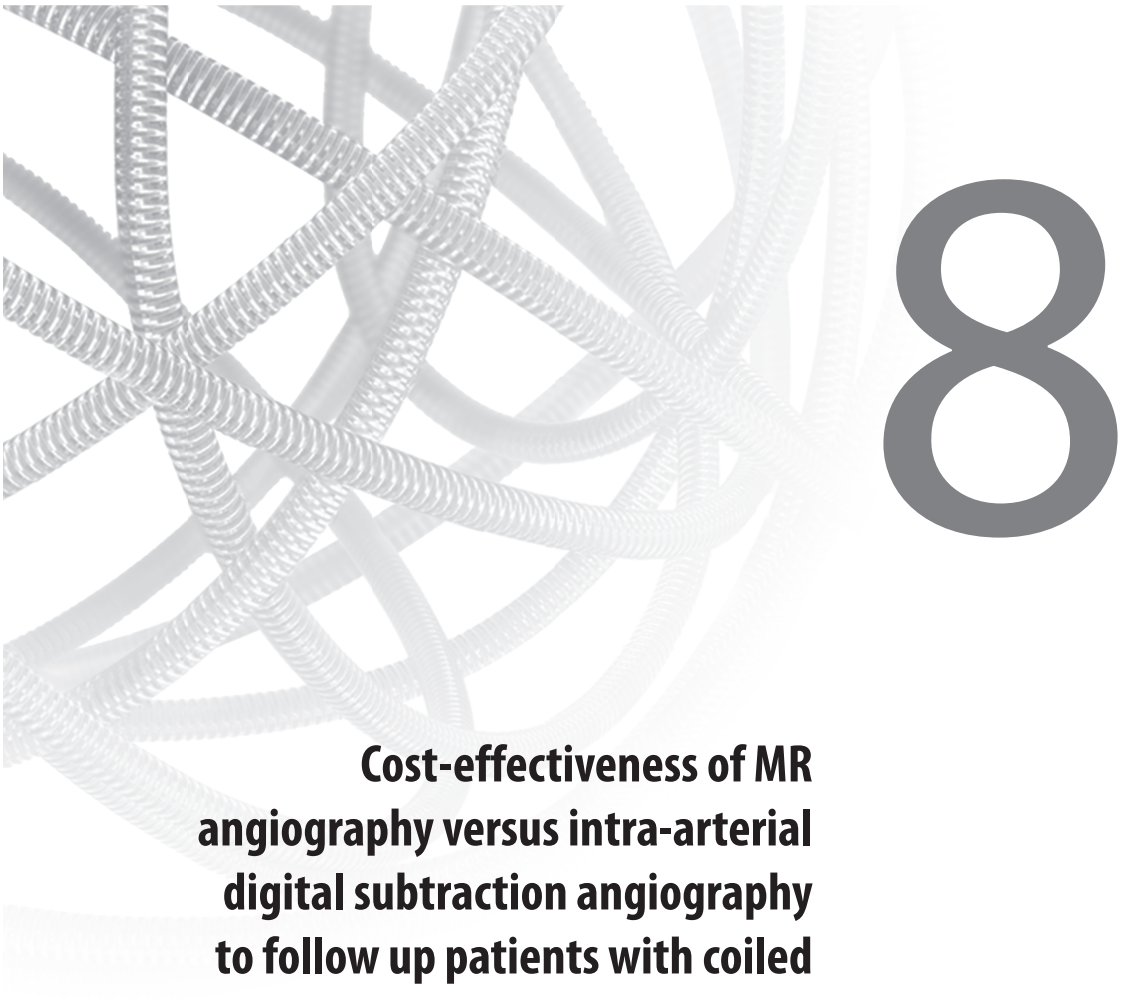

8

Cost-effectiveness of MR angiography versus intra-arterial digital subtraction angiography to follow up patients with coiled intracranial aneurysms

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Abstract

Background and purpose: To follow up patients with coiled intracranial aneurysms, magnetic resonance angiography (MRA) is a promising noninvasive alternative to current standard intra-arterial digital subtraction angiography (IA-DSA). MRA test results do not always concord with those of IA-DSA, and the impact of discrepancies on health benefits and costs is unknown. We evaluated the cost-effectiveness of follow-up with MRA versus IA-DSA to assess whether in this setting MRA may replace IA-DSA.

Methods: We studied aneurysm occlusion on MRA in addition to follow-up IA-DSA in 310 patients with 341 coiled intracranial aneurysms. The observed sensitivity (82%) and specificity (89%) of MRA for detection of reopening with IA-DSA as a reference were used as input for a Markov decision-analytical model. Other determinants were derived from the literature. We compared life expectancy, quality-adjusted life-years (QALY), costs, and expected number of events for the two strategies.

Results: Follow-up with MRA yielded similar life expectancy (MRA, 26.66 years; IA-DSA, 26.63 years; difference, 0.03 years (95% CI, -0.17 to 0.23)), and QALY (MRA, 10.96; IA-DSA, 10.95; difference, 0.01 QALY (95% CI, -0.05 to 0.08)), at lower costs (MRA, $7,003; IA-DSA, $8,241 per patient; difference -$1,238 (95% CI, -2,617 to -36)). The expected number of events was comparable except for complications from IA-DSA.

Conclusion: MRA provided equivalent health benefits as IA-DSA and was cost-saving. MRA dominates and should replace routine IA-DSA to follow up patients with coiled aneurysms.

Introduction

Follow-up after occlusion of intracranial aneurysms with coils is required because reopening and subsequent rupture may occur.[1-3] Intra-arterial digital subtraction angiography (IA-DSA) is the standard modality to detect reopening after coiling but is invasive and irradiating.[4] Furthermore, the procedure may cause patient discomfort and requires substantial capacity of the angiography suite and inpatient clinic. Magnetic resonance angiography (MRA) is an alternative technique that is noninvasive, nonirradiating, and can be performed in an outpatient setting.

To investigate whether MRA can replace IA-DSA for follow-up of coiled patients, complete diagnostic evaluation of MRA is required. This should include assessment of its test characteristics, effect on clinical outcome, and cost-effectiveness.[5]

Although test characteristics have been reported, we could not find studies on effects on clinical outcome and cost-effectiveness in this clinical setting. In a large prospective series of patients, we have recently compared MRA and IA-DSA to assess reopening of coiled aneurysms.[6] This enabled us to use the observed test characteristics of MRA with IA-DSA as a reference to assess the expected changes in health benefits and costs incurred using MRA or IA-DSA.

Materials and methods

Using a cross-sectional design, we previously assessed the accuracy for detection of reopened aneurysms in MRA with IA-DSA as a reference in 310 coiled patients (mean age, 51±12; 71% women).[6] Unenhanced (time-of-flight) and contrast-enhanced MRA was performed in each patient in addition to routine IA-DSA. Two observers classified, independently from each other, the level of occlusion as adequate or reopening on IA-DSA and on MRA. They were blinded for the parallel imaging modality. Sensitivity of MRA for detection of reopened aneurysms was 82% (95% CI, 72 to 89%) and specificity was 89% (95% CI, 85 to 93%). Contrast-enhanced MRA did not provide additional information to unenhanced MRA. The mean residual lumen of undetected reopened aneurysms on MRA was 3 mm versus 6 mm for detected reopened aneurysms. Retreatment was performed when the residual lumen appeared large enough for additional coiling, which was the case in 44 of 76 patients (58%; 95% CI, 47 to 68%) with reopened aneurysms on IA-DSA.

Evaluation of health benefits and costs: a Markov model

We developed a Markov decision-analytical model (TreeAge Software) to assess differences in health benefits and costs for follow-up with MRA versus follow-up with IA-DSA.[7] A Markov

model is based on probabilities of transitions between health states that we predefined as "healthy with an occluded aneurysm", "healthy with a reopened aneurysm", "disabled"(severe disability requiring a nursing home), and "death" (Figure 8.1). To each health state we assigned a measure for utility that was ultimately used to estimate quality-adjusted life-years (QALY). Various events could cause transitions between health states, such as complications of the diagnostic procedure or treatment, recurrent subarachnoid hemorrhage, or unrelated events. The probabilities of occurrence of these events and their costs were the input parameters for the model. Then, a hypothetical cohort of patients was run through the model with one-month time cycles. All started in "healthy with an occluded aneurysm" and could transit to other health states depending on occurring events. A lifetime horizon was used. This allowed us to simulate the individual life course of a large hypothetical cohort to assess the change in health benefits (QALY) and costs for a follow-up strategy with MRA versus IA-DSA.

Model scenarios

In clinical practice, coiled patients are eligible for follow-up IA-DSA when they regain independence for daily activities after subarachnoid hemorrhage. In analogy to clinical practice, our model structure was as follows: fictive patients who were independent for daily activities entered the model at six months after coiling for the first follow-up procedure, which was either IA-DSA or MRA. In case of detected aneurysm reopening, patients could be recoiled.

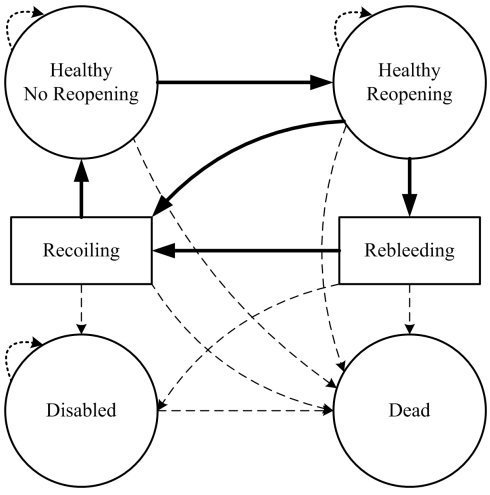

Figure 8.1 State transition model. Possible transitions between health states (circles) in our Markov model. Patients may develop reopening, remain in the same health state, or may move to the disability and death state because of complications of diagnostic testing, recoiling, rebleeding, or unrelated events.

Recoiling was also considered for patients with a falsely assumed reopening on MRA. The coiling procedure that requires IA-DSA would be interrupted upon detecting an aneurysm on IA-DSA that is actually sufficiently occluded. Conversely, undetected reopened aneurysms on MRA or untreated reopened aneurysms could cause recurrent subarachnoid hemorrhage. A second follow-up procedure was performed at 18 months after coiling. If the aneurysm was still occluded at 18 months of follow-up, then patients were discharged. Patients with untreated reopened aneurysms at 18 months after coiling were screened once more at 3.5 years after coiling. If the aneurysm was left untreated after the 3.5-year screening, then patients were discharged from follow-up. Complications of screening and recoiling procedures could cause disability and death (Figure 8.2).

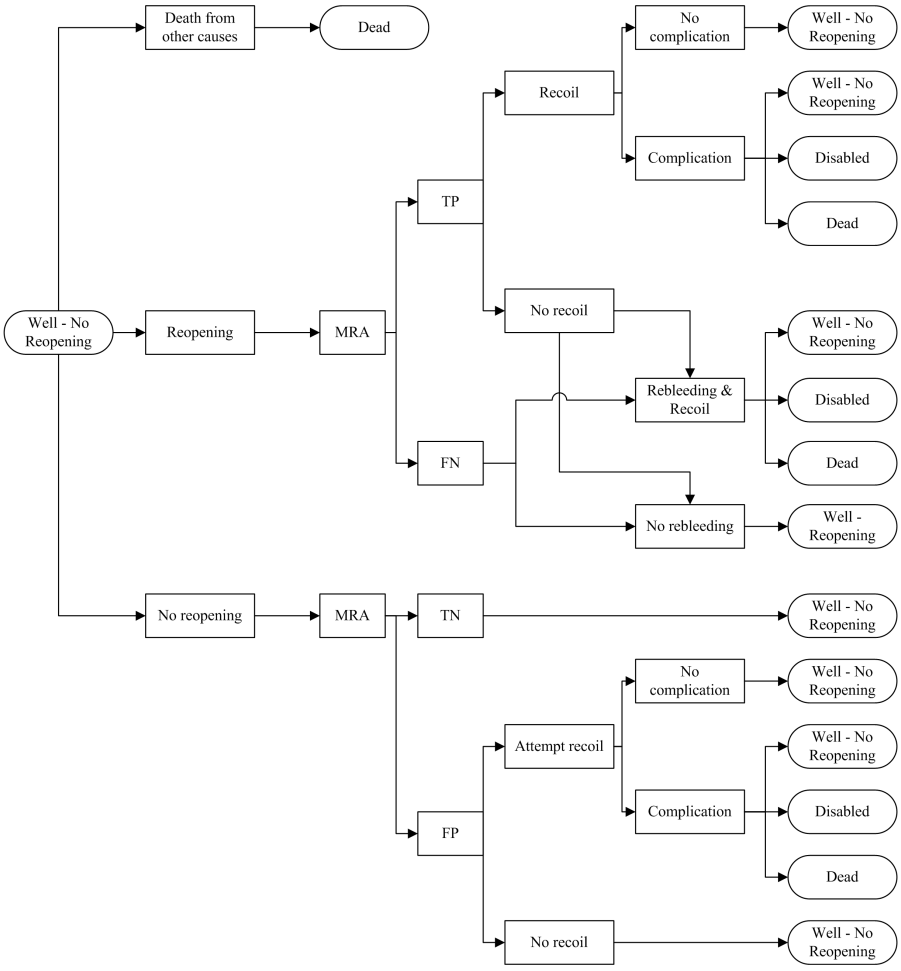

Figure 8.2 This simplified part of the decision tree used in the Markov model illustrates follow-up with MRA. TP, true-positive; FN, false-negative; TN, true-negative; FP, false-positive test result. The branch for IA-DSA is not displayed.

Model parameters

Age, gender, sensitivity and specificity of MRA, and probability of recoiling obtained from our clinical cohort were used as input parameters of the Markov model. Other input parameters on probabilities of health state transitions, utilities, and costs were derived from the literature after a systematic PubMed search. All parameters were discussed in a multidisciplinary setting (Table 8.1). For patients who died from unrelated causes, we used age- and gender-specific mortality rates provided by the national center of statistics in the Netherlands (CBS), adjusted for the standardized mortality ratios of patients after subarachnoid hemorrhage.[8]

The risk of reopening of coiled aneurysms decreases over time.[9-14] Based on the results of studies with different time intervals of follow-up, we developed a univariate regression function to predict long-term reopening risks after coiling (Figure 8.3).

Direct medical costs were incorporated. Instantaneous costs were used for IA-DSA, MRA, recoiling, recurrent subarachnoid hemorrhage, and death. Long-term costs were used for disabled patients residing in a nursing home. All costs were updated to 2007 with Dutch inflation indices and converted to US dollars (1€=1.38$, June 2009; Table 8.1).

Future costs and effects were discounted with 4% according to current Dutch guidelines.[15]

Model assumptions

We assumed that reopened aneurysms do not occlude spontaneously because progressive occlusion is rare.[10, 14] We furthermore assumed that the risk of rupture of reopened aneurysms is constant and similar for untreatable reopened aneurysms, undetected reopened aneurysms, or aneurysms that reopened after discharge from follow-up.

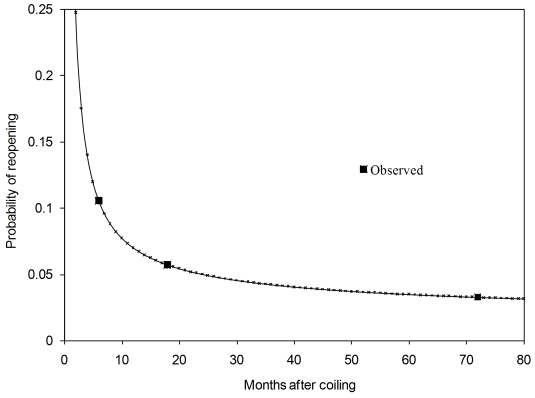

Figure 8.3 Probability function for reopening over time based on data retrieved from the literature (see also Table 8.1).

Table 8.1 Model input parameters

Model parameter	Value	95% CI/range*	Distribution	Source
Probabilities				
Sensitivity MRA	0.82	0.72-0.89	beta	CS
Specificity MRA	0.89	0.85-0.93	beta	CS
p(case fatality of IA-DSA)	0.0006	0.0003-0.0010	beta	[4]
p(morbidity of IA-DSA)	0.0010	0.0006-0.0015	beta	[4]
p(case fatality of MRA)	0.0000000	-	-	[17, 18]
p(morbidity of MRA)	0.0000053	0.0000026-0.0000088	beta	[17, 18]
p(case fatality recoiling)	0.0056	0.0018-0.0120	beta	[24-27]
p(morbidity recoiling)	0.011	0.004-0.021	beta	[26, 27]
p(case fatality rebleeding)				[28]
30-39 y	0.182	0.162-0.204	beta	
40-49 y	0.225	0.211-0.240	beta	
50-59 y	0.249	0.236-0.262	beta	
60-69 y	0.317	0.310-0.324	beta	
70-79 y	0.455	0.438-0.472	beta	
>80 y	0.576	0.553-0.598	beta	
p(morbidity rebleeding)	0.09	0.08-0.11	beta	[29, 30]
p(case fatality disabled patients) per year	0.24	0.10-0.36	uniform	[28, 31]
p(reopening) up to 6 mo after coiling†	0.119	0.097-0.144	beta	[10, 11, 13]
p(reopening) 6-18 mo after coiling†	0.055	0.019-0.110	beta	[9, 11, 14]
p(reopening) 18 mo-6 y after coiling†	0.036	0.010-0.078	beta	[12]
p(recoiling reopened aneurysm)	0.58	0.47-0.68	beta	CS
p(rupture risk reopening) per year	0.017	0.014-0.020	uniform	[10, 12, 22, 23, 32]
Costs ($)				
Costs IA-DSA	$838	-	-	[33]
Costs MRA	$371	-	-	[33]
Costs of rebleeding including recoiling	$36,920	-	-	[34, 35]
Costs of elective recoiling	$12,646	-	-	[33]
Costs nursing home per year	$107,711	-	-	[15]
Costs of patient death	$3,585	-	-	[36]
Utilities				
Well after subarachnoid hemorrhage	0.72	0.65-0.80	triangular	[37]
Disabled	0.25	0.21-0.30	triangular	[37]
Dead	0	-	-	
Discounting				
Cost discount per year	4%	-	-	-
Effect discount per year	4%	-	-	-

CS indicates data obtained from our clinical study.
* 95% CI for beta distribution; range for uniform/triangular distribution.
† A mathematical function based on these results was used (Figure 8.3).
All rates obtained were converted to probabilities per month.

Model simulation and outcome measures

In our baseline scenario, we evaluated the outcomes for 50-year-old patients with parameter values as in Table 8.1. Simulations were performed for 2,500 hypothetical cohorts consisting of 5,000 patients each. We compared life expectancy, health benefits in QALY, inherent costs, and the expected number of events for follow-up with IA-DSA and for follow-up with MRA.

We repeated the analysis for 35- and 65-year-old patient subgroups. We also performed cost-effectiveness analyses for the three age subgroups with a discount rate of 1.5% instead of 4% for costs and effects.[15] Because the aim of follow-up is to prevent recurrent subarachnoid hemorrhage, and because insufficient data on the rupture risk of reopened aneurysms were available, we repeated the analysis for different rupture rates.

Sensitivity analyses

We explored uncertainty regarding the model input parameters with probabilistic sensitivity analysis using Monte Carlo simulation.[7,16] With Monte Carlo simulation, different samples are taken from parameter distributions for the hypothetical cohorts to assess uncertainty in cost-effectiveness estimates.

We performed additional univariate sensitivity analysis for all model parameters defined by distributions to evaluate the association between the model parameters with associated uncertainty and changes in costs, effects in QALY, and cost-effectiveness.[16]

Results

For the baseline model, life expectancy and QALY were in the same range for follow-up with MRA and for follow-up with IA-DSA, whereas MRA significantly reduced costs (Tables 8.2 and 8.3, Figure 8.4).

MRA induced health gain while saving costs in 67% of our samples and induced health gain while increasing costs in 1%. Conversely, MRA reduced health benefits at lower costs in 31% of our samples and reduced health benefits at increased costs in 1% (Figure 8.4).

Life expectancy was 39.42 years (95% CI, 39.03 to 39.80) after IA-DSA versus 39.47 years (95% CI, 39.04 to 39.91) after MRA for 35-year-old patients, 26.63 years (95% CI, 26.31 to 26.95) after IA-DSA versus 26.66 years (95% CI, 26.35 to 26.98) after MRA for 50-year-old patients, and 15.81 years (95% CI, 15.59 to 16.02) after IA-DSA versus 15.82 years (95% CI, 15.59 to 16.02) after MRA for 65-year-old patients.

Table 8.2 Costs and effects for follow-up with IA-DSA versus MRA

	IA-DSA	MRA	Difference	(95% CI)
Life expectancy per patient (yrs)	26.63	26.66	0.03	(-0.17 to 0.23)
QALY per patient	10.95	10.96	0.01	(-0.05 to 0.08)
Total case fatality strategy (n)	125	120	-5	(-24 to 13)
Total morbidity strategy (n)	38	34	-4	(-16 to 11)
Case fatality Recoiling (n)	5	5	0	(-3 to 2)
Morbidity Recoiling (n)	9	9	0	(-4 to 3)
Case fatality Test (n)	7	0	-7	(-14 to -2)*
Morbidity Test (n)	11	0	-11	(-20 to -4)*
Reopened aneurysms (n)	1,359	1,360	1	(-28 to 31)
Recoiling procedures (n)	728	718	-10	(-29 to 7)
Rebleedings (n)	191	196	5	(-12 to 22)
Costs per patient	$8,241	$ 7,003	$-1,238	(-2,617 to -36)*

The cost-effectiveness estimates based on simulations of 2,500 cohorts of 5,000 patients each.
* Statistically significant.

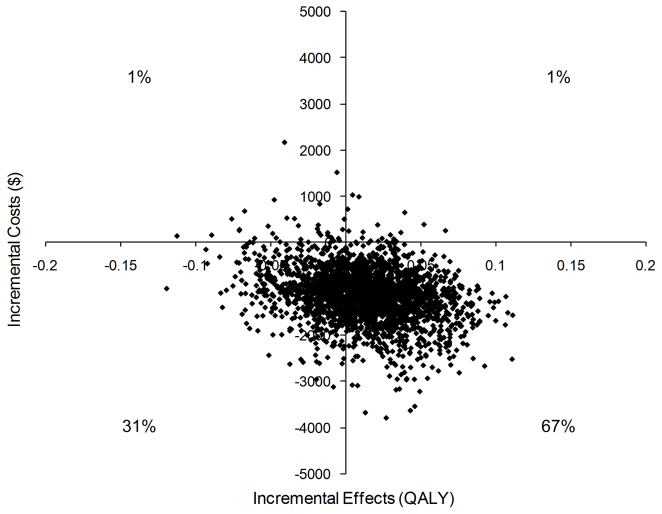

Figure 8.4 This cost-effectiveness graph shows the increment in QALY versus the increment in costs induced by MRA for 2,500 simulations. Each dot represents one simulation for 5,000 patients for which input values were sampled from the parameter distributions given in Table 8.1. The percentages of samples per quadrant are indicated.

Table 8.3 Scenario analyses

Age (y)	DR (%)	Rupture risk*	Costs ($)		QALY		ΔCosts	(95% CI)	ΔQALY	(95% CI)
			IA-DSA	MRA	IA-DSA	MRA				
35	4	0.017	8,240	7,001	13.40	13.42	-1,238	(-2,663 to -75)	0.02	(-0.04 to 0.08)
50	4	0.017	8,241	7,003	10.95	10.96	-1,238	(-2,617 to -36)	0.01	(-0.05 to 0.08)
65	4	0.017	8,290	7,015	7.95	7.96	-1,275	(-2,523 to -199)	0.01	(-0.04 to 0.06)
35	1.5	0.017	11,322	10,068	20.76	20.79	-1,254	(-2,899 to 290)	0.03	(-0.09 to 0.13)
50	1.5	0.017	10,438	9,153	15.29	15.31	-1,284	(-2,979 to 72)	0.02	(-0.08 to 0.12)
65	1.5	0.017	9,743	8,403	9.90	9.91	-1,340	(-2,894 to -50)	0.01	(-0.06 to 0.09)
50	4	0.034	9,284	8,056	10.90	10.91	-1,227	(-2,588 to -6)	0.01	(-0.05 to 0.07)
50	4	0.014	7,897	6,653	10.96	10.98	-1,244	(-2,295 to -108)	0.02	(-0.05 to 0.09)
50	4	0.009	7,546	6,291	10.98	10.99	-1,255	(-2,492 to -61)	0.01	(-0.05 to 0.07)
50	4	0.005	7,135	5,871	11.00	11.01	-1,264	(-2,677 to -122)	0.01	(-0.05 to 0.08)

Each analysis comprised 1,000 simulations for 5,000 patients. DR indicates discount rate. * Rupture risk of reopened aneurysm per year.

The number of events during follow-up with IA-DSA and MRA was not different except for case fatality and morbidity caused by IA-DSA (Table 8.2). The incidence of recurrent subarachnoid hemorrhage was not significantly higher for MRA than for IA-DSA. The difference in the overall case fatality and morbidity between the diagnostic strategies was 9 out of 5,000 patients in favor of follow-up by MRA.

Scenario analyses for different ages, discount rates, and rupture rates of reopened aneurysms yielded similar results as for the baseline model. MRA remained cost-saving with a similar change in QALY compared to IA-DSA (Table 8.3). For 50-year-old patients, MRA gained slightly more QALY in 68%; for 35-year-old patients, in 72%; and for 65-year-old patients, in 64% of the sampled cohorts. So, the probability of health gain by MRA increases with decreasing age. The cost-saving provided by MRA was similar in all our scenarios and was apparently not largely influenced by patient age, the rupture risk, or the discount rate used in the model.

Sensitivity analysis demonstrated that the distribution of input parameters did not significantly influence costs or QALY. We did not find an association between values of single-model parameters and cost-effectiveness estimates.

Discussion

Follow-up after coiling of intracranial aneurysms by MRA results in similar health benefits but lower costs than follow-up by IA-DSA.

The expected number of events was similar for both strategies, except for morbidity and case fatality caused by IA-DSA. Nevertheless, these complications did not have a major impact on cost-effectiveness because the total number of expected complications of IA-DSA remained small, particularly in comparison to patients with atherosclerosis.[4] The complication risk of MRA with contrast agent is extremely small.[17,18] We incorporated this small risk into the model, even though in our clinical study and other studies contrast-enhanced MRA did not provide significant additional information to unenhanced MRA.[19,20] So, the administration of contrast agent is often unnecessary, which decreases the morbidity risk of MRA even further. Moreover, those reopened aneurysms on IA-DSA that were not identified on MRA, did not significantly increase the expected incidence of subarachnoid hemorrhage for patients followed up with MRA.

As a result of less than optimal quality of life after subarachnoid hemorrhage, life expectancy considerably surpasses the number of QALY, regardless of the strategy.

MRA appeared to be cost-saving. Because the number of events does not largely differ between the two strategies, the difference in costs is likely to be caused by the lower costs of MRA

compared to the IA-DSA procedure. When cost reduction is not taken into consideration, there is still a substantial chance that MRA is the preferred strategy with a small gain in QALY, especially for younger patients.

We could not find other studies on cost-effectiveness of MRA versus IA-DSA after coiling. Using a Markov model we integrated the best available evidence for computation of the expected long-term outcomes. A diagnostic randomized clinical trial, although theoretically more accurate, would be infeasible because a large number of participants and long follow-up are required to ascertain the incidence of rupture of undetected or untreated reopened aneurysms.[5]

We intended to construct a detailed Markov model that appropriately reflects clinical practice, although we faced some limitations. First, IA-DSA is not a perfect reference standard for follow-up of coiled aneurysms. For example, the two-dimensional images restrict visualization of residual flow in case of superimposition of coils or surrounding arteries.[21] Consequently, discrepant results on MRA had to be labeled as "false-positive" or "false-negative", whereas MRA may provide the more realistic visualization. Thus, the model represented the least favorable scenario for MRA and therefore may underestimate its diagnostic performance. MRA still appeared dominant, thus strengthening the conclusion that MRA may replace IA-DSA.

Second, input parameters originated from our clinical study and from the literature. Because coiling has been available since 1992, only limited data on reopening and subsequent rupture rates more than 5 to 10 years after coiling are available.[1,2,10,22,23] Reopening rates could only be estimated from a few studies with a systematic long-term follow-up at fixed time intervals.[3,9-12,14]

Third, for the model, we assumed a similar rupture rate for aneurysms that reopened after follow-up for untreatable and for undetected reopened aneurysms, whereas the actual rupture risks may differ in each situation. Undetected reopened aneurysms in our clinical study were smaller and therefore probably had a lower rupture rate than larger reopened aneurysms that are left untreated. By assuming a similar rupture rate, we overestimated the health loss from undetected aneurysms when using MRA and therefore underestimated the health benefits provided by MRA. Repeated analyses for different rupture rates resulted in marginal and similar changes in QALY and costs. So, the uncertainty around the exact rupture rate did not influence the cost-effectiveness of MRA compared to IA-DSA. We furthermore assumed that reopened aneurysms never occlude spontaneously. In case of spontaneous occlusion, the potential hazard of a nonidentified reopened aneurysm on MRA would be smaller. So, again, we applied the least favorable scenario for MRA to avoid positive bias.

Fourth, we did not evaluate the influence of uncertainty in costs on the cost-effectiveness of MRA versus IA-DSA because insufficient evidence was available to define their distribution.

Finally, because information on actual dependencies between model parameters could not be obtained, all parameters were, by necessity, assumed to be independent in our probabilistic sensitivity analysis. This assumption may not hold for all parameters, e.g., for sensitivity and specificity. Nevertheless, because the sensitivity analyses showed overall robust outcomes, we feel that our general conclusion remains justified.

MRA is a safe technique that can be performed in an outpatient setting. Our results show that the consequences of misdiagnosis by MRA outweigh the complications caused by IA-DSA and that MRA reduces costs. We therefore recommend using MRA instead of IA-DSA to follow up coiled patients. The exact timing of reopening and subsequent rupture after coiling is unclear. Additional studies on timing of follow-up MRA are warranted to assess the short-term and long-term evolution of coiled aneurysms.

Conclusion

Cost-effectiveness analysis by Markov modeling shows that potential consequences of misdiagnosis by MRA will be offset by the direct risk of complications associated with IA-DSA, and MRA will reduce costs considerably. Patients therefore should be followed up by MRA instead of IA-DSA to detect reopening after coiling of intracranial aneurysms.

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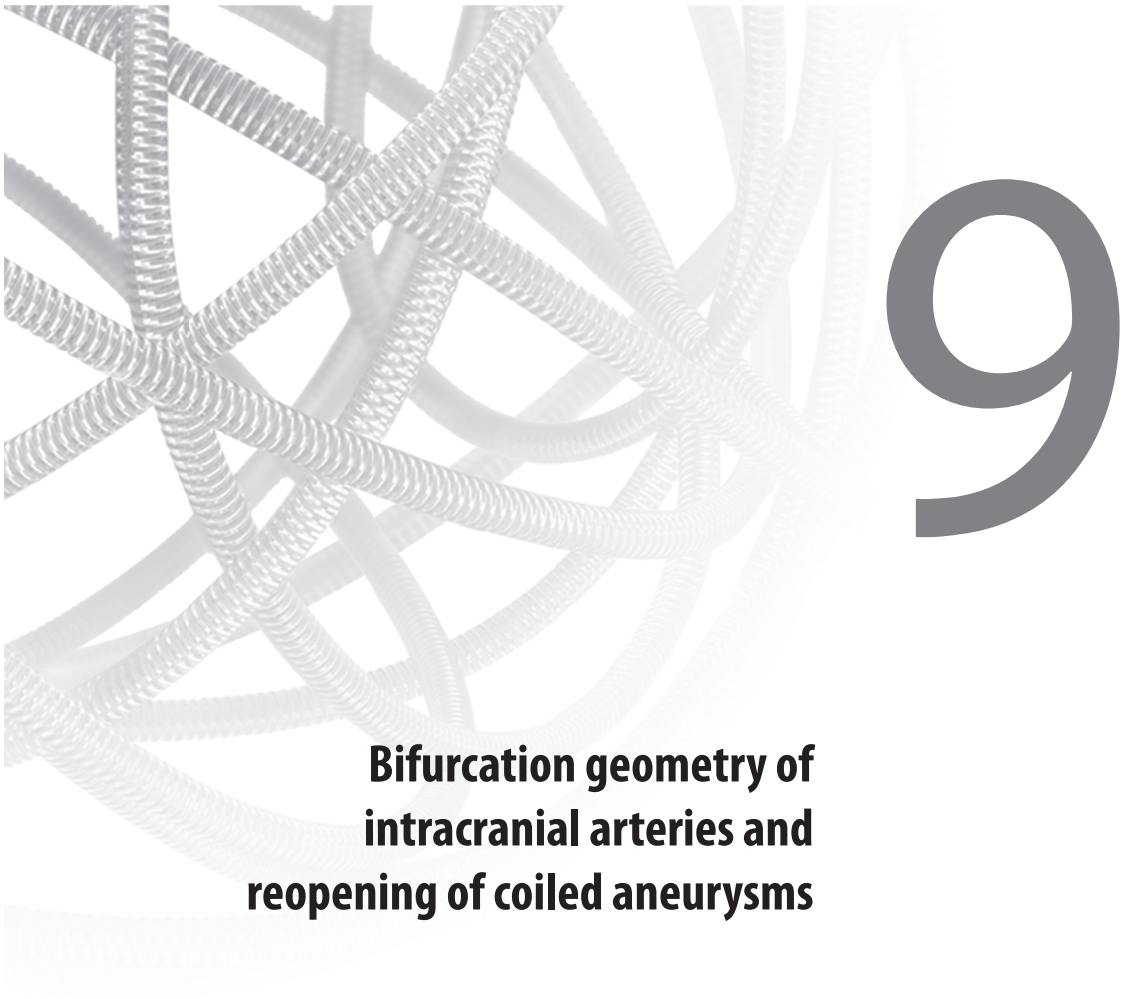

9

Bifurcation geometry of intracranial arteries and reopening of coiled aneurysms

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Abstract

Background and purpose: To assess whether bifurcation angles of blood vessels at the base of coiled intracranial aneurysms are related to reopening.

Methods: Two observers, blinded for presence of reopening, measured angles on CT angiography between parent and branch arteries of aneurysms at bifurcations. Two other observers scored the presence of reopening on follow-up intra-arterial digital subtraction angiography (IA-DSA) after coiling. Logistic regression analysis was used to assess the association between bifurcation-angle tertiles and reopening.

Results: In 82 patients with 86 aneurysms, 25 aneurysms reopened on follow-up IA-DSA. Sharper bifurcation angles, indicating more flow deviation, tended to be related to reopening (odds ratio: 2.9; 95% CI: 0.8,11.4).

Conclusion: Bifurcation angles of blood vessels at coiled aneurysms seem to have impact on reopening after coiling.

Introduction

Endovascular occlusion with coils is an established treatment for intracranial aneurysms.[1] Around 20% of coiled patients develop reopening of the aneurysm because of coil impaction, dissolution of thrombus, or aneurismal growth.[2] Thus far, a few risk factors for reopening have been identified, such as incomplete occlusion at treatment, large aneurysms, large neck-to-dome ratios, and smoking.[2-4]

Intracranial aneurysms often develop at bifurcations and the change in flow direction at the bifurcation seems to be associated with the development of aneurysms[5] and with aneurysm rupture.[6] We hypothesized that more flow deviation at the base of coiled aneurysms would create a higher pressure on the coils, which would induce reopening.

Materials and methods

Patient inclusion

This was an ethical committee-approved study. All patients gave informed consent. We included consecutive patients with coiled intracranial aneurysms who had CT angiography (CTA) as part of the work-up before coiling and who underwent routine follow-up imaging after coiling. For a previous study, intra-arterial digital subtraction angiography (IA-DSA) and magnetic resonance angiography (MRA) were performed in each patient and showed similar occlusion levels.[7] We used their IA-DSAs for this study to be able to compare them with the IA-DSAs made during coiling. Patients with side-wall aneurysms were excluded.

CTA

The CTA from C2 to the vertex of the brain was performed on a 16-slice CT-scanner (MX 8000 IDT or Brilliance 16P, Philips Medical Systems, Best, the Netherlands). Scan parameters were: 16×0.75mm collimation, 0.75s rotation time, exposure settings 90kVp and 330mAs. Reconstructed slice thickness was 1mm with 0.5mm increment; field-of-view was 160mm. Seventy milliliter of contrast material (Iopromide [300mgI/mL], Bayer-Schering AG) was injected for 17 seconds (50mL at 5mL/s and 20mL at 3mL/s). A test bolus was applied to determine the individual scan delay. The CTA datasets were transferred to a workstation (Extended Brilliance Workspace; Philips Medical Systems, Best, The Netherlands) for analysis.

Follow-up IA-DSA

Follow-up IA-DSA was performed on an angiographic unit (Integris BV5000, Philips Medical Systems, Best, the Netherlands). The following standard projections were made: 1) anterior-posterior view; 2) lateral view; and 3) the optimal projection used at coil-embolization. A maximum of 8mL of non-ionic contrast agent (300mmol/mL) was injected per view with a velocity of 4mL/s.

Image interpretation

CTA

Two observers (AR, JS), blinded for presence of reopening, independently measured on thin-slice multi-planar reformatted (MPR) images the two angles between the parent vessel and branch arteries of the aneurysms. Each angle was measured in the MPR that included at least 5mm of both the parent and one of the branch arteries as a continuous vessel (Figure 9.1). The angles were used as a measure for flow deviation at the bifurcation. The smaller the bifurcation angles, the larger the flow deviation and the higher the expected pressure on the coil mesh. When measurements between observers differed more than 10°, consensus was reached by repeating the measurement together. The direct angle between the two branch arteries was not used for analysis as it could not be reliably reproduced.

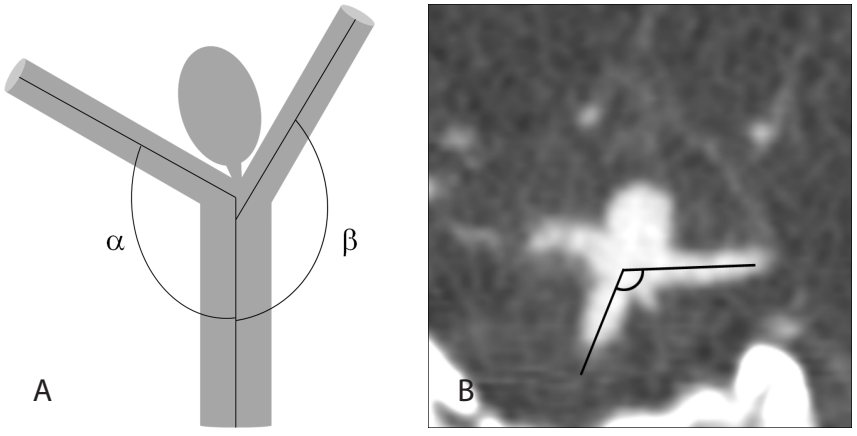

Figure 9.1 Measurement of bifurcation angles. **(A)** Smallest (α) and largest (β) bifurcation angle. **(B)** Angle measurement between the basilar artery and the left posterior cerebral artery (MPR).

IA-DSA

Two different observers (RL, TW) independently assessed on IA-DSA whether the aneurysm had reopened. A reopening was defined as new flow or an increase of flow in the aneurysm compared to the IA-DSA during coiling. The observers indicated if only the neck reopened or also the aneurysm sack. Discrepant results were solved by consensus-reading.

Statistical analysis

Interobserver agreement was assessed by calculating the Pearson's correlation coefficient for angle measurements and by calculating the kappa for presence of reopening on IA-DSA. We divided bifurcation angles into tertiles and used logistic regression analysis to evaluate the association between bifurcation-angle tertiles and reopening. The third tertile, with the largest angles and thus the smallest flow deviation, was used as a reference. We repeated the analysis for reopening of the aneurysm sack.

Results

We included 82 patients (59 women (72%), mean age 52) with 86 coiled aneurysms (mean size 7mm).

Measurement of bifurcation angles was not possible in three patients because of poor CTA quality and in three other patients because the branch arteries originated from the aneurysm. All IA-DSAs could be evaluated.

The interobserver agreement for measurements of bifurcation angles was high (Pearson's correlation coefficient: 0.87 ($p<0.001$)) and for presence of reopening substantial (κ: 0.64; 95% CI: 0.50,0.78).

The observers found 25 reopened aneurysms (29%). In 13 (15%) aneurysms, the sack also reopened. The odds ratio for reopening of aneurysms at sharper bifurcation angles, thus more flow deviation, was 1.9 (95% CI: 0.6,5.6) for all reopened aneurysms and 2.9 (95% CI: 0.8,11.4) for reopening of the aneurysm sack (Table 9.1, Figure 9.2).

Table 9.1 The association between bifurcation-angle tertiles and reopening

			Reopening (odds ratio (95% CI)	
			All	Aneurysm sack
Smallest angle	1st tertile	(26-81°)	1.8 (0.5-5.7)	2.4 (0.6-9.6)
	2nd tertile	(81-104°)	1.2 (0.4-4.1)	0.5 (0.1-3.3)
	3rd tertile	(104-142°)	Reference	Reference
Largest angle	1st tertile	(90-121°)	1.7 (0.6-5.2)	2.3 (0.6-9.6)
	2nd tertile	(121-132°)	1.2 (0.3-4.3)	2.7 (0.6-12.4)
	3rd tertile	(132-160°)	Reference	Reference
Sum of angles	1st tertile	(153-194°)	1.9 (0.6-5.6)	2.9 (0.8-11.4)
	2nd tertile	(194-231°)	1.2 (0.3-4.1)	1.0 (0.2-6.1)
	3rd tertile	(231-294°)	Reference	Reference

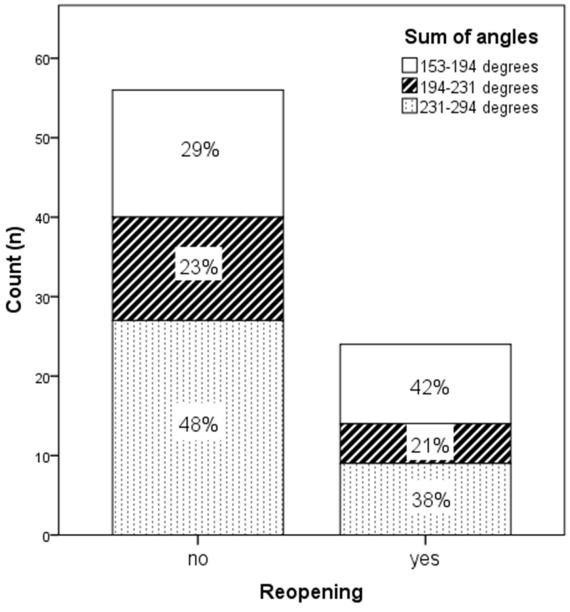

Figure 9.2 Distribution of bifurcation-angle tertiles. Each box represents a tertile for the sum of bifurcation angles for aneurysms with and without reopening. The smaller the angle, the larger the flow deviation.

Discussion

Bifurcation angles seem to be related to reopening after coiling but the odds ratios were not statistically significant.

The interobserver agreement on bifurcation angles was good, so the internal validity of the method to measure these angles was good. With respect to its external validity, we used a similar method as a study that found an association between angle measurements on CTA and aneurysm rupture.[6] Image evaluation on IA-DSA is an approved technique to detect reopening after coiling, so we expect the IA-DSA results to be valid.

Two recent studies on the association between blood vessel anatomy and development of reopening after coiling showed that asymmetrical A1 segments and an asymmetrical basilar tip increased the reopening risk.[8,9] Bifurcation angles were not measured in these studies. We decided to focus on bifurcation angles as this would be a practical measurement for clinical use, realizing that other risk factors such as smoking, large neck-to-dome ratio, incomplete coiling, large aneurysm size, and A1- or basilar tip-asymmetry, may surpass an eventual predictive value of bifurcation angles.

The main limitation of our study was the relatively small sample size. The point estimates, i.e. the odds ratios, for the tertile with the smallest angles, and thus more flow deviation, are promising but their confidence intervals are wide despite the combination of angles into tertiles. Therefore, we could not show a strong association in our series.

In clinical practice the ultimate goal of aneurysm treatment is prevention of rupture. Since the current knowledge about risk factors for reopening is insufficient to select patients who are at risk, all coiled patients still need to be followed up.

In conclusion, smaller bifurcation angles, and thus more flow deviation, at coiled aneurysms are likely to be associated with reopening after coiling. If these results can be confirmed in a larger series, this would facilitate the selection of a subgroup of patients who are at a higher risk for reopening after coiling.

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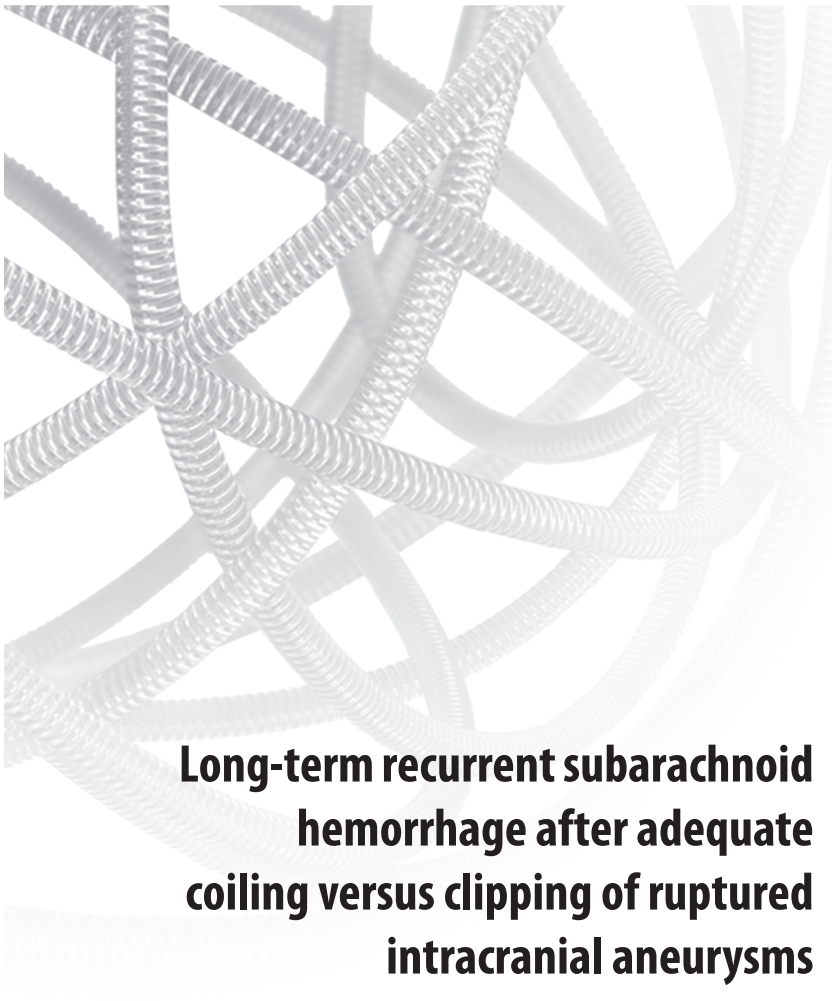

10

Long-term recurrent subarachnoid hemorrhage after adequate coiling versus clipping of ruptured intracranial aneurysms

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Abstract

Background and purpose: Coiling is increasingly used as treatment for intracranial aneurysms. Despite its favorable short-term outcome concerns exist about long-term reopening and inherent risk of recurrent subarachnoid hemorrhage (SAH). We hypothesized a higher risk for recurrent SAH after adequate coiling compared with clipping.

Methods: Patients with ruptured intracranial aneurysms coiled between 1994 and 2002 with adequate (>90%) aneurysm occlusion at 6-month follow-up angiographies were included. We interviewed these patients about new episodes of SAH. By survival analysis we assessed the cumulative incidence of recurrent SAH after coiling and compared it with the incidence of recurrent SAH in a cohort of 748 patients with clipped aneurysms by calculating age- and sex-adjusted hazard ratios.

Results: Of 283 coiled patients with a total follow-up of 1,778 patient-years (mean, 6.3 years) one patient had a recurrent SAH (0.4%) and 2 patients had a possible recurrent SAH. For recurrent SAH within the first 8 years after treatment, the cumulative incidence was 0.4% (95% CI, 0.0 to 1.2) after coiling versus 2.6% (95% CI, 1.2 to 4.0) after clipping (hazard ratio, 0.2; 95% CI, 0.03 to 1.6). For possible and confirmed recurrent SAH combined, the cumulative incidence was 0.7% (95% CI, 0.3 to 1.7) after coiling versus 3.0% (95% CI, 1.3 to 4.6) after clipping (hazard ratio, 0.7; 95% CI, 0.2 to 2.3).

Conclusion: Patients with adequately occluded aneurysms by coiling at short-term follow-up are at low risk for recurrent SAH in the long-term. Within the first 8 years after treatment, the risk of recurrent SAH is not higher after adequate coiling than after clipping.

Introduction

Endovascular treatment of intracranial aneurysms by coiling results in better short-term outcome than clipping in patients with aneurysmal subarachnoid hemorrhage (SAH).[1] An important drawback of coiling is reopening of the aneurysm as a result of coil compaction, growth of a neck remnant or dissolution of an intraluminal thrombus. Reopening occurs in around 20% of coiled aneurysms, predominantly within the first year after coiling, and exposes the patient to the risk for recurrent SAH in the long-term.[2-8] Therefore, most centers perform one or more follow-up angiographies during the initial years after coiling. It is unknown for how long and how often coiled aneurysms need to be followed up and whether certain subgroups carry a higher risk for reopening. In patients with complete or near complete occlusion at 6-month follow-up angiography, the long-term risk for reopening appears to be low.[7,9]

The incidence of recurrent SAH after clipping is low with a cumulative incidence of around 3% within the initial 10 years after treatment. Recurrent SAH after clipping is caused by rupture of a recurrent aneurysm at the clip site or by rupture of an untreated additional or a *de novo* aneurysm.[10] Long-term follow-up data on recurrent SAH after coiling are scarce. Because of the concern of late reopening after coiling we aimed to evaluate whether adequately coiled aneurysms carry a higher risk of recurrent SAH than clipped aneurysms. Therefore, we assessed the cumulative incidence of long-term recurrent SAH in patients with complete or near complete occlusion at 6-month follow-up angiographies after coiling and compared it with the cumulative incidence of long-term recurrent SAH after clipping.

Methods

This study was approved by the Institutional Review Boards of both participating hospitals.

Patients with coiled ruptured aneurysms

In two centers in the Netherlands (St. Elisabeth Ziekenhuis Tilburg and UMC Utrecht) with ample experience in endovascular treatment of aneurysms we retrieved from the prospectively collected databases consecutive patients who met the following criteria: 1) admission with aneurysmal SAH between November 1994 and December 2002; 2) selective coil treatment of the ruptured intracranial aneurysm; 3) adequate (>90%) occlusion at 6 months' follow-up after the initial coiling procedure; and 4) age >20 years. Patients with additional untreated aneurysms were not excluded. Patients who were discharged to a nursing home and resided there at 6 months after the SAH were not called back for follow-up angiography and thus were not eligible for the current study.

For those patients that fulfilled the inclusion criteria we first contacted the general practitioner to inquire if patients were still alive. The medical records of patients who had died during the follow-up period were reviewed to retrieve the exact cause of death. All other patients were contacted by telephone. During a semistructured interview we asked whether a recurrent SAH had occurred. When no phone number was provided we sent a short questionnaire by mail.

For all patients, data on age, sex, and site of aneurysms at time of the initial SAH were collected. When a recurrent SAH or other type of stroke was reported by the patient or the general practitioner, we retrieved data from the hospitals where these patients had been admitted. All brain imaging was reviewed to assess the cause of stroke and to evaluate the degree of occlusion of the coiled aneurysm at the time of recurrent SAH.

When patients had died suddenly without being admitted, we classified the event as a possible recurrent SAH if no further information was available.

Patients with clipped ruptured aneurysms

The patient retrieval and methods of follow-up of the clipped patients have been described previously.[10] From the database of the UMC Utrecht we retrieved patients with aneurysmal SAH and clipping of the ruptured aneurysm between 1985 and 2001. Patients who were discharged to a nursing home and patients <20 years old were not included. A postoperative angiography was performed in a minority of patients. The decision to perform postoperative angiographies was left to the discretion of the treating neurosurgeon.

Data analysis

Survival analysis was used to assess the cumulative incidence for recurrent SAH after adequate coiling and after clipping. The follow-up period after coiling started at the 6-month follow-up angiography. In parallel, we used follow-up data starting from 6 months after clipping. We stopped continuing the survival analysis when the cohort no longer exceeded 50 patients.

The incidence rate per 100,000 patient-years with corresponding 95% CIs was calculated for episodes of confirmed recurrent SAH only and for episodes of confirmed and possible recurrent SAH combined. When patients died during follow-up from another cause other than SAH or were lost to follow-up, they were censored at that time.

We compared the results of the survival analysis for clipped and coiled patients by calculating the age- and sex-adjusted hazard ratio with corresponding CI for recurrent SAH after coiling versus clipping by Cox regression analysis.

Results

Patients with coiled aneurysms

Between 1994 and 2002, 476 patients admitted with aneurysmal SAH were treated by coiling. Of these 476 patients, 112 (24%) were not followed-up by angiography at 6 months: 64 patients (13%) died before follow-up; 21 patients (4%) were admitted to a nursing home; 16 patients (3%) declined follow-up angiography; in 6 elderly patients (1%), follow-up was judged not indicated; 3 patients (0.6%) did not show up for follow-up angiography; and for 2 patients (0.4%), the reason was unknown (Figure 10.1). Of the 364 patients with follow-up angiography at 6 months, 290 (80%) showed adequate aneurysm occlusion and were eligible for this study. Follow-up data of 283 patients were retrieved. For 7 patients (2%), we could not contact the patient or their general practitioner. The address and phone number of 3 patients was unknown, 2 patients had emigrated, and 2 patients did not respond to phone calls or to the letter. Mean duration of

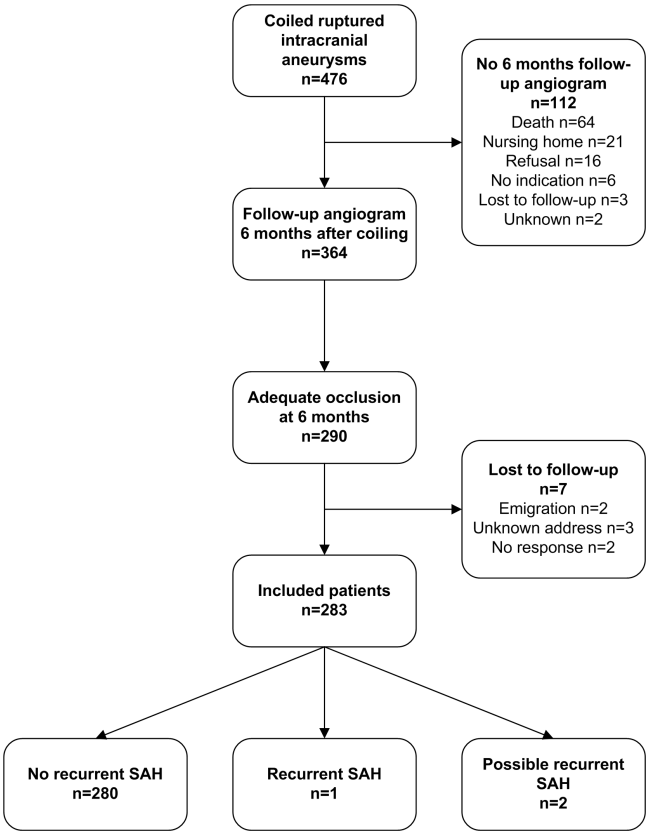


Figure 10.1 Flow diagram of included patients with coiled aneurysms.

follow-up was 6.3 years (range, 1.0 to 12.2 years) with a total of 1,778 patient-years (Table 10.1). Baseline characteristics of these patients were comparable to those of the excluded 74 patients with incompletely occluded aneurysms at the 6-month angiography. Mean age of patients with incompletely occluded aneurysms was 53 years, 62% were female, and the distribution of aneurysm location was as follows: internal carotid artery, 22%; anterior cerebral artery, 28%; middle cerebral artery, 10%; and posterior circulation, 40%. However, the mean aneurysm size was 8.3 mm for adequately occluded aneurysms and 13.4 mm for incompletely occluded aneurysms.

Patients with clipped aneurysms

Of the 930 patients who survived SAH, 154 did not meet the inclusion criteria (17%): 64 patients were admitted to a nursing home after hospitalization; 4 patients were <20 years old; 30 patients were coiled or had received intracranial bypass surgery; and for 26 patients, the aneurysm was left untreated. The remaining 776 patients met the inclusion criteria. Of these patients, 24 (3%) patients were lost to follow-up: 7 patients lived abroad; 2 patients did not respond to the invitation letter; and of 15 patients, the address was unknown, rendering 752 patients with a mean duration of follow-up of 8.0 years (range, 0.2 to 20.1 years) and a total of 6,016 patient-years.[10] Because we used follow-up data starting from 6 months after clipping in analogy to coiling, 4 patients with a shorter follow-up duration than 6 months were excluded. One of these 4 patients died from rebleeding within 6 months after clipping. Thus, we included for the analysis 748 clipped patients with a mean duration of follow-up of 7.6 years (range, 0.04 to 19.5 years) and a total of 5,661 patient-years. Baseline characteristics of both patient populations are summarized in Table 10.1.

Table 10.1 Baseline characteristics of included patients with coiled and clipped aneurysms

Characteristics	Patients with coiled aneurysms (n=283)	Patients with clipped aneurysms (n=748)
Mean age at initial SAH in years ±SD (range)	51.0 ± 11.0 (26-82)	50.4 ± 12.3 (21-84)
Women (%)	201 (71)	499 (67)
Mean follow-up in years (range)	6.3 (1.0-12.2)	7.6 (0.04-19.5)
Aneurysm site (%)		
ICA	66 (23)	155 (21)
ACA	99 (35)	270 (36)
MCA	18 (6)	133 (18)
Posterior circulation	100 (35)	39 (5)
Unknown	0	151 (20)

ICA indicates internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery.

Recurrent episodes of SAH

One of 283 included coiled patients had a recurrent episode of SAH (0.4%; 95% CI, 0% to 2.0%). The incidence rate of recurrent SAH was 57 per 100,000 patient-years (95% CI, 6 to 311 per 100,000) for the first 10 years of follow-up. Recurrent SAH occurred 23 months after coiling of a small basilar tip aneurysm in a 52-year-old man (Figure 10.2). The aneurysm was adequately occluded by recoiling after the recurrent SAH, but reopened again and was coiled for a third time. This patient survived and was slightly disabled but independent for activities of daily life 7 years after the recurrent SAH.

Of 283 coiled patients, 2 had died suddenly without available imaging. These patients were found dead in bed 2 and 10 years after coiling. These events were defined as possible recurrent SAH.

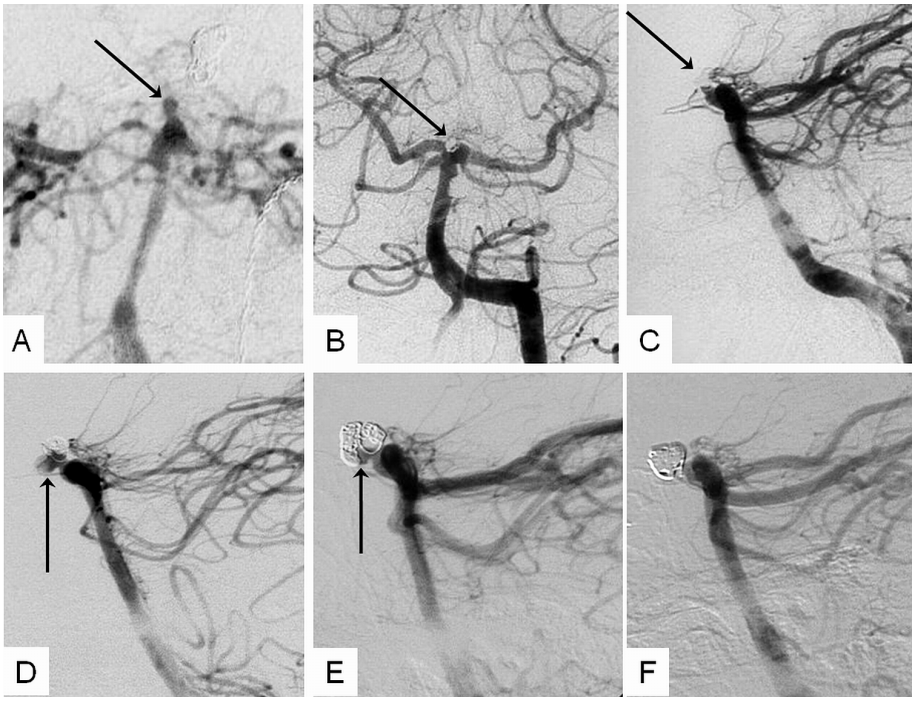


Figure 10.2 Angiography series of a 52-year-old man with recurrent SAH 23 months after coiling of a basilar tip aneurysm. A, Small ruptured basilar tip aneurysm (arrow). B-C, Adequate occlusion at 6 months on frontal (B) and lateral (C) view (arrows). D, Angiogram after recurrent SAH at 23 months shows reopening and enlargement of the aneurysm (arrow). The aneurysm was coiled for a second time. E, Six months after second coiling again, reopening (arrow) and enlargement of the aneurysm and third coiling followed. F, Five years after third coiling, stable complete occlusion. Note enlargement of the aneurysm over the years, probably as a result of slow resolution of initially present intraluminal thrombus.

Combining those 2 patients with the patient with confirmed recurrent SAH, the frequency of recurrent SAH would be 1.1% (95% CI, 0.2% to 3.1) with an incidence rate of 171 per 100,000 patient-years (95% CI, 31 to 494 per 100,000) within the first 10 years of follow-up. These 3 patients with confirmed or possible recurrent SAH after coiling are summarized in Table 10.2.

Recurrent SAH after clipping occurred in 17 of 748 patients (2.3%; 95% CI, 1.3% to 3.6%). The incidence rate after clipping was 247per 100,000 patient-years (95% CI, 118 to 377 per 100,000) for the first 10 years of follow-up. The history of another 2 patients was suggestive of SAH and was classified as possible recurrent SAH. In 4 patients with recurrent SAH, an aneurysm at the clip site was found. In one of these patients, also a second aneurysm at another location was detected. The remaining 13 patients had no aneurysm at the clip site but had developed a *de novo* aneurysm or had bled from an aneurysm that was not identified at the time of the initial SAH.

Two coiled patients (0.7%) had died from intracerebral hemorrhage originating from the basal ganglia after 6 and 8 years of follow-up. One of these patients had a history of hypertension and had been treated with oral anticoagulation. The second patient had no oral anticoagulation and a history of hypertension was unknown. For both patients, the last follow-up angiography after coiling showed complete occlusion. Within the cohort of clipped patients, 10 instances of intracerebral hemorrhage occurred (1.3%).

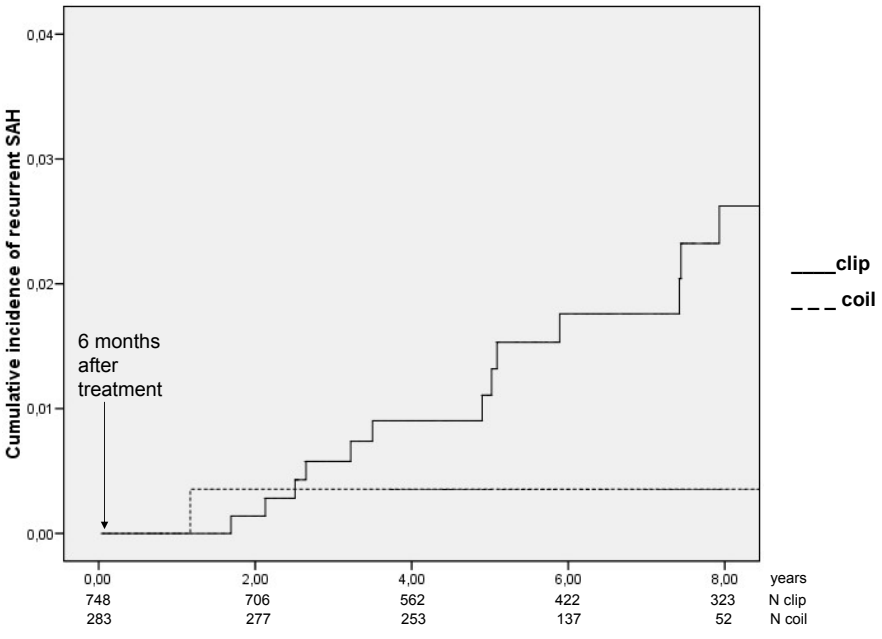
Survival analysis

Survival analysis was performed for the first 8 years, because at 8 years of follow-up, the number of patients in the cohort no longer exceeded 50 coiled patients (Figure 10.3). The cumulative incidence of confirmed recurrent SAH was 0.4% (95% CI, 0.0 to 1.2) after coiling and 2.6%

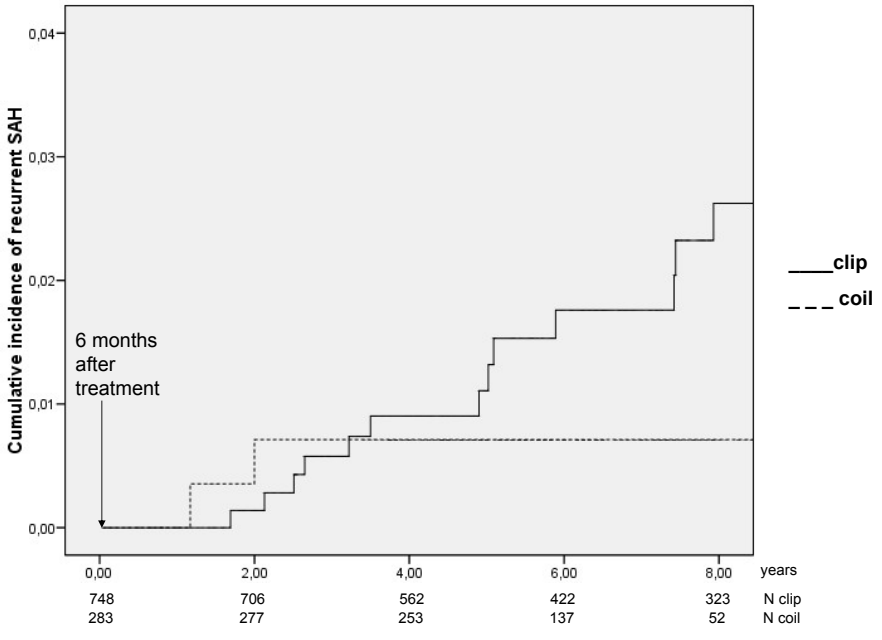
Table 10.2 Patient and aneurysm characteristics of the 3 patients with confirmed or possible recurrent SAH after coiling

Sex, age (yrs)	Aneurysm location and size	Confirmed / possible recurrent SAH	Delay recurrent SAH after coiling	Imaging after recurrent SAH?	Additional coiling?	Outcome
Male, 52	Basilar tip, 7mm	Confirmed	23 months	Yes: incomplete occlusion	Yes, twice	Mild disability
Female, 66	SCA, 15mm	Possible (found dead in bed)	2 years	No	No	Death
Female, 53	MCA, 12mm	Possible (found dead in bed)	10 years	No	No	Death

SCA indicates superior cerebellar artery; MCA, middle cerebral artery.



A



B

Figure 10.3 Kaplan-Meier curves for the cumulative incidence of confirmed recurrent SAH (A) and combined confirmed and possible recurrent SAH (B) in patients with coiled and in patients with clipped aneurysms.

(95% CI, 1.2 to 4.0) after clipping. The age- and sex-adjusted hazard ratio for recurrent SAH after coiling versus clipping was 0.2 (95% CI, 0.03 to 1.6).

The cumulative incidence of confirmed and possible recurrent SAH was 0.7% (95% CI, 0.3 to 1.7%) after coiling and 3.0% (95% CI, 1.3 to 4.6%) after clipping. The age- and sex-adjusted hazard ratio for recurrent SAH after coiling versus clipping was 0.7 (95% CI, 0.2 to 2.3).

Discussion

In the first 8 years after treatment, the long-term risk of recurrent SAH is small both after clipping and after adequate coiling. For adequately coiled aneurysms, this risk was lower than anticipated and did not exceed the incidence of recurrent SAH after clipping. From our data, however, we cannot conclude that coiling is superior to clipping. Because the incidence of recurrent SAH is small, the corresponding CIs are wide, which leaves some uncertainty regarding the hazard ratio for recurrent SAH after coiling versus clipping.

The selection of patients with adequate occlusion at 6-month follow-up imaging is a likely explanation for the low incidence of recurrent bleeding after coiling. Observational studies have shown that the reopening rate is highest within the first 6 months after coiling and decreases thereafter.[3,4] Interpretation of these studies is impeded by a variety of time intervals of follow-up angiography, so late-detected reopening had possibly developed earlier. In a series of 126 patients with fixed angiographic follow-up intervals at 6 and 18 months after coiling, all reopened aneurysms were found at 6-month angiography.[7] As a consequence of early reopening, the majority of recurrent treatment occurs within 10 months after initial coiling.[11,12] Coiled aneurysms in these patients may form a separate group that behaves differently and that may carry a higher risk of repetitive reopening. Therefore, prolonged follow-up imaging for these aneurysms is recommended.[12,13] In our study, we excluded this subgroup of patients, so we had presumed a small risk of recurrent SAH.

The distribution of aneurysm sites between coiled and clipped patients showed a larger proportion of aneurysms located in the posterior circulation within the coiled group (Table 10.1). Although there are hardly any data on the relation between rebleeding risk after treatment and aneurysm site, there is good evidence that unruptured aneurysms in the posterior circulation carry a higher rupture risk than unruptured aneurysms in the anterior circulation.[14] This might imply a higher rebleeding rate for the coiled cohort, which has not been confirmed by our study results. Thus, the absence of a higher rebleeding rate in the coiled group is unlikely to be explained by differences in aneurysm sites between the 2 cohorts.

Despite the concerns regarding late reopening, the incidence of recurrent SAH after coiling was not higher than after clipping. This could be the result of some important differences between the follow-up of coiled and clipped aneurysms. By the end of the coiling procedure, the occlusion status of the aneurysm is known in contrast to clipping. In general, imaging was not performed in our patients immediately after clipping and a residual neck could have remained unnoticed. Another aspect is the presence of additional untreated aneurysms. The majority of the recurrent episodes of SAH after clipping were caused by additional aneurysms that were in retrospect present at the initial SAH or by *de novo* aneurysms that developed afterwards. The awareness of the prevalence and development of multiple aneurysms by clinicians and the fast development of new techniques to detect aneurysms since the introduction of coiling procedures could explain the relatively large number of recurrent SAH from additional and *de novo* aneurysms in the older cohort of clipped patients. In our study population, 10% of coiled patients had one or more additional aneurysms that were coiled in the same or a repeat procedure. As a result of the small number of episodes of recurrent SAH and insufficient information regarding possible recurrent SAH, we could not assess the proportion of recurrent SAH from coiled aneurysms versus additional untreated aneurysms.

Awaiting the results from a large randomized clinical trial,[1] a few other observational studies have assessed recurrent SAH after coiling, but these studies did not focus on adequately occluded aneurysms at 6 months' follow-up.[2,8,15-18] A large cohort study with a mean follow-up period of 4.0 years, including 295 coiled patients and 706 clipped patients, found a rerupture rate of 3.5% for coiled patients versus 1.3% for clipped patients.[16] This difference was not statistically significant. The rerupture rate of coiled aneurysms was inversely related to the level of aneurysm occlusion after treatment. For completely occluded aneurysms immediately after treatment, the authors found an overall rerupture rate of 1.1%, which corresponds with the rerupture rate we found for confirmed and possible recurrent SAH together. The vast majority of reruptures occurred in the first month after coiling, which is also found in another observational study that focused on early rerupture after coiling.[18] Late rebleeding after coiling appears to occur predominantly in patients without regular follow-up angiography and hence not timely detected reopening or in patients with an untreatable reopening of the coiled aneurysm.[8] These studies indicate that the short-term risk for recurrent SAH after coiling seems to be more important than the long-term risk. This may have significant implications for the follow-up imaging schedules after coiling.

A limitation of our study was the definition of 'adequate occlusion', which meant aneurysm occlusion of more than 90%. This is a partly subjective measure depending on the interpretation of the radiologist. As a consequence, aneurysms with a little lower occlusion grade than 90%

could have been included and, conversely, aneurysms with a little higher occlusion grade than 90% could have been excluded. We tended to include cases with an uncertain aneurysm occlusion grade, so the incidence of recurrent SAH may be slightly overestimated. Despite including these sub totally occluded aneurysms, the incidence of recurrent SAH remained low. So small neck remnants seem to carry a low rerupture risk.

The low incidence rate of recurrent SAH after adequate coiling would not justify frequent follow-up within the first 8 years after coiling in the subset of patients with adequate occlusion at 6 months' follow-up, particularly not by invasive imaging techniques. A decision analytic model showed that long-term follow-up imaging after clipping to detect recurrent aneurysms at the clip-site or *de novo* aneurysms was not (cost-)effective and is generally not recommended.[19] Development of a similar decision model is needed to evaluate the effectiveness of short-term and long-term follow-up strategies for preventing recurrent SAH after coiling.

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11

General discussion

From the studies described in this thesis, we conclude that magnetic resonance angiography (MRA) can replace intra-arterial digital subtraction angiography (IA-DSA) as the standard follow-up imaging technique to detect reopening after coiling of intracranial aneurysms. This conclusion is based on the results of the different steps of diagnostic research that we took: assessment of test characteristics, additional value, clinical outcome, and cost-effectiveness (chapter 2). First of all, the test characteristics of MRA were good and similar at 1.5 and 3.0 Tesla, despite fewer disturbances by artifacts and somewhat more residual flow at 3.0 Tesla than at 1.5 Tesla (chapter 3, 4). Secondly, contrast enhancement did not have additional value to time-of-flight MRA (TOF-MRA) and is therefore not required (chapter 3, 6). Thirdly, decisions on additional treatment were on a group level similar for MRA and IA-DSA (chapter 7), and finally, MRA was cost-effective compared to IA-DSA (chapter 8).

We furthermore found that patients with coiled aneurysms at sharper bifurcation angles, indicating more deviation of flow at the base of the aneurysm, might have a higher risk for reopening (chapter 9). Conversely, patients with adequate occlusion on their 6-month follow-up IA-DSA carried a very small risk of aneurysm rupture on the long-term (chapter 10).

Diagnostic performance of MRA

The test characteristics of MRA were assessed in a large series of patients by multiple observers and in multiple centers, which increased the robustness of our results. We compared 1.5-Tesla with 3.0-Tesla MRA, and time-of-flight MRA (TOF-MRA) with contrast enhanced MRA (CE-MRA), both in a direct and indirect way (chapter 3, 4, 6). Other studies assessed diagnostic accuracy of MRA in smaller samples and most of them did not include both field strengths as well as TOF- and CE-MRA.[1-15] One study in 58 patients did, and no statistically significant difference was found between the two field strengths with a tendency for a better performance of CE-MRA in large aneurysms.[16] In those aneurysms, part of the flow is likely to be slow and therefore rapidly saturated. As a consequence, this slow flow does not give a signal on TOF-MRA and is therefore not visible. Also the echo time can be shorter for CE-MRA than for TOF-MRA, which reduces artifact formation (chapter 4). Conversely, venous contamination decreases image quality of CE-MRA (chapter 6). CE-MRA carries a risk of nephrogenic systemic sclerosis, so it is better to avoid it even though this risk is very small.

Thus far, coil-induced artifacts had been mostly studied *in vitro*.[17-19] We needed an *in vitro* experiment to interpret the results of our *in vivo* study on coil artifacts (chapter 4). This way, it became clear that intravoxel dephasing is the dominant mechanism in coil-artifact formation on TOF-MRA, and that this effect can even overrule the effect of field strength on artifacts. So,

coiled patients can be followed up at 1.5 Tesla as long as the echo time is as short as possible to optimize image quality and coil artifacts do not enlarge at 3.0 Tesla because the echo time can be shorter while keeping acceptable SNR. Even though the 3.0-Tesla images look better than the 1.5-Tesla images, aneurysm classification is similar and thereby also the therapeutic consequences. In addition, 1.5-Tesla scanners are still more available than 3.0-Tesla scanners.

Patients treated with Nexus coils should not be followed-up by MRA. The artifacts from Nexus coils were substantially larger than those from GDC, Axium, and Matrix coils (chapter 5) and the MRA of the only patient treated with Nexus coils in the large series, was not interpretable (chapter 3).

We found comparable treatment decisions based on MRA to those based on IA-DSA despite the fact that such decisions are highly subjective.[20] This encourages the use of MRA for decision making in clinical practice. The somewhat low positive predictive value of MRA would suggest that further diagnostic IA-DSA is needed to confirm incomplete occlusion on MRA to prevent unnecessary additional treatment, but the study on policy decisions did not show an increased frequency of additional treatment based on MRA. There was a tendency for more frequent follow-up imaging after MRA than after IA-DSA though, both because more neck remnants are seen on MRA and because it is easier to repeat non-invasive imaging.

Moreover, the cost-effectiveness analysis showed stable results in favor of MRA after several analyses while the model represented the least favorable scenarios for MRA, thus strengthening our conclusion that MRA can replace IA-DSA (chapter 8).

We naturally faced limitations that are important to be aware of while interpreting these results. For the assessment of test characteristics of MRA, the three main limitations were the subjectivity of the classification scale for occlusion, the need for dichotomization of this scale, and the lack of a perfect reference standard.

The classification for occlusion that we applied, is being widely used.[21,22] Although the comparison between IA-DSA and MRA results was influenced by the interpretation of this scale by the observers, the interobserver agreement was still substantial (chapter 3). At present, there is also no good alternative. We could have measured and compared the volumes of residual flow on IA-DSA and MRA but a classification that gives information about the configuration of residual flow related to the aneurysm is more useful for therapeutic decision making than just a volume measure.

Dichotomization creates loss of information about the original scores because nuances between different results on MRA and IA-DSA disappear. For example, borderline incomplete occlusion

on IA-DSA with borderline subtotal occlusion on MRA is comparable, while incomplete occlusion on IA-DSA with complete occlusion on MRA is an important discrepancy. After dichotomization between subtotal and incomplete occlusion, MRA would be 'false-negative' in both cases. Likelihood ratios could have been alternatively calculated for each level of occlusion but we had concerns about the implementation of likelihood ratios in clinical practice because of unfamiliarity with this type of test characteristics.[23] So, we provided test characteristics for the two possible cut-off points on the three-point scale and visualized these results in receiver operating characteristic (ROC) curves (chapter 3).

Since IA-DSA was considered the reference standard, all discrepant results on MRA were either labeled as 'false-positive' or 'false-negative'. IA-DSA is not a perfect test, though (chapter 2). Part of the 'false-negative' results can be explained by borderline subtotal occlusion on MRA with incomplete occlusion on IA-DSA and part of the 'false-positive' results is probably 'real-positive', where MRA provides more information on residual flow than IA-DSA. An important fact is that no incomplete occlusion missed on MRA needed treatment and additional incomplete occlusion on MRA did not increase the frequency of treatment (chapter 7).

These three general limitations have probably resulted in an underestimation of the diagnostic performance of MRA, thus not changing the conclusion that IA-DSA can be replaced by MRA.

With respect to field strength, the comparison between 1.5-Tesla and 3.0-Tesla MRA was limited by the unequal proportion of patients scanned at each field strength with only a small subset of patients scanned at both field strengths. Availability of 1.5-Tesla and 3.0-Tesla MR scanners varies in hospitals. We could not scan each patient at both field strengths because of financial and logistic restrictions. Also CE-MRA and TOF-MRA should have been evaluated separately as has been done in a subgroup (chapter 6). Despite these restrictions, our results together with those found in other studies, provide insufficient indications that field strength matters or that CE-MRA has additional value to TOF-MRA.[2,3,5,10,12,14,15,24,25]

Decision making on MRA and IA-DSA did not fully reflect clinical practice because treatment decisions are usually taken in a multidisciplinary team. Yet, there was a good agreement on treatment between these two techniques, despite the fact that treatment decisions are subjective.[20]

As a last limitation, a Markov model will never completely reflect reality and its results should be interpreted with caution. That is why we chose the least favorable scenarios for MRA to prevent overestimation of its value. Still, MRA remained cost-effective compared to IA-DSA.

Implementation of the study results

There are some important aspects to the implementation of these study results. First of all, every clinic where patients are coiled, have a 1.5- or 3.0-Tesla scanner, so availability of MRA is not expected to be a bottle neck. The neuroradiologists need to be familiar with interpretation of these images. Furthermore, we found a large majority of patients (94%) who preferred MRA over IA-DSA. On a scale from 0 (not unpleasant) to10 (extremely unpleasant), the median score for MRA was 2 and for IA-DSA 5 (Wilcoxon signed rank test: $p<0.01$)). A higher score on the scale for MRA was related to disturbance by the noise and to claustrophobia (both Spearman's rho 0.5, $p<0.01$) and a higher score on the scale for IA-DSA was related to discomfort (Spearman's rho 0.4, $p<0.01$) and to the need for immobilization after the procedure (Spearman's rho 0.3, $p<0.05$). Four per cent of the patients had been excluded from participation because of claustrophobia as a contraindication for MRA. Wide bore MR scanners are now on the market and they reduce claustrophobia induced by the confined space. Besides claustrophobia, also neurosurgical clips limit the use of MRA, but over the years there will be fewer patients with MR-incompatible clips. All together, we do not expect important limitations in the usage of MRA in coiled patients.

However, in the meantime, new endovascular techniques have been developed, such as stent-assisted coiling or placement of a flow diverter. These metal devices produce artifacts on MRA that precluded aneurysm evaluation in two small series of patients (n=5) treated with stents.[26,27] Still, patients are primarily treated by coiling.

Towards a tailored approach to follow up coiled patients

We found a tendency to a higher reopening risk for patients with coiled aneurysms at sharper bifurcation angles, i.e. more deviation of flow at the base of the aneurysm. These results should be confirmed in a larger study, though, because our study population was unfortunately too small. There are other risk factors for reopening, such as a large aneurysm size, incomplete occlusion after coiling, a large neck-to-dome ratio, A1- or basilar tip asymmetry, and smoking.[28-33]

The ultimate goal is to offer a tailored follow-up schedule for patients with coiled aneurysms based upon their risk profile for reopening and aneurysm rupture. The threshold for follow-up MRA is lower than for IA-DSA because MRA is safe and cheaper, but more evidence is needed on risk factors of reopening and timing of follow-up examinations. With respect to duration of follow-up, we found a very low long-term aneurysm rupture risk among patients

with adequate occlusion on their 6-month follow-up IA-DSA (chapter 10), so this patient group does not need long-term follow-up imaging. This has been confirmed in a larger cohort of patients with adequate occlusion at 6-months follow-up, where a very small reopening rate has been found.[28]

The data on rupture after coiling that have been published over the last few years, showed that most ruptures seem to occur shortly after coiling.[34-36] A baseline MRA before hospital discharge after treatment would detect early reopening and would facilitate direct comparison with the next follow-up MRA. Still, it is unclear whether this baseline MRA should be performed immediately or a few days after treatment. So far, we cannot create specific follow-up schedules for subgroups of coiled patients.

Evaluation of this research project

The time investment and financial investment for this research project raises the question if it is cost-effective to perform such a study. We could have started with a cost-effectiveness analysis based on the available information to assess the value of additional information.[37] The required test characteristics for cost-effectiveness of MRA compared to IA-DSA could have been calculated and compared to those from previous studies. Even though models are of great value, we believe that for the implementation of such study results it is important to carry out a cross-sectional study to understand the benefits and drawbacks of MRA, and use these results as input parameters for a model.

Directions for future research

With respect to the diagnostic accuracy of MRA, future studies could assess the additional value of CE-MRA in large or giant coiled aneurysms. More importantly, the timing and duration of follow-up after coiling should be assessed as well as the risk profile of patients who develop reopening of their coiled aneurysm. Only then, a tailored follow-up schedule can be offered, which increases the cost-effectiveness of MRA in patients after coiling of intracranial aneurysms.

Advances in knowledge

- Test characteristics of MRA are good and similar at 1.5 and 3.0 Tesla
- Contrast enhancement does not have additional value to time-of-flight MRA
- Intravoxel dephasing is the dominant mechanism in coil-artifact formation on TOF-MRA
- Decisions on additional treatment for coiled aneurysms are similar on MRA and IA-DSA
- MRA is cost-effective compared to IA-DSA
- Aneurysms at sharper bifurcation angles seem to have a higher risk for reopening
- The long-term rupture risk of sufficiently occluded aneurysms at 6-months follow-up is very low.

Implications for patient care

- Patients should be followed-up by MRA instead of IA-DSA to detect reopening after coiling of intracranial aneurysms
- 1.5-Tesla or 3.0-Tesla MRA can be used for follow-up
- Contrast enhancement is not necessary
- The echo time on TOF-MRA should be shortened while keeping acceptable SNR
- MRA can be used for therapeutic decision making on additional coiling
- Additional IA-DSA in patients with incompletely occluded aneurysms on MRA is usually not necessary
- Long-term follow-up imaging for patients with sufficient occlusion at 6-months follow-up is not indicated

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Appendix

Imaging parameters for Magnetic Resonance Angiography (MRA) at 3.0 Tesla

The protocol included transversal T1-weighted spin echo and T2-weighted fast spin echo sequences, phase contrast survey MRA as preparation for MRA, three-dimensional time-of-flight (TOF) MRA with multiple overlapping thin slab acquisition (MOTSA) and contrast-enhanced (CE) MRA sequences.

T1-weighted spin echo sequence

500/10 (TR/TE), 256x256 matrix (reconstructed to 512x512), 230-mm FOV, 80% rectangular FOV and 4-mm slice thickness with a 1-mm gap.

T2-weighted fast spin echo sequence

3000/80 (TR/TE), 400x400 matrix (reconstructed to 512x512), 230-mm FOV, 80% rectangular FOV, 4-mm slice thickness with a 1-mm gap and turbo-spin-echo factor 15.

Transversal MOTSA 3D TOF-MRA gradient echo sequence

20/3.9 (TR/TE, shortest), flip angle 20°, water-fat-shift set to 6 pixels, 512x512 matrix (reconstructed to 1024x1024), 200-mm FOV, 85% rectangular FOV, 1.0-mm thick sections interpolated to 0.5 mm, 220 sections acquired in ten chunks resulting in a coverage area of 110 mm, measured voxel size 0.39x0.61x1 mm, and reconstructed voxel size 0.2x0.2x0.5 mm. The scan time of MOTSA 3D TOF sequences was reduced by using sensitivity encoding (SENSE). For this technique less gradient encodings are required because multiple coil elements are activated to encode spatial information. We used a SENSE reduction factor of 1.5, which resulted in an acquisition time of 7 minutes. Tilted optimized non-saturation excitation was used to optimize excitation profiles.

Transversal 3D CE-MRA gradient echo sequence

The timing for the 3D CE-MRA was calculated from the time to peak of a dynamic 2D (0.9 sec cycle time) gradient echo sequence with a mid sagittal slice of 50-mm thickness following injection of 1 mL of gadopentetate dimeglumine intravenously. Subsequently 15 mL of gadopentetate dimeglumine was injected with a rate of 2 mL/s for acquisition of 3D CE-MRA. Imaging parameters were as follows: 5.3/1.7 (TR/TE, shortest), flip angle 30°, 368x368 matrix (reconstructed to 512x512), 250-mm FOV, 80% rectangular FOV, 1.0-mm-thick sections

interpolated to 0.5 mm, measured voxel size 0.68x0.76x1.00 mm, and reconstructed voxel size 0.49x0.49x0.50 mm. We used a SENSE reduction factor of 2, which resulted in an acquisition time of 36 seconds.

Imaging parameters for Magnetic Resonance Angiography (MRA) at 1.5 Tesla

The protocol consisted of transversal T1-weighted spin echo and T2-weighted fast spin echo sequences, phase contrast survey MRA as preparation for MRA, transversal 3D TOF-MRA and CE-MRA sequences.

T1-weighted spin echo sequence

620/15 (TR shortest/TE), 256x256 matrix, 230-mm FOV, 80% rectangular FOV, 5-mm slice thickness with a 1.20-mm gap.

T2-weighted fast spin echo sequence

2200/shortest/100 (TR/TE 1st/TE 2nd), 256x256 matrix, 230-mm FOV, 75% rectangular FOV, 5-mm slice thickness with a 1.20-mm gap and TSE (FSE) factor 14.

Transversal 3D TOF-MRA gradient echo sequence

25/6.9 (TR/TE), flip angle 20°, water-fat-shift set to 2 pixels, 496x496 matrix (reconstructed to 512x512), 200-mm FOV, 0.5-mm thick slices, measured voxel size 0.40x0.70x1.00 mm, and reconstructed voxel size 0.39x0.39x0.50 mm. We used a SENSE reduction factor of 2, which resulted in an acquisition time of 6 minutes.

Transversal 3D CE-MRA gradient echo sequence

The timing for the CE-MRA was calculated from the time to peak of a dynamic 2D (0.9 sec cycle time) gradient echo sequence with a mid sagittal slice of 50-mm thickness following injection of 1 mL of gadopentetate dimeglumine intravenously. Subsequently, 30 mL of gadopentetate dimeglumine was injected with a rate of 3 mL/s for acquisition of 3D CE-MRA. Imaging parameters were as follows: 6.2/1.9 (TR/TE, shortest), flip angle 30°, 400x400 matrix (reconstructed to 512x512), 210-mm FOV, 85% rectangular FOV, 0.45-mm thick slices, measured voxel size 0.52x0.69x0.90 mm, and reconstructed voxel size 0.41x0.41x0.45 mm. We used a SENSE reduction factor of 2.5, which resulted in a acquisition time 43 seconds.

Samenvatting
(Summary in Dutch)

Een intracranieel aneurysma is een uitstulping van een slagader in de hersenen. Deze uitstulping kan barsten en daarmee een bloeding veroorzaken die we een 'subarachnoïdale bloeding' noemen. Dit type bloeding heeft een hoge mortaliteit en morbiditeit.

Tot een decennium geleden was de standaardbehandeling voor een aneurysma een operatie waarbij het aneurysma wordt afgesloten door een clip op de hals van het aneurysma te zetten. In de jaren negentig van de vorige eeuw werd een alternatieve behandeling voor intracraniële aneurysmata ontwikkeld waarbij het aneurysma wordt opgevuld met flexibele metaaldraden, zogenaamde 'coils', die met behulp van een catheter via de liesslagader worden ingebracht in het aneurysma. Het nadeel van deze behandeling is dat ongeveer 20% van de gecoilde aneurysmata deels weer open gaat als gevolg van impactie van de coils, het oplossen van een stolsel dat in het aneurysma zat, of van groei van het aneurysma. Dit noemen we rekanalisatie. In de helft van deze gevallen moet het aneurysma opnieuw behandeld worden.

Vanwege het risico op rekanalisatie moeten patiënten met een gecoild aneurysma vervolgd worden. Tot op heden werd dit standaard gedaan door middel van een intra-arteriële digitale subtractie angiografie (IA-DSA), een invasief onderzoek waarbij patiënten blootgesteld worden aan straling en contrastmiddel en waarvoor een kortdurende ziekenhuisopname noodzakelijk is.

Het voornaamste doel van dit proefschrift is om na te gaan of magnetische resonantie angiografie (MRA) een goed alternatief vormt voor IA-DSA, omdat MRA niet invasief is, patiënten niet blootstelt aan straling en poliklinisch kan plaatsvinden. We weten echter niet of dit onderzoek even goed rekanalisaties kan detecteren als IA-DSA. Om dit te onderzoeken hebben we de verschillende fases van diagnostisch onderzoek doorlopen. Tenslotte hebben we in de laatste twee hoofdstukken getracht de follow-up van patiënten na coiling in enig perspectief te zetten.

Hoofdstuk 2. De plaats van besliskundige analyse binnen diagnostisch onderzoek: een brug tussen testkarakteristieken en kosteneffectiviteit

Om de diagnostische waarde van een test vast te stellen, moeten verschillende stappen genomen worden die in dit hoofdstuk worden beschreven. 'Als eerste moeten de testkarakteristieken, te noemen sensitiviteit, specificiteit en voorspellende waarden, van deze test worden vastgesteld door de test te vergelijken met een referentiestandaard. Vervolgens moet de additionele waarde van deze test bepaald worden ten opzichte van de gegevens die al bekend zijn voordat de test gedaan wordt. Het uiteindelijke doel van het doen van een test is verbetering van de gezondheidstoestand. Daarom moet de klinische uitkomst van patiënten die de nieuwe test krijgen, worden vastgesteld en vergeleken worden met die van de standaardprocedure. Hiervoor is een diagnostische gerandomiseerde trial de aangewezen methode, maar deze is zowel tijd-

als geldrovend. Als 'second best' alternatief kan een besliskundig model, bijvoorbeeld een Markov-model, worden gemaakt op basis van de gegevens die al bekend zijn. Hiermee kan een inschatting worden gemaakt van het te verwachten effect van het gebruik van de nieuwe test. Daarnaast maken deze modellen kosteneffectiviteitanalyses mogelijk die voor beleidsmakers zo welkom zijn. Vanwege deze voordelen wordt in dit hoofdstuk het belang van besliskundige modellen onderstreept. Het hoofdstuk vormt min of meer een leidraad voor de daarop volgende hoofdstukken waarin de verschillende fasen van het vaststellen van de diagnostische waarde van MRA ten opzichte van IA-DSA worden doorlopen.

Hoofdstuk 3. Testkarakteristieken van MRA ten opzichte van IA-DSA voor detectie van rekanalisatie na coilen

Als eerste stap binnen diagnostisch onderzoek, hebben we de testkarakteristieken van MRA ten opzichte van IA-DSA voor de detectie van rekanalisatie bepaald binnen een groep van 310 patiënten in vier academische centra. Een deel van de patiënten is op een 1.5-Tesla scanner gescand en een deel op een 3.0-Tesla scanner. Deze laatste scanner heeft een sterkere magneet en creëert een hogere veldsterkte. De testkarakteristieken voor beide groepen verschillen niet duidelijk van elkaar, dus patiënten kunnen zowel op 1.5 Tesla als op 3.0 Tesla worden gescand. Daarnaast heeft MRA met contrast geen toegevoegde waarde op MRA zonder contrast, dus is toediening van contrastmiddel niet nodig voor MRA.

De bevindingen zijn veelbelovend, maar we kunnen niet concluderen of de testkarakteristieken van MRA goed genoeg zijn om IA-DSA te kunnen vervangen, omdat de klinische impact van discrepantie tussen beide onderzoeken onbekend is.

Hoofdstuk 4. Veldsterkte en artefactvorming

Dit hoofdstuk vormt een zijstap in de evaluatie van de diagnostische waarde van MRA. Wij richten ons hier vooral op artefacten die coils kunnen veroorzaken op MRA, wat een nadeel kan vormen voor de beeldkwaliteit en daarmee de beoordeelbaarheid.

Metaalartefacten worden groter op hogere veldsterkte (dus groter op 3.0 Tesla dan op 1.5 Tesla), maar de signaalruisverhouding wordt beter op hogere veldsterkte.

Een aantal patiënten is gescand op zowel 1.5 als 3.0 Tesla. Voor de beoordeling van de aneurysmata viel op dat op 1.5 Tesla coilartefacten veel storender waren dan op 3.0 Tesla. Op 3.0 Tesla werd zelfs bij dezelfde patiënten een wat grotere rekanalisatie gezien dan op 1.5 Tesla en op IA-DSA. Naast veldsterkte hebben ook enkele scanparameters invloed op metaalartefacten. We hebben de bijdrage van deze scanparameters aan het ontstaan van artefacten nader onderzocht.

Omdat de grootte van het artefact niet nauwkeurig gemeten kan worden op de MRA's van patiënten, hebben we een coilmodel gemaakt waarbij dit wel mogelijk was. Dit coilmodel is volgens de klinische protocollen gescand op 1.5 en 3.0 Tesla, waarna we scanparameters die artefactvorming beïnvloeden hebben gevarieerd.

De resultaten tonen aan dat de echotijd, één van de scanparameters, cruciaal is voor de grootte van het artefact op MRA zonder contrast. De mogelijkheid tot echotijdverkorting met daardoor artefactverkleining op 3.0-Tesla MRA doet zelfs het effect van artefactvergroting op hogere veldsterkte teniet. MRA op 3.0 Tesla moet dus zeker niet gemeden worden uit bezorgdheid om toename van coilartefacten.

Hoofdstuk 5. Coilmateriaal en artefactvorming

Nu we weten welke scanparameters van belang zijn om artefacten te reduceren, willen we ook nagaan of het uitmaakt met welke soort coil patiënten behandeld zijn. We hebben 4 modellen van verschillende soorten coils gemaakt en hun artefact vergeleken op MRA. Nexus coils produceren grotere artefacten dan de andere coils die onderling een vergelijkbare artefactgrootte hebben. Patiënten die behandeld zijn met Nexus coils kunnen hierdoor niet vervolgd worden met MRA.

Hoofdstuk 6. Vergelijking van contrast-MRA met MRA zonder contrastmiddel

Binnen de groep van 310 patiënten was het logistiek niet mogelijk om de MRA's zonder en de MRA's met contrastmiddel separaat te laten beoordelen. In eerste instantie werd naar de MRA zonder contrastmiddel gekeken en vervolgens naar de MRA met contrastmiddel om na te gaan of het oordeel veranderde (hoofdstuk 3). Voor een subgroep was het echter wel mogelijk om de MRA's zonder en met contrast onafhankelijk van elkaar te laten beoordelen (hoofdstuk 6). Hieruit blijkt dat de beoordelingen op MRA met en zonder contrastmiddel grotendeels met elkaar overeen komen. Dit bevestigt onze bevindingen van hoofdstuk 3. Contrastmiddel is dus niet noodzakelijk voor MRA na coilen.

Hoofdstuk 7. Beleidsvorming op basis van MRA in vergelijking tot IA-DSA

Het is weliswaar belangrijk om op MRA rekanalisatie te kunnen detecteren, maar we willen ook graag beleid kunnen maken op basis van MRA zonder daarvoor alsnog een IA-DSA nodig te hebben. Daarom hebben we in dit hoofdstuk beleidsbeslissingen tussen MRA en IA-DSA met elkaar vergeleken. Deze blijken niet duidelijk van elkaar te verschillen. De belangrijkste bevinding is dat geen enkele patiënt op basis van MRA zou worden ontslagen uit follow-up, terwijl deze op basis van IA-DSA aanvullend zou zijn behandeld.

Hoofdstuk 8. Kosteneffectiviteit van MRA ten opzichte van IA-DSA

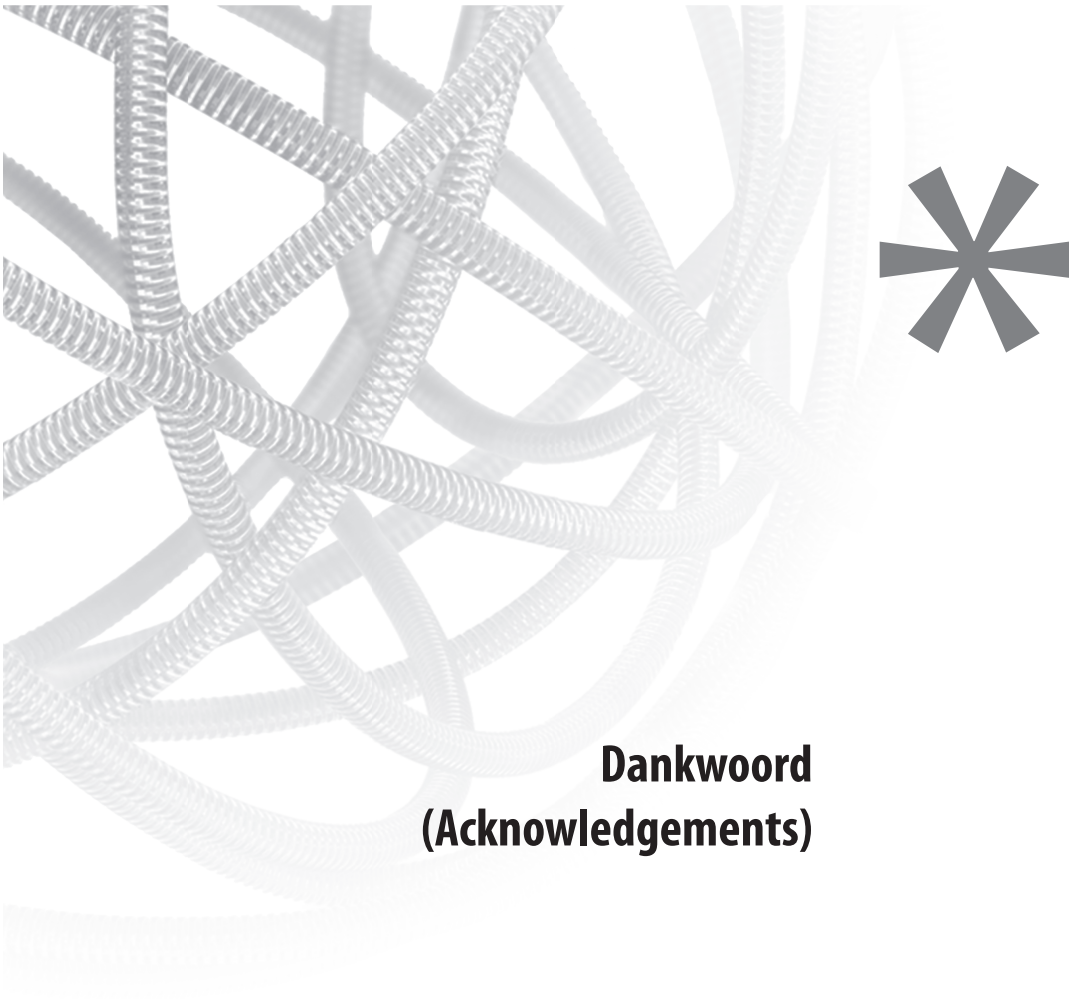
Om de vraag te kunnen beantwoorden of MRA daadwerkelijk IA-DSA kan vervangen, is een kosteneffectiviteitanalyse nodig om een indruk te krijgen van de te verwachten impact op gezondheid en kosten van discrepanties tussen deze twee onderzoeken. Wij hebben ervoor gekozen om een Markov-model (hoofdstuk 2) te maken om vervolgens simulaties te kunnen doen voor fictieve cohorten patiënten. Uit deze analyses blijkt dat het effect op gezondheid van beide onderzoeken vergelijkbaar is, maar dat de kosten voor follow-up met MRA beduidend lager zijn. Daarmee kunnen we concluderen dat MRA kosteneffectief is ten opzichte van IA-DSA.

Hoofdstuk 9. De invloed van configuratie van de intracraniële bloedvaten op het ontwikkelen van rekanalisatie

Nadat we hebben vastgesteld dat IA-DSA vervangen kan worden door MRA in de follow-up van patiënten met een gecoild aneurysma, willen we nagaan of we op basis van de configuratie van hersenvaten iets kunnen zeggen over het risico op rekanalisatie. Aneurysmata ontstaan meestal op een splitsing van bloedvaten en het lijkt voor de hand liggend dat hoe groter de hoek tussen de vaatafsplitsing is, hoe sterker de bloedstroom afbuigt, des te meer druk er op de coilmassa ontstaat en daardoor rekanalisatie wordt geïnduceerd. Onze resultaten wijzen ook in deze richting, maar helaas is de patiëntengroep te klein om de uitkomsten statistisch significant te maken. Deze bevinding zou in een grotere groep patiënten bevestigd moeten worden.

Hoofdstuk 10. Het langetermijnrisico op ruptuur van een gecoild aneurysma

Het uiteindelijke doel van follow-up na coilen is om een bloeding uit het aneurysma te voorkomen. In deze studie hebben we gekeken naar het bloedingsrisico op de lange termijn onder patiënten die een adequaat afgesloten aneurysma hadden bij controleonderzoek dat 6 maanden na coilen plaatsvond. Dit bloedingsrisico blijkt zeer laag te zijn en niet hoger dan na een operatie waarbij het aneurysma wordt geclipt. Het is dus gerechtvaardigd om deze patiëntengroep niet langdurig te vervolgen, al moeten we ons realiseren dat deze uitkomst gebaseerd is op een follow-upduur van 8 jaar na coilen. Ook uit andere studies blijkt dat het risico op rekanalisatie op lange termijn onder deze patiënten zeer klein is. Met de jaren zullen we meer gegevens verkrijgen over langetermijneffecten na coilen van intracraniële aneurysmata.



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About the author

Curriculum vitae

Joanna Daniëlle Schaafsma werd geboren op 24 maart 1979 in Sneek. In 1997 behaalde zij haar gymnasiumdiploma aan het Bogerman College te Sneek. In datzelfde jaar begon zij aan haar studie geneeskunde aan de Rijksuniversiteit Groningen. Al snel had zij interesse in de neurologie. Voor een wetenschappelijke stage vertrok zij in 2001 samen met Anna Bartels naar Tel Aviv, waar zij een onderzoeksproject uitvoerden op de afdeling bewegingsstoornissen in samenwerking met de afdeling neurologie van het UMC Groningen onder begeleiding van Prof. Dr. K.L. Leenders, Prof. Dr. N. Giladi en Prof. Dr. J.M. Hausdorff. Uit dit project zijn verschillende publicaties voortgekomen. Het laatste deel van haar artsenopleiding volgde ze op de afdeling neurologie van l'hôpital Lariboisière in Parijs, onder supervisie van Prof. Dr. M.-G. Bousser. In 2004 behaalde ze haar artsexamen waarna ze als arts-assistent op de afdeling neurologie werkte van l'hôpital Tenon in Parijs onder supervisie van Prof. Dr. S. Alamowitch en Prof. Dr. E. Roullet. Daar groeide ook haar interesse in de neuroradiologie. In 2005 keerde zij terug naar Nederland waar ze haar promotieonderzoek begon onder begeleiding van Prof. Dr. G.J.E. Rinkel en Dr. B.K. Velthuis in het UMC Utrecht. De resultaten van dit project staan beschreven in dit proefschrift. In 2007 werd zij aangenomen voor de opleiding tot neuroloog in het UMC Utrecht (Prof. Dr. J.H.J. Wokke, Prof. Dr. L.J. Kappelle). Tijdens haar promotieonderzoek en neurologie-opleiding werd haar duidelijk dat zij een combinatie van neurologie, radiologie en het doen van interventies ambieert. Daarom zal zij in het laatste jaar van haar opleiding in het AMC beginnen aan haar opleiding neurointerventieradiologie onder begeleiding van Dr. R. van den Berg en Prof. Dr. C.B.L.M. Majoie.

List of publications

1. **Schaafsma JD**, Rutten A, Velthuis BK, Lo TH, Witkamp TD, Rinkel GJE. Bifurcation geometry of intracranial arteries and reopening of coiled aneurysms. *Submitted*.
2. **Schaafsma JD**, Velthuis BK, Vincken KL, De Kort GAP, Bartels LW. Comparison of MR artifacts induced by various coils used for endovascular occlusion of intracranial aneurysms – a technical note. *Submitted*.
3. **Schaafsma JD**, Velthuis BK, Van den Berg R, Brouwer PA, Majoie CBLM, Barkhof F, Eshghi O, De Kort GAP, Lo TH, Sprengers MES, Van Rooij WJ, Bot JC, Rinkel GJE. Decision making on additional treatment for coiled aneurysms based on magnetic resonance angiography versus intra-arterial digital subtraction angiography. *Under revision*.

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