Noninvasive imaging of intracranial aneurysms

Westerlaan, Henriëtte Ellen

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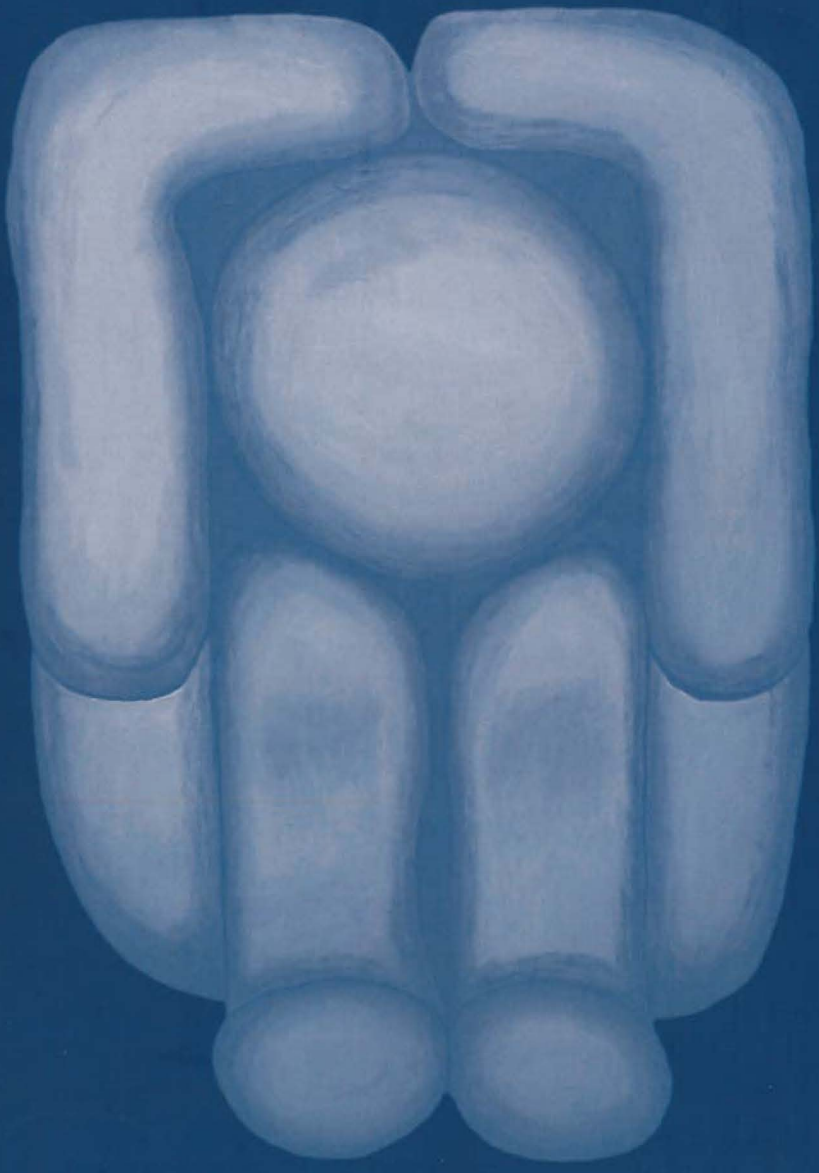
Initial diagnosis in subarachnoid hemorrhage and follow-up after endovascular treatment



Henriëtte E. Westerlaan

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1. Multidetector CTA is de nieuwe gouden standaard in de diagnostiek en therapieplanning van intracraniële aneurysmata bij patiënten met een acute subarachnoidale bloeding.
2. Een negatieve CTA bij een patiënt met een acute subarachnoidale bloeding zou bevestigd moeten worden met een second reading.
3. Indien het voorkomt dat een CTA, ondanks second reading, fout-negatief is, zou deze opnieuw beoordeeld moeten worden om de sensitiviteit van de beoordelaar te verhogen.
4. De uitvoering en beoordeling van een CTA bij patiënten met een acute subarachnoidale bloeding horen bij voorkeur plaats te vinden in een neurochirurgisch verwijscentrum.
5. De kans op een fout negatieve uitslag van CTA bij patiënten met een acute subarachnoidale bloeding is kleiner dan die van selectieve cerebrale angiografie en vergelijkbaar met de kans op complicaties met selectieve cerebrale angiografie.
6. De toegevoegde waarde van een selectieve cerebrale angiografie na een negatieve CTA bij patiënten met een aneurysmatische subarachnoidale bloeding is nihil.
7. 3D TOF MRA is een goede niet invasieve beeldvormende techniek om de mate van occlusie van gecoilde aneurysmata te beoordelen en kan gebruikt worden in de follow-up na coiling van intracraniële aneurysmata.
8. De CTA kan de lumbaalpunctie bij patiënten met acute "donderslag" hoofdpijn en een negatieve blanco CT niet vervangen.
9. Hoe meer radiodiagnostische onderzoeken een arts tot zijn beschikking heeft, des te minder hij op zijn eigen klinische vaardigheden zal vertrouwen.
10. Het leveren van radiodiagnostische kwaliteit kost geld, het niet leveren van radiodiagnostische kwaliteit kost kapitalen.
11. Brevity is the soul of wit. (William Shakespeare 1564-1616)
12. Als je gezond wilt zijn - ren,
    Als je mooi wilt zijn - ren,
    Als je slim wilt zijn – ren *Grieks aforisme*

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Promotor:	Prof. dr. M. Oudkerk
Copromotor:	Dr. R.J.M. Groen
Beoordelingscommissie:	Prof. dr. J.J.A. Mooij
	Prof. dr. W.P.Th.M. Mali
	Prof. dr. H.P.H. Kremer

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Aan mijn ouders

Voor Mark en Bram

Qui scribit bis legit.
Hij die schrijft, leest twee keer.

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Chapter 1

General introduction

Nontraumatic subarachnoid hemorrhage (SAH) is a neurologic emergency characterized by the extravasation of blood into the spaces covering the central nervous system that are filled with cerebrospinal fluid. The leading cause of nontraumatic SAH is rupture of an intracranial aneurysm, a focal outpouching of a cerebral artery, which accounts for about 80% of cases and has a high rate of death and complications.[1] Nonaneurysmal SAH, including isolated perimesencephalic SAH, occurs in about 20% of cases and carries a good prognosis with uncommon neurologic complications.[2]

An estimated 2 to 5% of cases of stroke are related to ruptured intracranial aneurysms.[3;4] The worldwide incidence of SAH is about 10.5 cases per 100.000 person-years.[5] The incidence increases with age, with a mean age at presentation of 55 years.[3] The risk for women is 1.6 times that of men, and the risk for blacks is 2.1 times that of whites.[6;7] The average case fatality rate for SAH is 51%, with approximately one third of survivors needing lifelong care.[8] Most deaths occur within two weeks after the ictus, with 10% occurring before the patient receives medical attention and 25% within 24 hours after the event.[9] SAH accounts for 5% of deaths from stroke but for 27% of all stroke-related years of potential life lost before the age of 65.[9]

Little is known about the cause of intracranial aneurysms or the process by which they form, grow, and rupture, although hypertension and smoking-induced vascular changes are thought to have a major role.[10-12] Patients with a family history of first-degree relatives with SAH or patients with certain heritable connective-tissue disorders are also at a higher risk.[10;13]

The clinical presentation of aneurysmal SAH is one of the most distinctive in medicine. The sine qua non of SAH in a wake patient is the complaint of "the worst headache of my life", described by ~ 80% of patients who can give a history, but a warning or sentinel headache is also described by ~ 20% of patients.[14;15] In one study of 107 patients with worst headache of life, 17% of patients were found to have SAH.[16] In the absence of this typical presentation SAH may be misdiagnosed as migraine and tension-type headaches.[14;17] An estimated 10% die before reaching medical attention, and many others present in a coma or with severe neurologic compromise.[9;18]

The major factors associated with poor outcome are the patient's level of consciousness on admission, age, and the amount of blood shown by initial computed tomography (CT) of the head.[19;20] The clinical scales of Hunt and Hess and the World Federation of Neurological Surgeons are most widely used to describe the neurologic condition on admission and are considered good predictors of ultimate outcome.[21;22] Different rating scales have been developed to describe the amount of blood on non-enhanced CT and to predict the occurrence of symptomatic vasospasm.[20;23-28]

Neurologic complications are common and include hydrocephalus, rebleeding and symptomatic vasospasm. Acute hydrocephalus (within 72 hours of the ictus) develops in about 31 to 36% of patients who have an aneurysmal SAH.[29;30] Patients with rebleeding have a high risk of permanent neurologic disability and a mortality rate of about 50%.[31] Rebleeding is more common in the initial few days (4% on the first day and 1.5% per day for the next two weeks).[32;33] Radiographic evidence of vasospasm develops in 60% to 70% of patients with SAH, but only half of these experience symptoms of delayed ischemic neurological deficits.[34-39] It accounts for up to 23% of disability and

deaths related to SAH.[35,36,40,41] Its predictable delayed onset is between day 5 and 15 after bleeding. In acutely ruptured aneurysms, the role of imaging is (a) to demonstrate the presence, extent and distribution of hemorrhage, (b) to identify the source of bleeding, (c) to provide a pre-treatment assessment of the detected aneurysm with the intention to decide whether coil embolization or neurosurgical clipping is the preferred therapy, (d) to rule out additional unruptured aneurysms, and (e) to detect acute hydrocephalus, intraparenchymal hematomas and cerebral edema. In the emergency setting of acute SAH unenhanced CT should be the first study performed. The sensitivity of CT in detecting nontraumatic SAH decreases as the time interval after onset of symptoms increases. The sensitivity of CT in detecting nontraumatic SAH is greater than 93% within the first 24 hours of symptom onset and decreases to 81-84% after the first 24 hours.[42-44] Lumbar puncture performed after 24 hours after supposed SAH is reserved for patients in whom CT reveals no abnormality, despite a history suggesting SAH. The combination of normal CT and lack of xanthochromia, owing to red-cell breakdown, on lumbar puncture is generally considered sufficient for excluding SAH.[45] Unenhanced CT can help predict the site of aneurysm rupture.[46-48] Furthermore, unenhanced CT has a strong predictive value for the occurrence of cerebral vasospasm and the patient's outcome.[20,23-26,28]

Part 1: Noninvasive imaging of intracranial aneurysms in patients with acute subarachnoid hemorrhage at presentation

Because of its high spatial and high temporal resolution, selective cerebral angiography has been the main technique for detecting and characterizing intracranial aneurysms and is considered the gold standard. However, selective cerebral angiography is invasive and time consuming, and carries a risk of neurological complications of 0.5–1.8% with permanent deficit in 0.09–0.5%.[49-54] Serious non-neurological complications, which occur in 0.6% of patients, include groin hematoma, peripheral thromboembolism, transient hypotension and arteriovenous fistulas in the groin. Further disadvantages of diagnostic selective cerebral angiography are high costs of the procedure including investments for the angiographic equipment, stand-by of educated and experienced personnel, and the need to hospitalize the majority of patients.

With the ongoing advances in cross-sectional imaging, the noninvasive imaging of vascular disorders has reached unprecedented quality. Since the introduction of magnetic resonance imaging (MRI) in the early 1980s, continuous improvements in hardware and software have taken place that have catapulted this imaging modality to the forefront of modern medical imaging. Three dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA) is the MRI technique most often used to depict intracranial arteries. The vessel contrast in TOF MRA is based on the inflow effect: stationary tissue is suppressed by repetitive radiofrequency pulses while unsaturated protons entering the imaging volume with the flowing blood yield high signal intensity.

With the introduction of spiral CT in the early 1990s, for the first time volume data could be acquired without misregistration of anatomic detail. Since then there has been a tremendous increase in scanner performance, with an increased number of detector rows and faster tube rotation. The year

2004 saw the transition from systems with 16 rows to those with 32, 40 and 64 active detector rows. Rotation times have decreased from 0.5 s to between 0.42 s and 0.33 s per rotation, depending on the manufacturer. Multidetector CT allows substantially increased spatial resolution along the z-axis, with isotropic resolution achieved with 16-section CT. Volume data with isotropic resolution also paved the way for the development of advanced 3D postprocessing techniques, further improving the diagnostic performance of computed tomographic angiography (CTA). CTA is nowadays a routine examination that has become fully integrated into the imaging and treatment algorithm of patients presenting with SAH in many centers in Europe and continues to grow as a replacement for selective cerebral angiography in neurovascular imaging.

In part 1 of this thesis, the role of modern cross-sectional imaging in the diagnosis and therapy planning of ruptured intracranial aneurysms is demonstrated.
In chapter 2 the results of our systematic review and meta-analysis in calculating the sensitivity and specificity of CTA in diagnosing cerebral aneurysms in patients with aneurysmal SAH are presented. In chapter 3 we report our clinical experience with both 16- and 64-detector row CTA as the first and intended only diagnostic and treatment decision-making study for intracranial aneurysms in patients with acute SAH. In chapter 4 we established whether 3D TOF MRA at 1.5 Tesla (T) can be applied to planning and performing surgery on ruptured intracranial aneurysms, especially in the early phase. This study was conducted before multidetector CT was available at our department.

Part 2: Noninvasive imaging of intracranial aneurysms after endovascular treatment
The major step forward in the endovascular treatment of intracranial aneurysms has been done by Guglielmi et al. with the development of the detachable platinum coil in 1991.[55;56] Its Food and Drug Administration approval in 1995 induced a revolution in the treatment of intracranial aneurysms. Since then, therapy strategies changed continuously toward the endovascular approach. The early results of the International Subarachnoid Aneurysm Trial (ISAT) indicated that for specific categories of patients with ruptured intracranial aneurysms, those treated with endovascular coiling are more likely to survive and live independently than those treated with surgical clipping.[57;58] Endovascular coiling is now often the primary method of treatment for ruptured intracranial aneurysms in most centers. The optimal treatment strategy for unruptured intracranial aneurysms is currently unknown. Although a clinical trial for ruptured intracranial aneurysms has been completed in the form of the ISAT, and prospective comparative data for unruptured aneurysms based on a standardized approach to patient entry and outcomes is available from the International Study of Unruptured Intracranial Aneurysms, current recommendations for management of unruptured intracranial aneurysms still depend on data from heterogeneous series.[57-59] Adverse outcome rates vary widely, and lack of comparability between studies and the presence of publication bias hinder accurate aggregate impressions of the literature. The results of the Trial on Endovascular Treatment of Unruptured Aneurysms (TEAM), the first international, randomized, controlled trial comparing

conservative management with endovascular treatment, have to be awaitened.[60]

A major concern of endovascular treatment is the possibility of incomplete occlusion at first treatment and the potential for reopening with time of an initially adequately occluded aneurysm as a result of instability and subsequent compaction of the original coil mass, dissolution of an intraluminal thrombus or migration of the coil mass into intra-aneurysmal thrombus or into the fundus of a continually expanding aneurysmal sac. Ferns et al. performed a systematic review and found an initial occlusion rate of 91.2%, an aneurysm reopening rate of 20.9% and a retreatment rate of 10.3% after coiling.[61] Data on the incidence of rebleeding after endovascular aneurysm therapy indicate that the rate is between 0.11-1.6% per annum.[58;62-64] The chance of rebleeding shown by the ISAT with annual rates of 0.2% after the first year with a mean follow-up of 4 years was low.[58]

Although the natural history of recurrent or residual aneurysms after endovascular coil embolization is often benign, bleeding from incompletely coiled aneurysms is a well-documented threat. Byrne et al. reported that rebleeding occurred in 3/38 (7.9%) recurrent aneurysms and in 1/122 (0.4%) aneurysms that appeared stable on angiograms.[65] Slob et al. observed no rebleeding in patients with complete or near-complete occlusions after additional coiling, but two episodes of rebleeding occurred during the added time of observation of 66 person-years (3.0%) in patients with incompletely occluded aneurysms.[66] The investigators of the Cerebral Aneurysm Rerupture After Treatment (CARAT) study found incomplete occlusion of the aneurysm a strong predictor of risk of rerupture (overall risk: 1.1% for complete occlusion, 2.9% for 91% to 99% occlusion, 5.9% for 70% to 90%, 17.6% for <70%).[67] In the study of Ferns et al. the annual event rate was 1.9%, the annual mortality was 0.7% and the annual rebleed rate was 1.0% in patients with coiled ruptured aneurysms with incomplete occlusion at 6 months.[68] In this study rebleeding and progressive mass effect of the aneurysm were responsible for the serious adverse events, not complications from additional treatment or angiographic follow-up. Also in the ISAT and in the study of Slob et al. aneurysm retreatment did not cause significant additional morbidity.[56;59] Therefore, aneurysms that are incompletely treated, which are more unstable, may be considered for retreatment with selective coiling. Partially thrombosed aneurysms with mass effect form a distinct entity. Parent vessel occlusion should be the endovascular treatment of choice for these aneurysms, and selective coiling should only be considered if there is no surgical treatment option.[70]

Aneurysm recurrences after coil embolization is dependent on multiple variables and it is impossible to prospectively and accurately predict which aneurysms will recur and require retreatment.[66;69;71-78] It has been shown that in patients with coiled aneurysms that are adequately occluded at 6 months, the risk of first-time reopening needing retreatment in the first 5-10 years after coiling is low and the risk of recurrent SAH is not higher than that after clipping.[79;80] These data also showed that virtually all aneurysm reopenings develop in the first 6 months after coiling. Furthermore, in the first 5 years after coiling, both the risk of de novo aneurysm formation and the risk of growth of existing untreated aneurysms are very low and thus the risk of SAH from such aneurysms.[81-84] These findings imply that the first imaging follow-up at 6 months is a crucial point in time: when the coiled

aneurysm is adequately occluded, the patient may be cured.

Although there are no general recommendations on time periods, frequency, or imaging methods, it is widely accepted that patients who undergo treatment of an intracranial aneurysm require follow-up by neurovascular imaging. Selective cerebral angiography has been established as the method of reference of aneurysm evaluation after coiling. However, selective cerebral angiography is an invasive method, exposes patients to ionizing radiation and the accumulating risk of vascular complications, and requires angiography suite facilities and personnell.[49-54] Minimizing morbidity related to angiographic surveillance is particularly important when analyzed within the context of the very low risk of rebleeding after successful coil embolization.[58,62-64] MRA may therefore be an excellent alternative to selective cerebral angiography, because it is noninvasive, can be performed in an outpatient setting, does not carry the risk of neurological complications, does not involve exposure to ionizing radiation and images are minimally impacted by coil-induced artifacts.

Part 2 of the thesis demonstrates the role of MRA in the follow-up after coil embolization.

In chapter 5 we aimed to compare 1.5 T 3D TOF MRA with selective cerebral angiography, as the gold standard, in the follow-up of intracranial aneurysms after endovascular treatment with Guglielmi detachable coils. In chapter 6 we determined whether 3D TOF MRA at 1.5 T could serve as the primary follow-up imaging modality after coiling.

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Chapter2

Intracranial Aneurysms in Patients with Subarachnoid Hemorrhage: CT Angiography as a Primary Examination Tool for Diagnosis—Systematic Review and Meta-Analysis

H. E. Westerlaan[1], J. M. C. van Dijk[2], M. C. Jansen-van der Weide[3], J. C. de Groot[1], R. J. M. Groen[2], J. J. A. Mooij[2] and M. Oudkerk[1]

[1]Department of Radiology, University Medical Center Groningen, The Netherlands
[2]Department of Neurosurgery, University Medical Center Groningen, The Netherlands
[3]Department of Epidemiology, University Medical Center Groningen, The Netherlands

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ABSTRACT

Purpose: To calculate the sensitivity and specificity of computed tomographic (CT) angiography in the diagnosis of cerebral aneurysms in patients with acute subarachnoid hemorrhage (SAH) at presentation.

Materials and Methods: A systematic search for relevant studies was performed of the PubMed/MEDLINE and EMBASE databases. Two reviewers independently assessed the methodologic quality of each study by using the Quality Assessment of Diagnostic Accuracy Studies tool. The inclusion criteria were met by 50 studies. Heterogeneity was tested, and the presence of publication bias was visually assessed (by using a funnel plot). A meta-analysis of the reported sensitivity and specificity of each study with 95% confidence intervals (CIs) was performed on a per-patient level.

Results: Concerning sensitivity, the selected studies showed moderate heterogeneity. For specificity, low heterogeneity was observed. Moderate-heterogeneity studies that investigated only sensitivity or specificity were excluded from the pooled analyses by using a bivariate random effects model. The majority of the studies (n = 30) used a four–detector row CT scanner. The studies had good methodologic quality. Pooled sensitivity was 98% (95% CI: 97%, 99%), and pooled specificity was 100% (95% CI: 97%, 100%). Potential sources of variability among the studies were variations in the methodologic features (quality score), CT examination procedure (number of rows on the multidetector CT scanner), the standard of reference used, and the prevalence of ruptured intracranial aneurysms. There was evidence for publication bias, which may have led to overestimation of the diagnostic accuracy of CT angiography.

Conclusion: Multidetector CT angiography can be used as a primary examination tool in the diagnostic work-up of patients with SAH.

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is caused by rupture of an intracranial aneurysm in 80%–90% of cases.[1,2] The mortality for untreated aneurysmal SAH is up to 50% in the 1st month, mainly because of rerupture.[3] Early identification and definitive treatment of underlying ruptured aneurysms is generally advocated to reduce the risk of rebleeding.[4-6]

Computed tomographic (CT) angiography of the intracranial vessels is now a routine examination that has become fully integrated into the imaging and treatment algorithm for patients with SAH at presentation in many centers in Europe.

The aim of this systematic review and meta-analysis was to calculate the sensitivity and specificity of CT angiography in the diagnosis of cerebral aneurysms in patients with acute SAH at presentation.

MATERIALS AND METHODS

Literature Review

A computerized search was performed in MEDLINE and EMBASE to identify relevant articles published from January 1, 1997, through September 1, 2009. In MEDLINE/PubMed, a search was performed for the following terms: "tomography, x-ray computed" (a Medical Subject Headings [MeSH] term) AND "intracranial aneurysm" (MeSH term) OR "subarachnoid hemorrhage" (MeSH term) OR "aneurysm, ruptured" (text word), combined with the diagnostic filter specified under clinical queries (broad search).[7] The search was limited to articles concerning humans and articles with abstracts. Case reports and reviews were excluded. In EMBASE we used the following terms: "computed tomography" AND "intracranial aneurysm" OR "subarachnoid hemorrhage" AND "angiography". The following record limits were selected: "article" (publication type), "humans" and "with abstracts". Two reviewers (H.E.W., with 5 years of experience, and J.M.C.v.D., with 10 years of experience) independently searched the reference list of all studies initially identified by the PubMed and EMBASE search strategies to identify additional studies. All languages were considered. The complete search yielded 2037 articles (Figure 1).

Eligibility Criteria

We searched for studies that assessed the value of CT angiography in patients with proven SAH; if a study included patients with clinical suspicion of the presence of intracranial aneurysms other than SAH (eg, cranial nerve palsies or brainstem dysfunction), the study was eligible if it provided separate patient-based analyses of patients with SAH. Articles were, furthermore, included if (a) all patients underwent selective cerebral angiography, surgery, endovascular treatment or autopsy as a reference standard and (b) absolute numbers of patients were reported or 2 × 2 tables could at least be deducted. If diagnostic accuracy was reported, but absolute numbers were not, the corresponding author was contacted, and the study was included if the absolute numbers were

provided. Studies were excluded if (a) fewer than 20 patients were included, because smaller studies are more likely to suffer from selection bias; (b) multiple reports were published for the same study population (in these cases, the publication with the largest study group was included in the analysis; in case of doubt about duplicate publications, the corresponding author was contacted); (c) the primary aim of the study was the evaluation of a technical or postprocessing protocol; or (d) the article was a review, case report, or editorial.

Data Collection and Quality Assessment

Two reviewers (HEW, JMCvD) independently selected articles on the basis of the title and abstract; if one or both reviewers considered the study potentially eligible, the full article was evaluated by both reviewers. Study quality was assessed independently by the same observers with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool; disagreement was resolved by consensus.[8] This evidence-based tool was developed specifically to assess the quality of diagnostic accuracy studies and includes 14 quality items. The 14 items, phrased as questions, are scored as "yes," "no," or "unclear." The quality assessment score can range from 0 (observed minimum) to 14 (observed maximum), where 14 is the maximum attainable score. A more detailed description of each item, together with a guide on how to score each item, is provided in the article by Whiting et al.[8]

The following study descriptives were extracted: prevalence of ruptured intracranial aneurysm, study design, type of CT scanner used, and diagnostic accuracy numbers (true-positive, false-positive, true-negative, and false-negative results). The study design was scored according to the authors' description in the Materials and Methods section of the article.

Study Selection

Fifty-five articles fulfilled the inclusion criteria of the meta-analysis. Five of these articles appeared to be duplicate publications regarding (parts of) the same patient population. This resulted in 50 studies being included in this meta-analysis.[9-58]

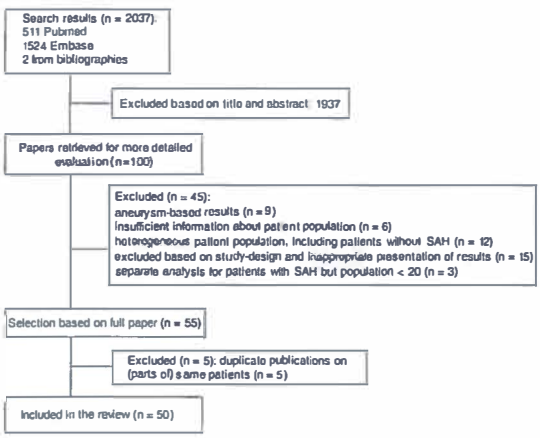

Figure 1: Flowchart of search results.

Statistical Analysis

Primary outcomes of this meta-analysis were sensitivity and specificity at a patient level. Pooling of data was performed within the bivariate mixed-effects binary regression modeling framework. Model specification, estimation, and prediction were performed with software (xtmelogit in Stata, release 10, 2001; Stata, College Station, Tex). Using the model-estimated coefficients and variance-covariance matrixes, this program calculates summary operating sensitivity and specificity values (with confidence and prediction contours in summary receiver operating characteristic space). A forest plot was generated that contained the individual study sensitivities and specificities with 95% confidence intervals (CIs) and the pooled sensitivity and specificity estimates. Because pooling assumes that there is one "true" underlying sensitivity and specificity for CT angiography, from which studies should only differ by chance factors, large differences in sensitivity and specificity across studies (called heterogeneity) would contradict this assumption and hence prohibit pooling of data. Heterogeneity was tested by using the Higgins and Thompson test to calculate the I^2 statistic.[59] This statistic uses the conventional Cochran Q statistic to calculate the percentage of tool variation heterogeneity on a scale ranging from 0% (no heterogeneity) to 100% (all variance due to heterogeneity). In contrast to the Cochran Q, the I^2 is less affected by the number of studies included in a meta-analysis. If no or moderate heterogeneity is found ($I^2 \leq 50\%$), pooling is justified.

The presence of publication bias was visually assessed by producing a funnel plot. In the Stata software, linear regression of log odds ratios on the inverse root of effective sample sizes was performed as a test for funnel plot asymmetry. The log odds ratios were defined as the log-transformed diagnostic odds ratios, which are needed for the performance of linear regression. Publication bias was considered to be present if there was a nonzero slope coefficient ($P < .10$), suggesting that only the small studies that reported a high accuracy for CT angiography had been published, whereas the small studies that reported a lower accuracy had not been published. Explanations for heterogeneity were analyzed by using stratification. Predefined potential sources of heterogeneity included methodologic features (study design and study quality), differences in the CT scanning procedure (type of scanner used), differences in the reference standard used (selective cerebral angiography, surgery, endovascular treatment, or autopsy), and differences in the prevalence of ruptured aneurysms. Data were analyzed with software (SPSS, version 16.0, SPSS, Chicago, Ill; Meta DiSc; and Stata, version 11.0; Stata).[60]

RESULTS

Study Characteristics

The study characteristics are shown in Table 1. The quality assessment scores ranged from 7 to 14, with a mean study quality score of 11. The majority of the studies (n = 37) used a four–detector row CT scanner. Most studies (n = 31) had a consecutive study design. Study patients who did not undergo a reference standard examination were excluded from further analysis. This means that the

Table 1: Study characteristics

Study (author, ref., year of publication)	Number of patients	Study design	Quality score	Number of CT detectors	Gold standard DSA	Surgery/embolization	None	Number of ruptured aneurysms (%)
Included for analysis:								
Agid (9) 2006	73	c-p	10	64	19	46	8	47 (72)
Anderson (10) 1999	152	c-p	11	4	26	126	0	126 (83)
Caruso (11) 2002	31	c	10	4	4	24	3	24 (86)
Colen (13) 2007	336	c-r	13	4,8 and 16	330	6	0	218 (65)
Dammert (14) 2004	50	c-r	12	4	50	0	0	41 (82)
Guo (18) 2008	80	nr	10	64	10	70	0	70 (87,5)
El Khaldi (16) 2007	130	c-p	10	16	21	109	0	110 (85)
Gonzalez-Darder (17) 2001	87	c	10	4	13	74	0	78 (90)
Halaji (19) 2006	42	r	8	4	15	27	0	28 (67)
Hoh (20) 2004	109	c-p	10	4	6	102	1	103 (95)
Jayaraman (21) 2004	35	c-p	13	4	35	0	0	21 (60)
Kadri (22) 2006	57	p	11	4	57	0	0	41 (72)
Karamessini (23) 2004	61	c	11	4	20	41	0	41 (67)
Kouskouras (25) 2004	33	NR	10	4	31	2	0	27 (82)
Lai (26) 1999	35	c-r	9	4	3	32	0	32 (91)
Lenhart (27) 1997	53	p	12	4	53	0	0	39 (74)
Lubicz (28) 2007	54	c-r	13	64	7	47	0	48 (89)
Lukosevicius (29) 2002	46	NR	8	4	44	2	0	24 (52)
Milosevic (32) 1999	52	p	10	4	10	42	0	42 (81)
Nijar (35) 2007	243	r	10	16	41	198	4	198 (83)
Papke (36) 2007	90	p	12	16	26	64	0	66 (73)
Pedersen (38) 2001	162	c	13	4	162	0	0	119 (73)
Pozzi (39) 2007	21	c	13	64	5	16	0	16 (76)
Rajagopal (40) 2003	50	nc	8	4	13	37	0	37 (74)
Rohnert (41) 1998	106	NR	9	4	106	0	0	64 (60)
Romijn (42) 2008	102	NR	11	4	102	0	0	82 (80)
Rotim (43) 2007	29	c-p	10	16	29	0	0	27 (93)

Study (author, ref., year of publication)	Number of patients	Study design	Quality score	Number of CT detectors	Gold standard DSA	Surgery/embolization	None	Number of ruptured aneurysms (%)
Included for analysis:								
Santos (44) 2001	57	NR	8	4	56	1	0	40 (70)
Sasiadek (45) 2002	196	NR	7	4	73	121	2	161 (83)
Seruga (46) 2001	30	c-p	14	4	30	0	0	27 (90)
Taschner (47) 2007	27	c-p	12	16	6	21	0	21 (78)
Teksam (48) 2004	54	c-r	10	4	54	0	0	42 (78)
Uysal (49) 2005	32	NR	12	4	6	26	0	28 (88)
Uysal (50) 2008	55	c-r	14	16	55	0	0	50 (91)
Velthuis (51) 1998	100	c-p	11	4	13	71	16	75 (89)
Velthuis (52) 1999	100	c-p	10	4	15	58	27	58 (79)
Velthuis (53) 1999	40	c-p	13	4	39	1	0	16 (40)
Westerlaan (54) 2007	224	c	11	16 and 64	69	153	2	158 (71)
White (55) 2001	56	c-p	11	4	56	0	0	32 (57)
Wintermark (56) 2003	37	c-p	14	4	37	0	0	33 (89)
Yan (57) 2007	86	NR	10	4	86	0	0	74 (86)
Zouaoui (58) 1997	120	NR	10	4	13	107	0	107 (89)
Excluded from analysis:								
Chen (12) 2008	41	nr	9	16	0	41	0	41 (100)
Dehdashti (15) 2003	100	c-p	11	4	4	94	2	98 (100)
Kershenovich (24) 2006	30	c-r	11	4	30	0	0	0 (0)
Matsumoto (30) 2002	60	c-p	10	4	60	0	0	60 (100)
Matsumoto (31) 2007	162	c	10	4	0	162	0	162 (100)
Muto (33) 1999	45	NR	11	4	45	0	0	45 (100)
Nakajima (34) 1998	42	c-p	9	4	5	37	0	42 (100)
Pechlivanis (37) 2005	84	c-p	11	4	0	84	0	84 (100)

c consecutive, *nc* non-consecutive, c-*p* consecutive prospective, c-*r* consecutive retrospective, *p* prospective, *r* retrospective, *NR* not reported

data presented in the meta-analysis results may not match the total number of patients in a study.

Assessment of Publication Bias

A nonzero slope coefficient (P = .02) indicated that there was evidence for publication bias (Figure 2). This suggests that there have been smaller studies with lower diagnostic accuracies that have not been published. This may have led to overestimation of the results in the meta-analysis.

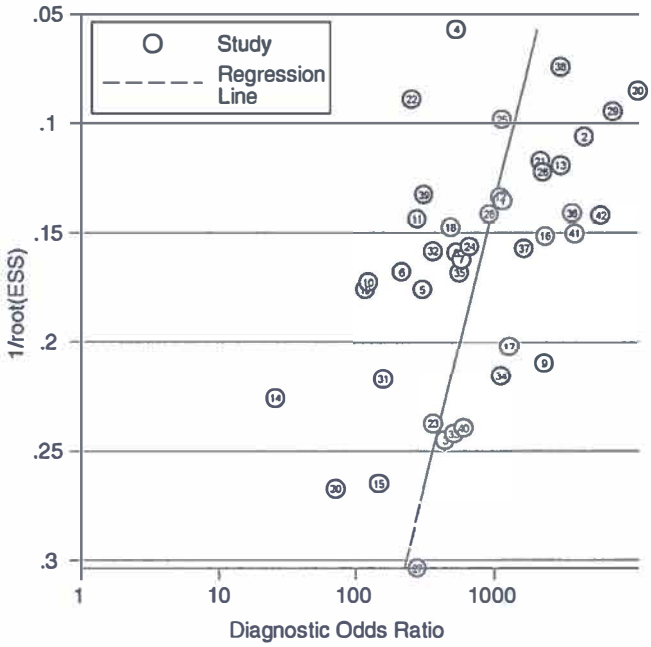

Figure 2: Results of Deeks funnel plot asymmetry test (P = .02) show log odds ratios on inverse root of effective sample sizes (ESS) for visualization of publication bias. Numbers in circles = numbers assigned to given articles in our bivariate model.

Analysis of Heterogeneity and Pooled Sensitivity and Specificity

All 50 studies were analyzed on a per-patient level; this process included 4097 patients.

The sensitivities ranged from 86% to 100%. Concerning sensitivity, the selected studies showed moderate heterogeneity (I^2 = 54%). For specificity, low heterogeneity was observed (I^2 = 19%); specificity ranged from 50% to 100%. Data of moderate heterogeneity were analyzed by using a bivariate random effects model that allowed for the negative correlation between sensitivity and specificity.[61] As a result, studies that investigated only sensitivity or specificity were excluded from the pooled analyses, as the bivariate model needed both outcomes to test for possible interaction.[12,15,24,30,31,33,34,37,62]

Overall pooled sensitivity of the 42 remaining studies was 98% (95% CI: 97%, 99%), and the pooled specificity was 100% (95% CI: 97%, 100%) (Figures 3, 4).

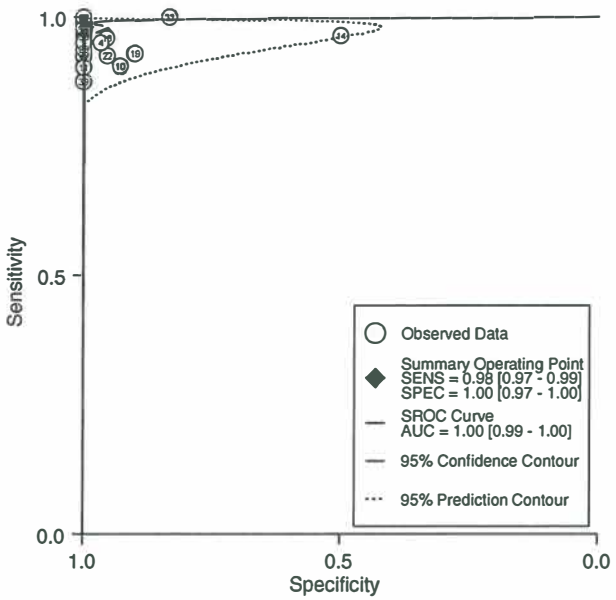

Figure 3: Summary receiver operating characteristic (SROC) curve with prediction and confidence contours. AUC = area under the curve, SENS = sensitivity, SPEC = specificity. Numbers in circles = numbers assigned to given articles in our bivariate model.

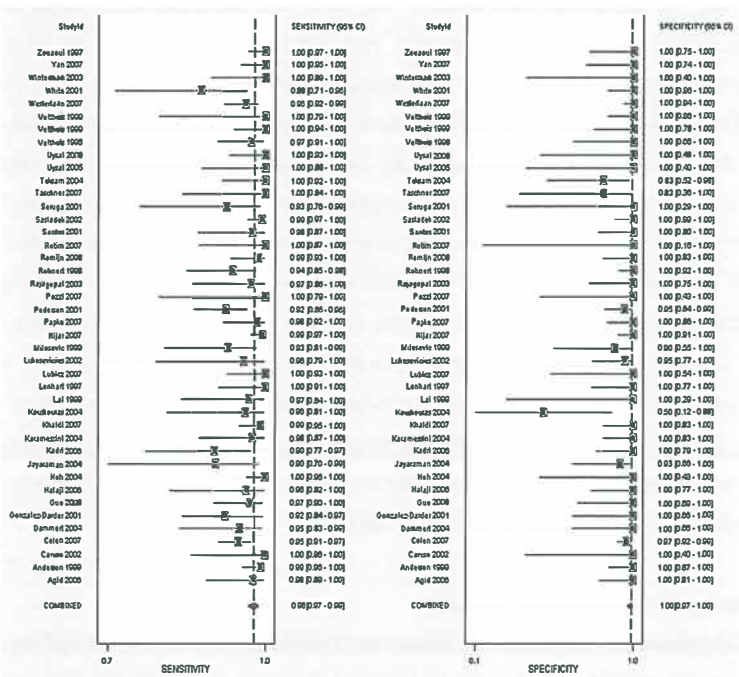

Figure 4: Forest plot shows sensitivity and specificity from individual studies and pooled estimates. Dotted squares = mean sensitivity or specificity for each study, horizontal lines = 95% CIs of sensitivity or specificity for each study, vertical red dashed line = pooled sensitivity or specificity for all 42 studies.

Most studies used a four–detector row scanner (n = 30), while 11 were performed with a 16– or 64–detector row CT scanner. Concerning sensitivity, studies performed with a 16– or 64–detector row scanner showed minimal heterogeneity (n = 11; I^2 = 15%; pooled sensitivity: 98%) compared with those performed with a four–detector row scanner (n = 30; I^2 = 57%; pooled sensitivity: 98%). The specificities for the four–detector row scanners and the 16– or 64–detector row scanners were comparable (both 100%). Note that one study that used four–, eight–, and 16–detector row scanners was excluded from this analysis because the results were not separately analyzed according to the type of scanner used. Sensitivity and specificity rates in studies performed with nonconsecutive patients were comparable in heterogeneity (n = 7; sensitivity: I^2 = 60%; pooled sensitivity: 98%; specificity: I^2 = 0%; pooled specificity: 100%) to those in studies performed with consecutive patients (n = 25; sensitivity: I^2 = 51%; pooled sensitivity: 98%; specificity: I^2 = 0%; pooled specificity: 98%). Note that 10 studies without a reported study design were excluded from this analysis. Concerning sensitivity, the studies with a lower quality score (QUADAS score ≤ 8) were more homogeneous (n = 5; I^2 = 0%; pooled sensitivity: 98%) than the studies with a higher quality score (QUADAS score ≥ 11) (n = 21; I^2 = 52%; pooled sensitivity: 97%). Both low- and high-quality studies were homogeneous concerning specificity (I^2 = 0%; pooled specificity: 99%). Note that 16 studies with a QUADAS score of 9 or 10 were excluded from this analysis.

Different reference standards were used in assessing the presence of aneurysms. High-quality reference standards (surgery, coil placement, and autopsy in > 70% of cases) showed moderate heterogeneity in sensitivity (n = 19; I^2 = 44%; pooled sensitivity: 99%). Studies that used a reference standard of lower quality (DSA in > 70% of cases) showed a higher heterogeneity (n = 19; I^2 = 53%; pooled sensitivity: 97%). Concerning specificity, the studies that used a reference standard of higher quality were more homogeneous (I^2 = 0%; pooled specificity: 99%) than those that used a lower-quality reference standard (I^2 = 40%; pooled specificity: 98%). Note that four studies in which DSA was used in less than 70% of cases or in which surgery, coil placement, or autopsy was used in less than 70% of cases were excluded from this analysis. Concerning sensitivity, the studies with a prevalence of ruptured aneurysms higher than 80% were more heterogeneous (n = 22; I^2 = 49%; pooled sensitivity: 99%) than studies with a prevalence of ruptured aneurysms lower than 80% (n = 20; I^2 = 38%; pooled sensitivity: 96%). Specificity rates in studies with a higher prevalence of ruptured aneurysms were comparable in heterogeneity (I^2 = 20%; pooled specificity: 100%) to studies with a lower prevalence (I^2 = 21%; pooled specificity: 98%).

False-Negative CT Angiography Results

Seventy-one ruptured aneurysms were missed at CT angiography. The location of the false-negative aneurysm was specified for 53 aneurysms (Table 2). The size of the false-negative aneurysms was given for 40 aneurysms: Nineteen were smaller than 3 mm, 17 were smaller than 5 mm, and four were 5–10 mm in diameter. At least 19 of the missed aneurysms could be detected retrospectively.

Table 2: Location of False-Negative Ruptured Intracranial Aneurysms at CT Angiography

Locations	No. of Aneurysms
Anterior circulation	
Pericallosal artery/anterior communicating artery/anterior cerebral artery	9
Internal carotid artery/posterior communicating artery	27
Middle cerebral artery	5
Posterior circulation	
Basilar artery	1
Anterior inferior cerebellar artery	1
Posterior inferior cerebellar artery	7
Posterior cerebral artery	2
Posterior fossa, not specified	1

False-Positive CT Angiography Results

There were 15 false-positive findings of ruptured aneurysm at CT angiography. The location was specified for nine such findings (Table 3). The size of the finding was given for only three false-positive findings; all were smaller than 3 mm. In four findings, CT angiography could not help differentiate a tortuous vessel or infundibular dilatation from an aneurysm.

Table 3: Location of False-Positive Findings of Ruptured Intracranial Aneurysms at CT Angiography

Location in Anterior Circulation	No. of findings
Anterior communicating artery/anterior cerebral artery	3
Internal carotid artery/posterior communicating artery	4
Middle cerebral artery	2

DISCUSSION

The results of this systematic review and meta-analysis show that CT angiography has a very high diagnostic value for the detection of ruptured intracranial aneurysms.

So far, to our knowledge, three earlier systematic reviews have been performed. The systematic review of studies performed with single–detector row CT angiography between 1988 and 1998 conducted by White et al demonstrated a per-patient sensitivity of 92% and a per-patient specificity of 94% for the detection of aneurysms as compared with selective cerebral angiography.[63] The per-aneurysm sensitivity was greater for detection of aneurysms larger than 3 mm than for detection of aneurysms 3 mm or smaller (96% vs 61%). Van Gelder undertook a further analysis of the accuracy of CT angiography, with the majority of studies performed between 1993 and 1998 (and therefore with single–detector row scanners).[64] The sensitivity of CT angiography ranged from 53% for 2-mm aneurysms to 95% for 7-mm aneurysms. The overall specificity was 99%. The median sensitivity

for ruptured aneurysms was 92%. A slightly more recent meta-analysis by Chappell et al showed CT angiography to have a per-patient sensitivity of 93% and a per-patient specificity of 88%.[65] The studies analyzed by White et al, van Gelder, and Chappell et al had a high prevalence of aneurysms, which is reflected in the favorable sensitivity for larger aneurysms.

The present investigation can be considered as a further update, with inclusion of studies that used newer generations of CT scanners. Important distinctions from the other reviews are that we used a homogeneous patient population and that, in addition to findings at selective cerebral angiography, findings at treatment and autopsy were used as the reference standard.

An important factor influencing the accuracy of CT angiography for the detection and depiction of intracranial aneurysms is the experience and the (perceptual) accuracy of the observer. Jayaraman et al reported sensitivities increasing from 69% for the detection of an initial 13 aneurysms to 84% for the detection of 13 subsequent aneurysms.[21] Pedersen et al reported an increase in sensitivity from 88% to 94% after 1 year of observer experience.[38] White et al compared the sensitivity and specificity of CT angiography for the detection of cerebral aneurysms between neuroradiologists and nonneuroradiologists and found neuroradiologists to perform consistently better than the other observers.[66]

Several of the studies included in our meta-analysis showed that a total of 19 false-negative aneurysms at CT angiography could be seen retrospectively.[9,16,18,21,32,36,38,41,54] These false-negative interpretations can therefore be categorized as perceptual in nature and could have been substantially bypassed by double reading.

CT angiography had a relatively high false-negative rate in the detection of small aneurysms near the central skull base—that is, aneurysms of the internal carotid artery and the posterior communicating artery. Despite the technical advancements with 64–detector row multidetector CT systems, detection of aneurysms adjacent to the skull base remains a challenging issue for CT angiography, because of the presence of overlying bone structures and the complex vascular anatomy.

Several studies that used four–detector row spiral machines restricted the area of coverage to the proximal circle of Willis and missed distal pericallosal and posterior inferior cerebellar aneurysms.[25,26,32,38,41] Perianeurysmal blood and the presence of intra-aneurysmal thrombus may reduce lesion conspicuity.[54] Surrounding arteries and fenestration of arteries may also obscure the presence of an aneurysm.[36] Furthermore, suboptimal arterial enhancement and artifacts caused by patient movement may limit the depiction of aneurysms.[17,35,41,42]

Vascular infundibula of the posterior communicating or anterior choroidal artery origins may be

mistaken for aneurysms if a vessel cannot be identified arising from them.[67] Tight vascular loops may also masquerade as aneurysms.[25,38] Furthermore, small aneurysms may carry a higher risk of being false-positive.[47,48]

Some considerations in the interpretation of the results of this systematic review and meta-analysis should be mentioned. First, the sensitivity of the selected studies showed moderate heterogeneity. Potential sources of variability among the studies were variations in the methodologic features (quality scores), CT scanning procedure (number of multidetector CT rows), the standard of reference used, and the prevalence of ruptured intracranial aneurysms. Second, a threat to the validity of any meta-analysis is publication bias. Smaller studies, and especially those with negative results, are less likely to be accepted for publication than larger studies, leading to an overestimation of the diagnostic accuracy of a test when one combines only published reports. Our analyses are strongly suggestive of publication bias, making the pooled sensitivity of 98% and the pooled specificity of 100% a potential overestimation of the true sensitivity and specificity had all studies in this field been published. Third, the CT angiography results are based on a patient population with a high pretest probability for intracranial aneurysm—that is, patients with acute SAH at presentation. Fourth, the results of the studies were not controlled for anatomic extent. Although it may seem obvious that sensitivity will increase with the size of the aneurysm, the anatomic extent of disease was often neglected or not presented appropriately in the included studies. This problem was overcome by using a homogeneous patient population—that is, patients with acute SAH at presentation. Fifth, we did not analyze the value of CT angiography in the diagnosis of additional asymptomatic intracranial aneurysms. Although additional aneurysms are clinically not relevant in the acute setting of SAH, their importance increases during follow-up. The annual rupture rate of unruptured intracranial aneurysms is 0.5%–1.4%.[68–70] A history of SAH has been shown to be a significant independent predictor for aneurysm rupture.[68,69] Sixth, the number of included studies using 16– or 64–detector row CT is limited. Because isotropic voxel resolutions are visible with 16 or more detectors, one would expect a marked study outcome difference between older and newer CT generations of CT scanners. However, this effect could not be supported by the data of this study. Finally, it should be mentioned that no studies that used three-dimensional rotational angiography for the detection of ruptured aneurysms in patients with SAH whose CT angiography and selective cerebral angiography results were initially negative for ruptured aneurysm were used. It has been shown that additional three-dimensional rotational angiography can depict ruptured occult aneurysms at two-dimensional selective cerebral angiography.[71–73] This technique needs further evaluation before any further role for three-dimensional rotational angiography can be implemented in the diagnostic work-up. Although selective cerebral angiography is considered a good reference standard, several of the included studies in which CT angiography–based surgery was performed showed that two-dimensional selective cerebral angiography can fail to depict ruptured intracranial aneurysms that were depicted by CT angiography.[18,23,36,41,44,45,54,58] Furthermore,

several studies have demonstrated that occult ruptured cerebral aneurysms can be revealed by repeat selective cerebral angiography, and a few reports have described the fact that, despite negative selective cerebral angiographic results, exploratory surgery can reveal aneurysms.[74–81]

There is ongoing debate as to whether CT angiography is good for patient care in the setting of SAH. Some investigators believe that selective cerebral angiography is still needed, regardless of whether a cause for hemorrhage is seen at CT angiography, and imply that CT angiography is inadequate for needed details in the management of aneurysms. However, the results of our systematic review and meta-analysis prove that CT angiography is an accurate tool in the diagnosis of ruptured intracranial aneurysms and can be integrated as a primary examination tool into the imaging and treatment algorithm for patients with SAH at presentation. The chance of missing a ruptured aneurysm at CT angiography is no more than 2%.

CT angiography is widely available, can be performed quickly, and is a noninvasive procedure. In comparison, diagnostic selective cerebral angiography is invasive and time consuming and carries a risk of neurologic complications of up to 2.3%, even in patients without vascular disease—complications that can lead to a permanent deficit in up to 0.5% of patients.[82–87] Furthermore (according to manufacturer data), CT angiography has a lower radiation exposure (1.0 mSv [at 200 mAs] with the Siemens Sensation 16 scanner and 1.8 mSv [at 380 mAs] with the Siemens Sensation 64 scanner) than selective cerebral angiography (3.5–6.5 mSv). Finally, CT angiography is cheaper than selective cerebral angiography.

In the present meta-analysis, CT angiography studies that used surgery, endovascular treatment, or autopsy as reference standards had better results than studies that used selective cerebral angiography as the reference standard. This further brings into question the role of diagnostic selective cerebral angiography as a reference standard, keeping in mind its complication rate, which in some studies nearly equaled the false-negative rate of CT angiography, and notwithstanding that the sensitivity of selective cerebral angiography performed by experienced angiographers varies between 92% and 97% when repeat selective cerebral angiography or three-dimensional rotational angiography are used as reference standards for initially negative findings.[72–75,79,82,86]

The lack of improvement in the sensitivity of CT angiography in studies that used newer generations of CT scanners suggests that the quality (of the interpretation) of the images and the awareness of possible interpretation pitfalls and blind spots are as important as any technologic development. In the present study, at least 19 (27%) of the 71 false-negative ruptured intracranial aneurysms could be detected at CT angiography retrospectively. Thus, implementation of double reading could have lowered the false-negative rate to 1%. For sensitivity improvement, double reading is often regarded as necessary in radiology (eg, in mammographic screening). Therefore, we recommend a

second reevaluation by an experienced (neuro)radiologist for every negative CT angiography result, thus minimizing the risk of missing a ruptured aneurysm and its risk of rebleeding and associated high mortality. Because patients with SAH at presentation are generally referred to clinical centers with neuroradiologic expertise, we believe that this recommendation of double reading of negative CT angiography studies should be reasonably followed. It is very likely that with improved technical acquisition and postprocessing techniques with isotropic voxel resolutions of up to 0.4 mm for 64–detector row CT angiography, experience will further improve the sensitivity of CT angiography.

To be cost effective, a clinical practice guideline may be that selective cerebral angiography can be omitted if CT angiography results are positive and that a negative CT angiography result should be confirmed with a second reevaluation by a radiologist; at that point, a negative CT angiography result should be accepted as the final diagnosis. Further prospective data collection should be performed to test this clinical practice guideline we recommend.

To reduce the risk of missing aneurysms near the central skull base, subtraction methods for bone "removal" have been promoted that involve both simple subtraction from enhanced data to unenhanced data and selective bone removal, or "matched mask bone elimination".[42,88–96] These data show a better delineation of the vasculature closely adjacent to bone structures with bone subtraction CT angiography. Problems with subtraction CT angiography might be an increase in radiation dose because of the acquisition of the additional unenhanced preliminary mask and the occurrence of misregistration artifacts when patients move between the two consecutive acquisitions. These problems might be overcome by performing dual-energy direct bone removal CT angiography. In the study of Watanabe et al, dual-energy direct bone removal CT angiography removed the bone structures from the image very well and depicted aneurysms adjacent to the skull base very clearly with a single data acquisition.[97]
When more data become available, an update of this analysis should be conducted. Further research into whether these methods and information improve decision making is required.

- **Advances in Knowledge**
  Multidetector CT angiography can reliably depict ruptured intracranial aneurysms, with a pooled sensitivity of 98% and a pooled specificity of 100%.
  Missed aneurysms at CT angiography are often small and located near the skull base.

- **Implication for Patient Care**
  Multidetector CT angiography can be integrated as a primary examination tool into the imaging and treatment algorithm for patients with subarachnoid hemorrhage at presentation.

Abbreviations:

CI = confidence interval

DSA = digital subtraction angiography

QUADAS = Quality Assessment of Diagnostic Accuracy Studies

SAH = subarachnoid hemorrhage

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Chapter 3

Multislice CT angiography in the selection of patients with ruptured intracranial aneurysms suitable for clipping or coiling

H. E. Westerlaan[1], J. Gravendeel[1], D. Fiore[1], J. D. M. Metzemaekers[2], R. J. M. Groen[2], J. J. A. Mooij[2] and M. Oudkerk[1]

[1]Department of Radiology, University Medical Center Groningen, The Netherlands
[2]Department of Neurosurgery, University Medical Center Groningen, The Netherlands

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ABSTRACT

Introduction: We sought to establish whether CT angiography (CTA) can be applied to the planning and performance of clipping or coiling in ruptured intracranial aneurysms without recourse to intraarterial digital subtraction angiography (IA-DSA).

Methods: Over the period April 2003 to January 2006 in all patients presenting with a subarachnoid haemorrhage CTA was performed primarily. If CTA demonstrated an aneurysm, coiling or clipping was undertaken. IA-DSA was limited to patients with negative or inconclusive CTA findings. We compared CTA images with findings at surgery or coiling in patients with positive CTA findings and in patients with negative and inconclusive findings in whom IA-DSA had been performed.

Results: In this study, 224 consecutive patients (mean age 52.7 years, 135 women) were included. In 133 patients (59%) CTA demonstrated an aneurysm, and CTA was followed directly by neurosurgical ($n=55$) or endovascular treatment ($n=78$). In 31 patients (14%) CTA findings were categorized as inconclusive, and in 60 (27%) CTA findings were negative. One patient received surgical treatment on the basis of false-positive CTA findings. In 17 patients in whom CTA findings were inconclusive, IA-DSA provided further diagnostic information required for correct patient selection for any therapy. Five ruptured aneurysms in patients with a nonperimesencephalic SAH were negative on CTA, and four of these were also false-negative on IA-DSA. On a patient basis the positive predictive value, negative predictive value, sensitivity, specificity and accuracy of CTA for symptomatic aneurysms were 99%, 90%, 96%, 98% and 96%, respectively.

Conclusion: CTA should be used as the first diagnostic modality in the selection of patients for surgical or endovascular treatment of ruptured intracranial aneurysms. If CTA renders inconclusive results, IA-DSA should be performed. With negative CTA results the complementary value of IA-DSA is marginal. IA-DSA is not needed in patients with negative CTA and classic perimesencephalic SAH. Repeat IA-DSA or CTA should still be performed in patients with a nonperimesencephalic SAH.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is caused by aneurysmal rupture in 70–85% of patients.[1-2] In a systematic review, Hop et al. found fatality rates ranging from 32% to 67%.[3] Furthermore, 10–20% of patients remained functionally dependent after SAH. Rapid diagnostic evaluation and treatment are crucial for the patient's outcome.

Intraarterial digital subtraction angiography (IA-DSA) has been the main technique for detecting and characterizing intracranial aneurysms and remains the gold standard. However, IA-DSA is invasive and time consuming, and carries a risk of neurological complications of 0.5–1.8% with permanent deficit in 0.09–0.5%.[4-6] Serious non-neurological complications, which occur in 0.6% of patients, include groin hematoma, peripheral thromboembolism, transient hypotension and arteriovenous fistulas.[4] Furthermore, IA-DSA may increase the risk of rebleeding.[7,8] It has been demonstrated that three-dimensional CT angiography (3D-CTA) can reliably detect intracranial aneurysms.[9-14] Only after replacement of IA-DSA by CTA can the advantages of CTA be fully realized in the clinical setting. We report here our clinical experience with both 16- and 64-detector row CTA as the first and intended only diagnostic and treatment decision-making study for intracranial aneurysms in patients with acute SAH.

MATERIALS AND METHODS

Subjects

Between April 2003 and January 2006 all patients presenting with a SAH to the University Medical Centre Groningen consecutively underwent CTA as the first diagnostic study. Based on the CTA findings, patients were selected for surgical clipping or endovascular coiling of a ruptured intracranial aneurysm. SAH was suspected on clinical grounds and confirmed by unenhanced CT or by blood pigments on lumbar puncture.

Imaging protocols

The CT examinations were performed on a 16- or 64-multidetector row spiral CT machine (Somatom Sensation 16 or 64; Siemens Medical Systems, Erlangen, Germany), based on a standard protocol. The 64-multisclice CT was implemented in the Emergency Department in December 2004.

- *Parameters for 16-slice CT for diagnosis of aneurysm*: via an intravenous cannula in the antecubital fossa, 80 ml of contrast agent (Visipaque 320) was injected with a power injector at a rate of 4 ml/s. Injection of contrast agent was followed by a flush of 50 ml 0.9% saline (Stellant; NaCl Neck Angio) injected at the same rate. A manual fluoroscopic bolus-triggered system, with the internal carotid arteries as reference point and a delay of 4 s, determined the optimal timing. The CTA protocol parameters were as follows: spiral mode, rotation time 0.5 s, reconstruction interval 0.75 mm at Kernel H20, 120 kV/200 mAs, acquisition time 10 s, scan range from the C1 vertebral body to the vertex parallel to the orbitomeatal line.

- *Parameters for 16-slice CT for diagnosis of SAH*: gantry un-angled, spiral mode, rotation time 0.75 s, 16-detector rows at 0.75-mm intervals, table speed 6 mm/rotation, reconstruction interval 3 mm at Kernel H30 and acquisition parameters 120 kV/200 mAs. The actual acquisition time was approximately 15 s.
- *Parameters for 64-slice CTA for diagnosis of aneurysm*: rotation time 1 s, table speed 15.4 mm/rotation, reconstruction interval 0.6 mm at Kernel H20, 120 kV/260 mAs, acquisition time 9 s and scan range extending from the C1 vertebral body to the vertex parallel to the orbitomeatal line. The protocol parameters for contrast agent injection remained unchanged.
- *Parameters for 64-slice CT for diagnosis of SAH*: gantry un-angled, spiral mode, rotation time 1 s, 64 detector rows at 0.6-mm intervals, table speed 9.6 mm/rotation, reconstruction interval 2 mm at Kernel H30, acquisition parameters 120 kV/260 mAs and acquisition time 14 s.

Postprocessing of CTA

Source images were transferred to a remote computer workstation (Odelft Benelux diagnostic imaging) for viewing. Initial careful review of axial images was considered imperative. During this review any areas of concern could be noted. Two-dimensional maximum intensity projection (MIP) views and three-dimensional (3-D) surface-rendered and volume-rendered reconstructions were reformatted from the raw image date on a Vitrea computer workstation by one of the neuroradiologists.

Parameters for IA-DSA and postprocessing

From April 2003 until April 2004 the IA-DSA studies were produced on a digital angiographic unit (Siemens Multiskop with InfiMed image processing) with a 512×512 pixel matrix. From April 2004 onwards the studies were performed on a Siemens Axiom Artis angiographic unit with a 1024×1024 pixel matrix. Selective four- or six-vessel angiography using a standard projection format was performed initially and additional views were obtained if required to identify the parent vessel and aneurysm neck more clearly. The amount of contrast medium (Visipaque 270) used was 8 ml for the internal carotid artery and 6 ml for the external carotid artery, and the injection rate was 6 ml/s when the tip of the catheter was in the internal carotid artery and 3-4 ml/s when the tip of the catheter was in the external carotid artery. The rate of injection into the vertebrobasilar system was 6-8 ml/s to a total amount of 8 ml.

In certain situations, rotational 3-D angiography was performed to better delineate the anatomic details of an aneurysm. Rotational 3-D angiography was performed on a Siemens Axiom Artis angiographic unit. The C-arm rotates in a continuous 200° arc around the patient's head during a prolonged intraarterial catheter injection of contrast medium (28 ml Visipaque, injection rate 4 ml/s). The raw date images were transferred to a Leonardo workstation (AX Applications) from which 3-D volume-rendered reconstructions were reformatted.

Image review and data analysis

The presence of an aneurysm, its size and morphology, its parent and feeding vessels and the collateral circulation at the circle of Willis were determined by one of the diagnostic or interventional neuroradiologists. If multiple aneurysms were detected, the usual criteria were applied to decide which aneurysm was responsible for the haemorrhage. These criteria included the unenhanced CT findings (distribution of blood) and the size and irregularity of the aneurysm.

All diagnostic findings were discussed with the neurosurgeons. The CTA results were categorized into proven ruptured aneurysm, inconclusive or negative. Patients with a proven ruptured aneurysm were selected subsequently for coiling or clipping. The surgical and endovascular findings were compared to the CTA findings. In general, ruptured aneurysms in the anterior circulation were selected for either coiling or clipping. Ruptured aneurysms located in the posterior circulation were preferably coiled. Giant intracranial aneurysms were preferably treated surgically. A ruptured aneurysm in association with an intraparenchymatous haemorrhage was most often selected for clipping of the aneurysm and surgical evacuation of the haematoma.

Patients categorized as inconclusive or negative underwent IA-DSA. In patients with a perimesencephalic blood distribution, one IA-DSA examination was performed. In patients with a nonperimesencephalic blood distribution a second IA-DSA was performed if the first one was negative. IA-DSA was considered the gold standard. CTA was considered false-negative when IA-DSA revealed a ruptured aneurysm or when rebleeding occurred.

The positive predictive value, negative predictive value, sensitivity, specificity and accuracy of CTA per patient were calculated. The chi-squared test was used to compare the performance of 16-slice CTA and 64-slice CTA for the identification of intracranial aneurysms. Differences with a P value less than 0.05 were considered significant.

The IA-DSA findings in patients in the inconclusive category were compared with the CTA findings to assess whether IA-DSA actually provided any additional information.

RESULTS

Patient population

From April 2003 until January 2006 292 patients with SAH underwent CTA. Excluded from the study were 68 patients, of whom 24 were excluded because of a nonaneurysmal cause of the SAH including trauma ($n=17$), arteriovenous malformation ($n=6$) and anticoagulant therapy ($n=1$), 3 because of hypertension and intracerebral haematoma, 4 because of comorbidity or advanced age, 2 were excluded because of poor clinical condition and 1 because of poor clinical grading and advanced age, and 31 died from the initial effect of SAH, rebleed or vasospasm with ischemia. Two patients refused therapy and one patient was referred to another hospital for treatment.

The study included 224 patients, 89 men and 135 women with a mean (±SD) age of 52.7 ± 10.7 years (range 22–79 years). Their clinical condition just before treatment was classified according to the original Hunt and Hess grading system: 99 patients were classified as grade I, 45 as grade II, 58 as grade III, 20 as grade IV, and 2 as grade V.[15]

Detection of intracranial aneurysms

Of the 224 patients, 140 underwent 16-slice CTA and 84 underwent 64-slice CTA. The CTA results were categorized as proven ruptured intracranial aneurysm (133 patients, 59%), inconclusive (31 patients, 14%), or negative for aneurysm (60 patients, 27%).

Positive CTA result

In this category 133 ruptured aneurysms were diagnosed in 133 patients. In 25 patients 32 associated unruptured aneurysms were diagnosed. The distributions of the locations and sizes of the aneurysms are shown in Tables 1, 2, 3, and 4. An overview of the results in this subgroup is presented in Figure 1.

Table 1: Location of symptomatic intracranial aneurysms in 224 patients

Aneurysm location		CTA-positive ($n=133$) Coiling ($n=78$)	CTA-positive ($n=133$) Clipping ($n=55$)	CTA-inconclusive ($n=31$)[a] Coiling ($n=8$)	CTA-inconclusive ($n=31$)[a] Clipping ($n=12$)	CTA-negative ($n=60$)[b]
Anterior circulation	Anterior communicating artery	34	25	5	5	1
	Pericallosal artery	2	2			
	Middle cerebral artery	3	18	1	6	1
	Internal carotid artery	3	1	1		1
	Posterior communicating artery	17	8		1	
	Anterior choroideal artery	1				
Posterior circulation	Basilar tip	11				
	Vertebral junction	1				
	Posterior cerebral artery					1
	Posterior inferior cerebellar artery	5	1	1		
	Superior cerebellar artery	1				

[a]11 patients had no proven aneurysm. [b]Five patients had false-negative CTA, in four of whom a ruptured aneurysm was diagnosed on repeat angiography.

Table 2: Size distribution of symptomatic intracranial aneurysms in 224 patients

Size (mm)	CTA-positive ($n=133$)	CTA-inconclusive ($n=31$)[a]	CTA-negative ($n=60$)[b]
<5	47	12	4
5–9	70	4	
10–14	14	3	
15–24	1	1	
≥25	1		

[a]11 patients had no proven aneurysm. [b]Five patients had false-negative CTA, in four of whom a ruptured aneurysm was diagnosed on repeat angiography.

Table 3: Location of asymptomatic intracranial aneurysms in 224 patients

Aneurysm location		CTA-positive	CTA-inconclusive
Anterior circulation	Anterior communicating artery	6[a]	3
	Pericallosal artery	2	
	Middle cerebral artery	11[b]	4
	Internal carotid artery	9[a]	
	Posterior communicating artery	6[a]	
Posterior circulation	Basilar tip	1	
	Junction of vertebral artery	1	
	Posterior inferior cerebellar artery	1	

[a]One false-negative on CTA.
[b]Two false-negatives on CTA.

Table 4: Size distribution of asymptomatic intracranial aneurysms in 224 patients

Size (mm)	CTA-positive	CTA-inconclusive
< 5	30[a]	4
5–9	6	3
10–14	1	

[a]Five false-negative on CTA.

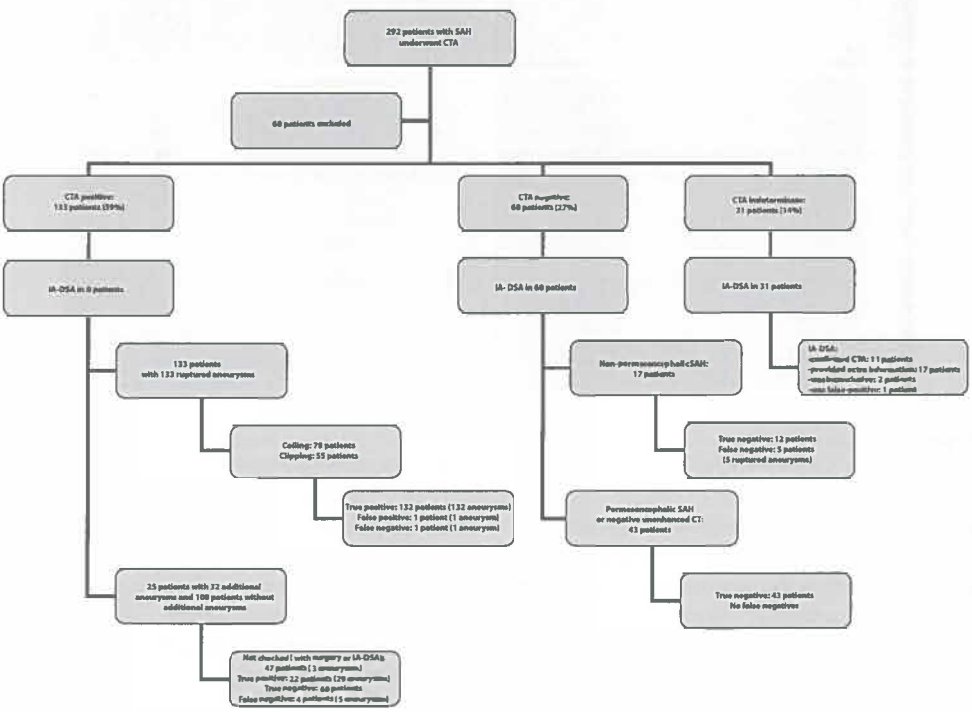

Figure 1: Flow chart of CTA results.

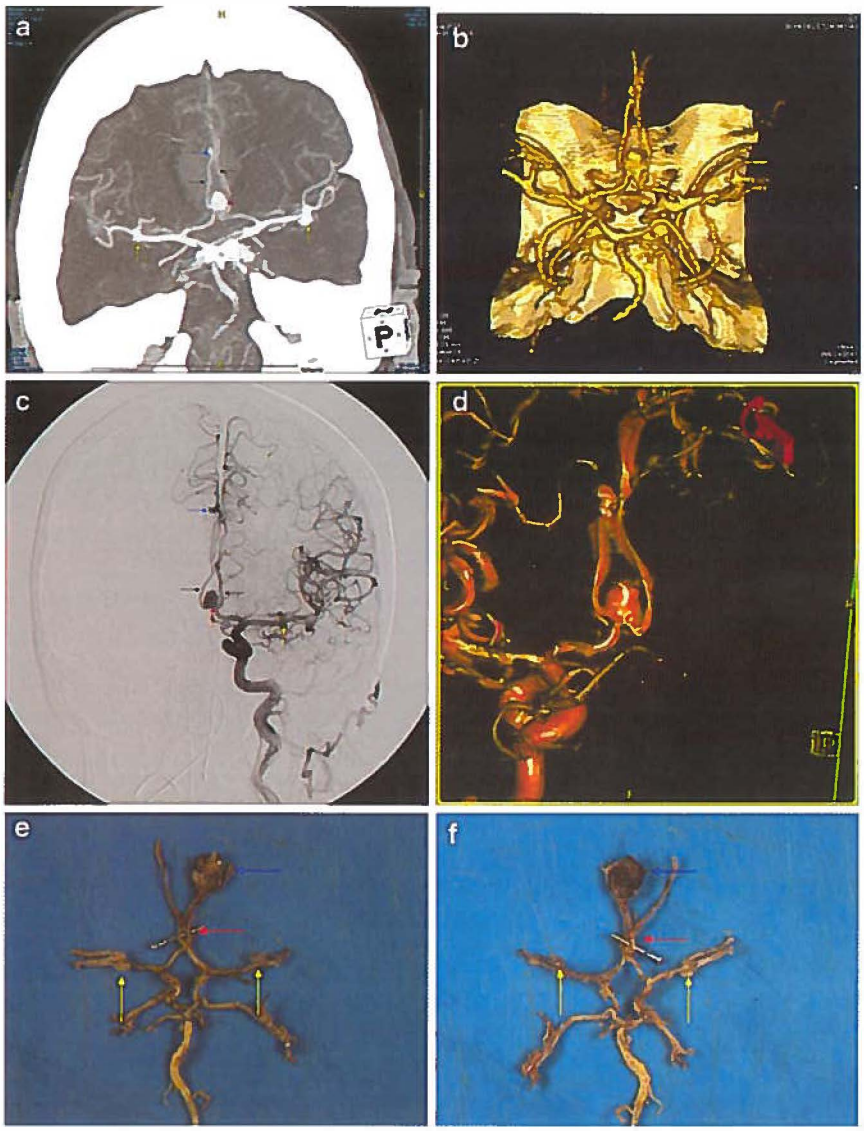

Figure 2: CTA and IA-DSA results in a 66-year-old woman with SAH Hunt and Hess grade III. CTA showed four aneurysms: an aneurysm of the anterior communicating artery (AComA) and two bilateral aneurysms of the middle cerebral artery and one aneurysm of the pericallosal artery. The aneurysm of the AComA was regarded as symptomatic at the time of initial SAH and its CTA-proven morphology showed both coiling and clipping to be a difficult challenge. Coiling of the AComA aneurysm was tried on the 2nd day. The session was aborted because the neck of the aneurysm was broad and the aneurysm incorporated both A2 segments. Unfortunately, rebleeding occurred after coiling. The morphology of the aneurysm excluded complete occlusion by clipping on the 25th day. In the postoperative course again two rebleedings occurred and the patient died. At autopsy a ruptured pericallosal aneurysm was seen more distal to the clipped aneurysm. **a** Coronal MIP CTA; **b** volume-rendered CTA; **c** AP view DSA, selective catheterization of left internal carotid artery; **d** volume-rendered IA-DSA; **e**, **f** autopsy (*red arrow* anterior communicating artery aneurysm, *yellow arrow* middle cerebral aneurysm, *black arrow* anterior cerebral artery (A2 segment), *blue arrow* pericallosal artery aneurysm.

The majority of patients were treated within 3 days of SAH ($n=99$, 75%). Of the 133 CTA-positive patients, 78 (59%) were coiled and 55 (41%) were clipped. Treatment conversion was needed in three patients, in two because of difficult aneurysm morphology and in one because of rebleeding during surgery (dura not yet opened). In two patients treatment conversion was necessary because of incorrect treatment selection based on CTA (Figure 2).

All ruptured intracranial aneurysms were confirmed by surgery or endovascular treatment. In two patients IA-DSA was performed after surgical treatment for evaluation of coiling of asymptomatic aneurysms.

In four patients (3%) a fatal rebleeding occurred during follow-up, in one patient soon after complete occlusion of the aneurysm with coiling, in one patient on the 5th day after clipping, in one patient 2 weeks after incomplete occlusion of the aneurysm with coiling and in one patient almost 3 years after clipping. In all patients the blood distribution of the rebleeding was the same as that of the primary SAH. Although permission was not granted for an autopsy in two patients, it was considered most probable that the rebleeding was caused by the treated aneurysm. In two patients an autopsy was performed. In one a ruptured pericallosal aneurysm was seen, 1.5 cm more distal from the clipped anterior communicating artery aneurysm which was regarded as symptomatic at the time of initial SAH (Figure 2), and in the other a haematoma surrounding a prepontine cavernous haemangioma and an endovascular treated dissecting aneurysm of the basilar artery were seen.

The presence of CT-diagnosed additional asymptomatic aneurysms was checked in 22 patients. These patients had 29 aneurysms. Five aneurysms were confirmed at surgery and subsequently clipped, 5 aneurysms were checked with IA-DSA and subsequently coiled and 19 aneurysms were confirmed with IA-DSA. Three aneurysms in three patients were not verified. In four patients five asymptomatic aneurysms were false-negative on CTA. All were smaller than 5 mm. Four aneurysms were diagnosed with IA-DSA during an embolization session, one of them was also embolized. Another aneurysm was considered a vessel loop of the middle cerebral artery on CTA. However, an aneurysm of the middle cerebral artery was seen during surgery of a ruptured aneurysm of the anterior communicating artery. Clipping of the aneurysm of the middle cerebral artery was also performed.

Inconclusive CTA result

In 31 patients IA-DSA was performed because of inconclusive CTA results. The indications for IA-DSA examination are presented in Table 5. An overview of the results in patients in this category is presented in Figure 1.

Table 5: Indications for IA-DSA examination in 31 patients

Indication		No. of patients
More information required regarding location and orientation	Symptomatic aneurysm	10
	Asymptomatic aneurysm	2
More information required regarding presence of intraaneurysmal thrombus in symptomatic giant aneurysm		2
Differentiation between asymptomatic and symptomatic aneurysm		1
Differentiation between infundibulum, vessel loop and aneurysm		5
Fisher grade IV SAH		1
Arterial vasospasm		3
Discrepancy between diagnosed intracranial aneurysm and distribution of blood		1
Incomplete angiography of circle of Willis		3
Overprojection of venous structures		1
Variance of normal intracranial vessel anatomy		1
Amalgam artefacts		1

In 11 patients (35%) IA-DSA confirmed the results of CTA. In 17 patients (55%) IA-DSA was able to give further diagnostic information required for a correct patient selection for therapy. In two patients (6%) no additional diagnostic information could be obtained from IA-DSA. In both patients vasospasm of a vertebral artery resulted in an inconclusive CTA, but also excluded selective catheterization with IA-DSA. A second CTA was negative in both patients. In one patient (3%) treatment selection was based on a false-positive IA-DSA. CTA was inconclusive because of amalgam artefacts in the region of the right posterior inferior cerebellar artery (PICA). An aneurysm of the right PICA was diagnosed on the first IA-DSA. A second IA-DSA was performed with the intention of coiling. However, with additional views the aneurysm turned out to be a vessel loop.

No aneurysms were found in ten patients (four nonperimesencephalic SAH, four with perimesencephalic SAH and two negative on unenhanced CT). In 20 patients 20 ruptured intracranial aneurysms and 6 additional unruptured aneurysms were found. In one patient only an asymptomatic aneurysm was diagnosed (Tables 1, 2, 3, and 4). Of the ruptured aneurysms, 12 were clipped and 6 were coiled. Two ruptured aneurysms were clipped after failure of endovascular treatment. Two asymptomatic aneurysms were clipped.

Negative CTA result

In 60 patients CTA was considered negative. An overview of the results in this category of patients is presented in Figure 1. Of these 60 patients, 13 (22%) had negative findings on unenhanced CT, and 47 (78%) had positive findings on unenhanced CT, and of the latter 30 had a perimesencephalic blood distribution and 17 had a nonperimesencephalic SAH.[16] In 11 (85%) of those with negative

findings on unenhanced CT, one IA-DSA was done. In one patient a second IA-DSA was performed and in one patient a second CTA was performed. No rebleedings occurred. CTA was true-negative in all these patients.

In 21 patients (70%) with perimesencephalic SAH, IA-DSA was performed once, and in one of them CTA was repeated once and in one CTA was repeated twice. In eight patients IA-DSA was repeated once and in one patient IA-DSA was repeated twice. In this category CTA was true-negative in all these patients. No rebleedings occurred.

In nine patients (53%) with nonperimesencephalic SAH IA-DSA was performed once, and in two of them a follow-up MRA was done and in one CTA was repeated. In seven patients a second IA-DSA was done. In one patient IA-DSA was repeated twice. In five patients (29%) with nonperimesencephalic SAH, CTA was false-negative (Tables 1 and 2). In one of these patients only IA-DSA was able to detect a 3-mm ruptured aneurysm of the anterior communicating artery, and in the other four a rebleeding occurred despite an initially negative CTA and IA-DSA. Repeat angiography was performed in three patients: a ruptured aneurysm was shown by CTA in two and by IA-DSA in one. One patient died before repeat angiography. Two patients were treated successfully. One patient died before treatment due to the direct effect of the rebleeding. The explanations for false-negative results were interpretation mistakes (two aneurysms recognized retrospectively on CTA and IA-DSA), and haematoma demonstrated on CTA surrounding and compressing the aneurysm leading to interpretation error on both CTA and IA-DSA in one patient and on only CTA in another (IA-DSA showed the aneurysm); the findings were uncertain in one patient.

Statistical analysis

The diagnostic value of both 16- and 64-slice CTA are outlined in Tables 6 and 7. A comparison of the results of 16-and 64-slice CTA is presented in Table 8. No statistically significant differences were found.

Table 6: Diagnostic value of CTA in ruptured aneurysms

True positive	132 patients
False positive	1 patient
True negative	55 patients
False negative	6 patients
Positive predictive value	99%
Negative predictive value	90%
Sensitivity	96%
Specificity	98%
Accuracy	96%

Table 7: Diagnostic value of CTA in additional aneurysms

Total number detected with CTA	25 patients (32 aneurysms)
Presence checked	22 patients (29 aneurysms)
True positive	22 patients (29 aneurysms)
False positive	0
True negative	120 patients[a]
False negative	4 patients (5 aneurysms)
Positive predictive value	100%
Negative predictive value	97%
Sensitivity	85%
Specificity	100%
Accuracy	97%

[a]Including 60 CTA-negative patients and 60 CTA-positive patients. Of the CTA-positive patients, 44 were not examined with IA-DSA as standard control.

Table 8: Comparison of results of 16- and 64-slice CTA for detection of intracranial aneurysms

		16-slice (n = 140 patients)	64-slice (n = 84 patients)
CTA result	Positive	74	59
	Negative	45	15
	Inconclusive[a]	21	10
Ruptured aneurysms	True positive	73	59
	False positive	1	0
	True negative	42	13
	False negative	4[b]	2
	Positive predictive value (%)	99	100
	Negative predictive value (%)	91	87
	Sensitivity (%)	95	97
	Specificity (%)	98	100
	Accuracy (%)	96	97
Unruptured aneurysms	Total number on CTA	12 (15 aneurysms)	13 (17 aneurysms)
	Presence checked	11 (14 aneurysms)	11 (15 aneurysms)
	True positive	11 (14 aneurysms)	11 (15 aneurysms)
	False positive	0	0
	True negative	75[c]	45[d]
	False negative	1 (1 aneurysm)	3 (4 aneurysms)
	Positive predictive value (%)	100	100
	Negative predictive value (%)	99	94
	Sensitivity (%)	92	79
	Specificity (%)	100	100
	Accuracy (%)	99	95

[a]Patients with an inconclusive result were not included in the statistical analysis.
[b]Including one CTA-positive patient.
[c]Including 45 CTA-negative patients and 30 CTA-positive patients. Of the CTA-positive patients, 31 were not examined with IA-DSA as standard control.
[d]Including 15 CTA-negative patients and 30 CTA-positive patients. Of the CTA-positive patients, 13 were not examined with IA-DSA.

DISCUSSION

Our primary aim was to assess whether CTA is useful clinically in planning and performing clipping or coiling, especially in the acute phase in ruptured intracranial aneurysms, without recourse to IA-DSA. We demonstrated that it was possible to treat more than half of all patients with a ruptured intracranial aneurysm using only CTA. By avoiding conventional angiography, it was possible to streamline the management of ruptured aneurysm during the acute phase. Further, 3D-CTA was able to help in deciding whether to clip or to coil; in only two patients was treatment conversion needed due to incorrect treatment selection based on CTA.

We found 3D-CTA to be a simple, reliable, quick and minimally invasive imaging modality that reduces the risk of complications caused by conventional angiography and reduces the delay between the patient's arrival at the hospital and treatment, leading to diminished rebleeding. Matsumoto et al. analyzed the rate of rebleeding of ruptured aneurysms during CTA and conventional angiography, and found 0% (none of 160 patients) for CTA and 1.5% (5 of 317 patients) for conventional angiography.[17] In patients with a ruptured aneurysm and intracerebral haemorrhage CTA saves time when aiming for a fast clot removal. Another advantage is that the radiation dosage is low compared to IA-DSA (1.0 mSv at 200 mAs with the CTA Siemens Sensation 16 and 1.8 mSv at 380 mAs with the CTA Siemens Sensation 64 compared with 3.5-6.5 mSv with conventional angiography). Furthermore, the cost of CTA is one-fourth that of conventional angiography.

Several other studies assessing whether CTA may serve as the sole imaging method for the preoperative work-up of patients with ruptured intracranial aneurysms have been published.[17-26] An overview of these previous studies is presented in Table 9. There is a wide variation in the percentage of patients who have had their symptomatic aneurysms treated based on CTA. This may be influenced positively by the very high aneurysm prevalence and the subsequent very low negative rates of CTA in some studies.[22,23,25] In other studies patients with a negative CTA were not enrolled at all.[17,20] In general, a mean of 15–20% negative angiographies after SAH is accepted.[27] The present study showed a high negative rate for CTA. This may reflect the good awareness of the diagnosis SAH in first-line and second-line health-care and the good access to CTA when the diagnosis SAH is considered. Furthermore, the wide variation in CTA-based treatment may be partially explained by differences in hardware and software used by each group, the rate of technical failures in performing CTA, scanning parameters set for screening the circle of Willis and more peripheral vessels, the experience and scrutiny of the neuroradiologist evaluating each CTA and the willingness of the neurosurgeon and neurointerventional radiologist to rely on CTA alone in each individual case.

In the present study CTA was false-negative in 8% of patients. The risk of rebleeding after a negative initial CTA was 7%. All false-negatives were in patients with a nonperimesencephalic blood

Table 9: Presentation of previous studies and present study

Study	No. of patients	CTA-positive			CTA-negative		CTA inconclusive or no CTA-based treatment
		Total patients	CTA-based treatment	True-positive CTA	Total patients	True-negative CTA	Total patients
21	87	46 (55%)	44 (96%)	44 (100%)	15 (17%)	6 (60%)	26 (30%)
22	109	88 (81%)	87 (99%)	87 (100%)	5 (5%)	5 (100%)	16 (15%)
23	84	62 (74%)	62 (100%)	62 (100%)	7 (8%)	0 (0%)	15 (18%)
19	90	45 (100%)	45 (100%)	45 (100%)	–	–	45 (50%)
18	150	61 (41%)	61 (100%)	60 (98%)[a]	24 (16%)	24 (100%)	65 (43%)
25	120	40 (33%)	40 (100%)	40 (100%)	13 (11%)	13 (100%)	67 (56%)
24	78	27 (35%)	27 (100%)	27 (100%)	20 (26%)	20 (100%)[b]	31 (40%)
17	100	93 (93%)	93 (100%)	93 (100%)	–	–	7 (7%)
20	96	87 (91%)	87 (100%)	86 (99%)[a]	–	–	9 (9%)
26	61	44 (72%)	44 (100%)	44 (100%)	15 (25%)	14 (93%)	2 (3%)
Present study	224	133 (59%)	133 (100%)	132 (99%)[a]	60 (27%)	55 (92%)	31 (14%)

[a]One false-negative and one false-positive ruptured aneurysm in one patient.
[b]In five patients with perimesencephalic SAH, IA-DSA as the gold standard control was not performed.

distribution, giving a false-negative rate of 29% and a risk of rebleeding of 24%. It seems unlikely that the false-negative rate of initial CTA and the risk of rebleeding despite a negative initial CTA in patients with a nonperimesencephalic SAH might be influenced negatively by the use of CTA as the first diagnostic tool. Firstly, in all patients with a rebleeding, repeat IA-DSA was also false-negative. Secondly, repeat angiography with CTA performed after a rebleeding still demonstrated an aneurysm. Furthermore, the findings of other studies using IA-DSA as the first diagnostic tool were similar. In the study by Urbach et al. in 67 patients with a negative initial angiogram after SAH, four ruptured aneurysms were revealed by repeat angiography.[28] Three patients presented with a nonperimesencephalic SAH and one presented with a perimesencephalic SAH. In the study by Bradac et al., 60 of the 440 patients presenting with spontaneous SAH had a negative angiogram.[29] A second angiogram performed 1-4 weeks later revealed a ruptured aneurysm in 5 of the 40 patients. Of these patients, 3 had a second SAH. In all patients a nonperimesencephalic blood distribution was seen on CT.

Because in the present study some aneurysms could be correctly identified retrospectively, we suggest that if, under strong clinical suspicion of a ruptured aneurysm, the CTA is reported as normal, the study should be reviewed by a second neuroradiologist before proceeding to repeat angiography. It is essential to perform a review of axial raw source images. Next, we recommend repeat CTA or IA-DSA when the initial CTA is negative in patients with a nonperimesencephalic SAH. There is no consensus about the time interval for repeat angiography. In practice, the guideline is

to repeat angiography after several days to months. The substantial risk of rebleeding in patients with an aneurysmal pattern of haemorrhage in the present study indicates that some cerebral aneurysms are occult on initial CTA. Several factors may explain this finding. Most importantly, there is a learning curve in assessing aneurysms on CTA. Pedersen et al. reported an increase in sensitivity from 88% to 94% after 1 year's experience.[30] Small aneurysms can be missed when using CTA. CTA had a sensitivity of 50% for aneurysms <2 mm in the study of Wintermark et al.[13] Distal pericallosal and PICA aneurysms can be missed when restricting the area of coverage to the proximal circle of Willis.[31 34] Thrombosis of the neck of the aneurysm or of the entire sac is another possible reason.[23] Perianeurysmal blood or haematoma may reduce lesion conspicuity.[34] Aneurysms may be mistaken for vascular infundibula (persistent fetal nonaneurysmal dilatation of the proximal vessel) of the posterior communicating or anterior choroidal artery origins if a vessel cannot be identified arising from them.[35] Aneurysms may masquerade as tight vascular loops if the MIP thickness is wide (>3 mm).[34] In patients with multiple intracranial aneurysms large aneurysms may obscure smaller ones on the CT reconstruction.[33] Aneurysms close to bone (e.g. carotid siphon, ophthalmic and posterior communicating artery) may be overlooked when relying on surface-rendering and volume-rendering techniques or using MIP with bone editing.[32 34 36 38] Aneurysms located within or close to the cavernous sinuses are easy to overlook unless thin-section axial and coronal MIP images are reviewed on a slightly wider window width.[9]

In patients with a perimesencephalic SAH the chance of finding a posterior fossa aneurysm is low: 2.5–5%.[39-40] Nonaneurysmal perimesencephalic haemorrhage carries no risk of vasospasm and rebleeding and has been shown to follow a benign course with an excellent prognosis.[41] The chance of finding an aneurysm in 5% of patients has to be weighed against the risk of complications from angiography imposed upon the remaining 95% of patients. CTA has a high accuracy for diagnosis of vertebrobasilar aneurysms and of intracranial aneurysms in general.[9-13 42] In the present study, in patients with a perimesencephalic SAH and a negative initial CTA, no rebleedings occurred and CTA was true-negative in all. Similarly, in the prospective study of Huttner et al., 69 patients with a perimesencephalic SAH had a negative initial CTA and IA-DSA.[43] A repeat IA-DSA was performed in 38 patients (55%). None of the repeat IA-DSAs showed any additional distinctive features with respect to the first IA-DSA. It therefore seems practical and safe to perform CTA as the first diagnostic tool and to omit repeat angiography if CTA is negative. A formal decision analysis based on these observations confirmed that a strategy where CTA is performed and not followed by conventional angiography, if negative, results in a better utility than a strategy of CTA followed by conventional angiography or of conventional angiography as primary investigation.[44]

According to the results of the present study, it seems important to distinguish the two patterns of SAH on CT. The CT criteria of perimesencephalic bleeding have been defined.[40] Different data show that experienced radiologists can accurately discriminate between a perimesencephalic and

nonperimesencephalic SAH.[12,40,45] Early CT within 3 days is necessary for reliable assessment of the pattern of haemorrhage.[12,40,46]

A criticism of this study might be that patients treated with endovascular coiling underwent IA-DSA as part of the endovascular procedure and thus should not be counted in the analysis of efficacy of the prospective protocol. However, a shift in management of ruptured intracranial aneurysm from surgery to endovascular treatment has appeared.[47] Endovascular treatment is replacing clipping. The use of CTA as the initial investigation for cerebral aneurysms may offset some of this increased workload whilst also improving workflow.

In conclusion, in this evaluation of the use of 16-row and 64-row multislice CTA in the management of ruptured intracranial aneurysms, we demonstrated that CTA can be used as the first-line diagnostic modality for the management of SAH patients. In CTA-negative patients IA-DSA provided no or marginal added value. IA-DSA is not needed in patients with negative CTA and classic perimesencephalic SAH. Repeat IA-DSA or CTA should still be performed in patients with a nonperimesencephalic SAH, due to false-negative CTAs and IA-DSAs in this patient group. The remaining true indication for IA-DSA was in patients with an inconclusive CTA result. In more than half of those IA-DSA provided relevant new diagnostic information.

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Chapter 4

Magnetic resonance angiography in the selection of patients suitable for neurosurgical intervention of ruptured intracranial aneurysms

H. E. Westerlaan[1], A. M. van der Vliet[1], J. M. Hew[2], J. D. M. Metzemaekers[3], J. J. A. Mooij[3] and M. Oudkerk[1]

[1]Department of Radiology, University Hospital, Groningen, The Netherlands
[2]Department of Radiology, Langeland Hospital, Zoetermeer, The Netherlands
[3]Department of Neurosurgery, University Hospital Groningen, Groningen, The Netherlands

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ABSTRACT

This study was aimed at establishing whether magnetic resonance angiography (MRA) can be applied to planning and performing surgery on ruptured intracranial aneurysms, especially in the early phase, without recourse to intra-arterial digital subtraction angiography (IA-DSA). From February 1998 to August 2001, in all patients presenting with a subarachnoid hemorrhage, MRA was performed first. A three-dimensional time-of-flight MRA protocol with T2-weighted coronal and axial images was used. If MRA demonstrated an aneurysm, surgery was undertaken. IA-DSA was limited to patients with negative or inconclusive MRA findings. We compared MRA images with operative findings in positive patients and with IA-DSA in negatives. IA-DSA was considered the gold standard when MRA findings were inconclusive. In this study, 205 consecutive patients (mean age 52.7 years, 69% women) were included. In 133 patients (64.9%) MRA demonstrated an aneurysm, directly followed by neurosurgical intervention. In 33 patients (16.1%) MRA findings were categorized as inconclusive. In 39 patients (19.0%) MRA results were negative. No false-negative ruptured aneurysms were selected by MRA. In only one patient surgical intervention was performed based on false-positive MRA findings. MRA can replace IA-DSA as a first diagnostic modality in the selection of patients suitable for surgical treatment of ruptured intracranial aneurysms.

INTRODUCTION

Intracranial aneurysms are acquired lesions that are most commonly located at the branching points of the major arteries coursing through the subarachnoid space at the base of the brain.[1] Autopsy and angiographic studies indicate that between 3.6% and 6% of the population harbor an intracranial aneurysm.[2]

Subarachnoid hemorrhage (SAH), mostly due to rupture of an intracranial aneurysm, has an incidence of 6–8 per 100,000 person years, peaking in the sixth decade of life and accounting for a quarter of cerebrovascular deaths.[3] Although the management of patients with ruptured intracranial aneurysms has passed through a phase of rapid evolution and modification, the overall morbidity and mortality rates following aneurysm rupture remain high.[4,5] One of the most important objectives in the management of aneurysmal SAH is to prevent aneurysm re-bleeding and delayed cerebral ischemia caused by arterial vasospasm. Most neurosurgeons, therefore, justify early detection and surgical obliteration of any aneurysm, especially in patients in a good clinical state.[6]

Because of its unsurpassed resolution, intra-arterial digital subtraction angiography (IA- DSA) is the gold standard in diagnosing intracranial aneurysms. IA-DSA has been the imaging modality of choice for many years, because it is reliable in the detection of aneurysms or other sources of hemorrhage, and because it can be used as a treatment tool. The latter is particularly advantageous since the recent publication in Lancet of results from the international subarachnoid aneurysm trial (ISAT)[7], showing that endovascular treatment should be the first line of treatment for ruptured cerebral aneurysms that have a suitable morphology.

Despite these advantages of IA-DSA and despite modern advances in the performance of cerebral angiography, the risk of neurological complications associated with this procedure is not negligible.[8-21] With the development of three-dimensional (3D) magnetic resonance angiography (MRA) and computerized tomographic angiography (CTA), the absolute reliance on IA-DSA for aneurysm detection and surgical planning is changing. Both diagnostic modalities have been used successfully as an alternative to IA-DSA for the surgical management of aneurysmal subarachnoid hemorrhage.[22-26] In the present study, we investigated whether (a) 3D time-of-flight (TOF) MRA is a reliable assessment tool in detecting or ruling out ruptured intracranial aneurysms; and whether (b) 3D TOF MRA can replace IA-DSA in the selection of patients suitable for surgical treatment of ruptured intracranial aneurysms. Furthermore, we checked the clinical outcome of the patients with an MRA-based diagnosis of ruptured aneurysm.

MRA was used as the initial imaging tool in acute SAH for several reasons. During the study period, we had no ability to perform CTA at our department. Furthermore, our study was performed before the results of ISAT were published, and it was not yet known that coiling is the first line of treatment

for ruptured aneurysms, which favors first performing IA-DSA instead of MRA. Besides that, in our hospital most ruptured intracranial aneurysms are still treated surgically, and endovascular coiling is restricted to a highly selected patient population, mainly patients with aneurysms of the basilar artery.

MATERIAL AND METHODS

Patient population

University Hospital Groningen is the reference center for intracranial aneurysm surgery for the northern provinces of the Netherlands. Starting in February 1998, all patients admitted to our hospital with an SAH consecutively underwent MR angiography as a first diagnostic tool. MRA was performed to select patients suitable for surgical clipping of a ruptured intracranial aneurysm. SAH was suspected on clinical grounds and confirmed by un-enhanced computed tomography (CT) and/or demonstration of blood and blood pigments by lumbar puncture. The study included 205 patients: 63 men and 142 women, with ages ranging 10–79 years (mean 52.7 years (+/- 12.4 SD). The clinical condition at admission of each patient presenting with SAH was categorized according to the original Hunt and Hess grading system.[27] When the condition of the patient changed between admission and operation, we adopted the condition just before surgery for the evaluation (Table 1).

Table 1: Clinical status of 205 consecutive patients

Clinical characteristic	Value
Age (years)	
Range	10–79
Mean (SD)	52.7 (12.4)
Sex	
Male	63
Female	142
Hunt and Hess grade	
1	108
2	49
3	45
4	2
5	1

Treatment protocol

All patients were under continuous observation in a neurosurgical intensive care unit until a few days after surgery. Medical consultations for perioperative care were obtained. While awaiting surgery, patients with an SAH were treated with calcium channel blockers. The presence of arterial vasospasm, suspected clinically and confirmed by transcranial Doppler examination, was an indication for triple-H therapy (induced hypervolemia, hemodilution and hypertension), preferably starting after surgery.

CT of the head was performed at admission and repeated after any clinical deterioration. All patients underwent MR angiography within 3 days after admission. If necessary, appropriate sedation was administered before the MR study. IA-DSA was restricted to patients in whom MRA was inconclusive or negative.

The patients were operated for clipping of the aneurysm as soon as possible after the diagnosis was established. Delayed operation was preferred for patients with poor clinical grading or for patients already with signs of vasospasm. Some of the late operations were due to delayed referral to our hospital. In patients with Hunt and Hess grades 3 and 4 and a large life-threatening intracerebral hematoma, an emergency operation was performed. The quality of the recovery in patients with an MRA-based diagnosis of ruptured aneurysm was estimated using the Glasgow Outcome Scale (GOS) at 2 months follow-up.[28]

Image acquisition

The T2 and the MRA sequence were carried out on a 1.5-T Siemens Magnetom Vision. The T2-TSE slices (TR (repetition time) / TE (echo time) = 3,500/22-90 ms) in axial and/or coronal planes were constructed with a 512×512 matrix, followed by the 3D-TOF MR angiograms (FISP 3D); TR/TE = 35/6.4 ms; flip angle 20°; matrix=160×512; magnetization transfer (MT) prepulse; time for acquisition (TA) =6.44 min, 24 slices with 1.5 mm effective thickness. No contrast was used. Spin-echo T1-weighted images were also obtained.

The intra-arterial DSA studies were produced on a digital angiography system (Siemens Multiskop with InfiMed image processing) with a 512×512 pixel matrix. Selective three-or four-vessel angiography using a standard projection format (anteroposterior, lateral and reverse-oblique) was performed initially and additional views were performed, if required, to identify the parent vessel and aneurysm neck more clearly. The amount of contrast medium (Omnipaque 300 in a 1:1 dilution) was 12 ml for each series, and the injection rate 10 ml/s when the tip of the catheter was placed proximal to the carotid bifurcation. Injections into the vertebrobasilar system had a rate of 8 ml/s to an overall amount of 8 ml.

Viewing and postprocessing

In order to ensure reproducibility, visualizations of MR data were produced by two experienced neuroradiologists with considerable experience in image postprocessing and who had been informed of the initial CT results, including the sites of SAH and degree of hemorrhage. Both workstation displays and hard copy images were used. Postprocessing consisted of 60° maximum intensity projections (MIP) at six increments for 360° around the head, in both a left-to-right rotation and a head-to-foot rotation. MIP reconstructions were made of the whole data set without editing. Source images were viewed on a routine basis.

The presence of an aneurysm, its site and the parent artery were analyzed. If multiple aneurysms were detected, the usual criteria were applied in an attempt to decide which aneurysm was responsible for the hemorrhage. These criteria included the CT findings (distribution of blood) and the size and irregularity of the aneurysm.

We compared 3D MRA images with surgical findings in positive cases. In negatives, we compared 3DTOF MRA findings with IA-DSA results. If MRA results were considered indeterminate, IA-DSA was the gold standard in the detection or exclusion of aneurysms. IA-DSA was performed and evaluated by the same neuroradiologists. Both the MRA and IA-DSA diagnosis was based on consensus between the two neuroradiologists. All diagnostic findings were discussed with the neurosurgeons, who decided which information was sufficient for them.

RESULTS

In 205 patients the MRA results were categorized into: proven aneurysm (*n*=133 (64.9%)); indeterminate (*n*=33 (16.1%)); or negative for aneurysm (*n*=39 (19.0%)). MRA was classified as inconclusive if the neuroradiologist was not certain about the MRA diagnosis after discussion with the neurosurgeon.

Positive MRA result

In the MRA-proven aneurysms, 133 ruptured aneurysms and 26 associated un-ruptured aneurysms were diagnosed. The distribution of the aneurysm location and size is shown in Table 2. The preoperative and peroperative findings are summarized in Table 3.

Surgery confirmed 132 ruptured aneurysms that were predicted by MRA, while one proved to be false positive. The patient in whom surgery was based on false-positive MRA findings, presented in Hunt and Hess grade 1 and had had a warning leak a few weeks prior to admission to the hospital. Lumbar puncture demonstrated blood pigments, while CT was negative. Although an aneurysm of the middle cerebral artery was diagnosed on the MR images, a tortuous loop was demonstrated at surgery (Figure 1). Additionally, no surrounding blood or other bleeding source was shown. No IA-DSA examination was performed postoperatively.

At surgery, we checked the presence of 15 of the 26 associated un-ruptured aneurysms detected on MRA. The remaining 11 aneurysms were not verified, because in these patients the surgical approach for the ruptured aneurysms was not suited for the un-ruptured aneurysms. Two aneurysms appeared false positive on MRA (two anterior communicating arteries). One of these lesions proved to be an infundibular dilatation, which was not suitable for surgical clipping. During surgical exploration of the other lesion, torsion of an adhesive anterior communicating complex was shown, with absence of an aneurysm. Two false-negative intracranial aneurysms (one middle

Table 2: Distribution of cerebral aneurysms in 205 patients

Site	Number of aneurysms MRA positive	MRA inconclusive	MRA negative
Anterior communicating artery	62	18	-
Middle cerebral artery	49	6	-
Posterior communicating artery	27	8	2
Internal carotid artery	9	8	-
Anterior cerebral artery	2	0	-
Posterior cerebral artery	0	1	-
Ophthalmic artery	5	1	-
Anterior choroidal artery	1	2	-
Posterior inferior cerebellar artery	1	0	-
Basilar artery	1	0	-
Vertebral artery	1	0	-
Superior cerebellar artery	0	1	-
Pericallosal artery	1	0	-
Size (mm)			-
<10	146	39	2
10–15	11	4	-
15–24	2	2	-
>25	0	0	-

Table 3: Comparison of preoperative and peroperative findings distributed over two subgroups

	Ruptured aneurysms	Unruptured aneurysms	Total
Detected	**133**	**26**	**159**
Verified (%)	133 (100)	15 (58)	148
Surgically clipped	132	15	147
Correctly predicted	132	13	145
False positive	1	2	3
False negative	0	2	2

cerebral artery and one anterior cerebral artery) were found in two patients. Both aneurysms were smaller than 3 mm in diameter.

Indeterminate MRA result

In 33 patients IA-DSA was performed because of inconclusive MRA findings. In the majority of these patients, IA-DSA was performed, because more information was required regarding the presence or the relative location and orientation of an aneurysm within the skull (Table 4). It is known that the quality of the MRA examination can be degraded because of the inability of the patient to cooperate. At our department, where anesthetic facilities are well-organized, MRA can even be performed on critically ill patients. In only two patients IA-DSA was performed because of considerable motion artifacts on MRA. Because no problems were noticed in even potentially risky patients (Hunt and Hess grades 2 and 3), we have not stated the number of patients that required sedation or anesthesia for performing the MRA examination.

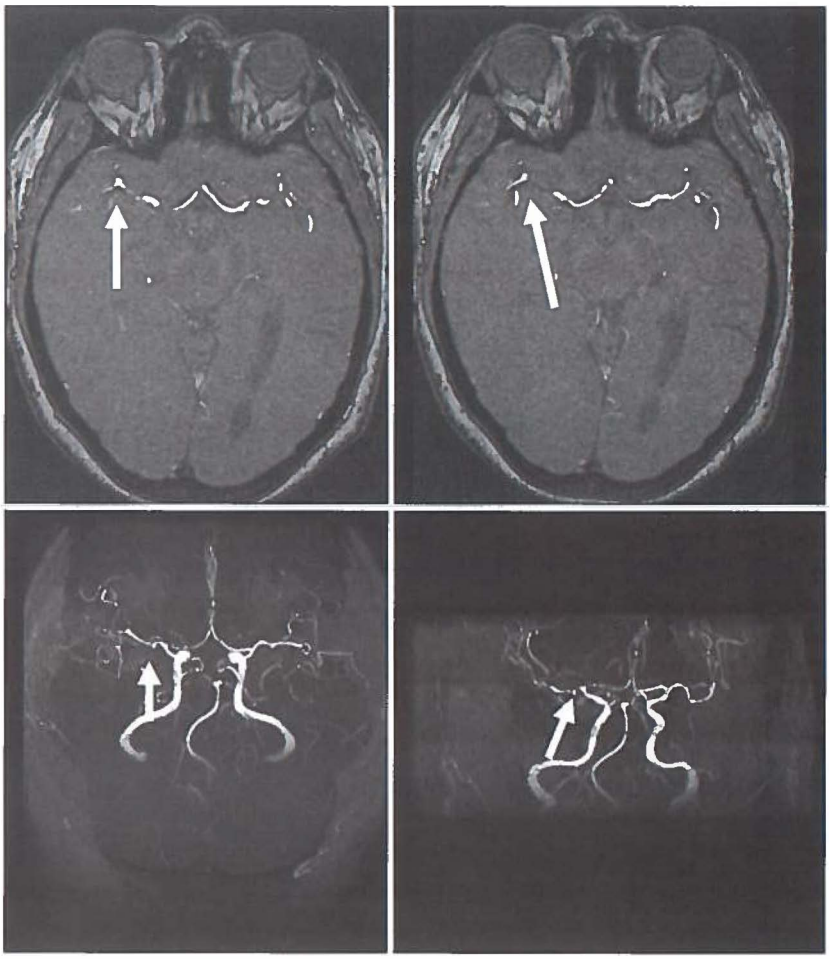

Figure 1: False-positive MRA findings. A ruptured aneurysm on the right side of the middle cerebral artery (*arrow*) was diagnosed by MRA. At surgery a tortuous loop was seen. *Upper right* and *upper left* are source images. *Bottom right* and *bottom left* are MIP reconstructions.

In 24 patients (73%) IA-DSA confirmed the results of MRA. In five patients there was doubt about the presence of an aneurysm (three located on the posterior communicating artery, one on the anterior communicating artery and one on the anterior choroidal artery). Subsequent IA-DSA examination was negative. In four patients MRA had false-negative results (two aneurysms on the sinus cavernosus, one on the anterior choroidal artery and one on the posterior communicating artery). The false-negative aneurysms were all smaller than 5 mm and asymptomatic. Two of them were treated surgically.

IA-DSA showed 28 ruptured and 17 associated un-ruptured aneurysms, confirmed at surgery in 28 patients and was negative in the remaining five patients (Table 2).

Table 4: Indications for IA-DSA examination in 33 patients

	Number
Location and orientation of aneurysm	18
Presence of arterial vasospasm	6
Differentiation infundibulum, vessel loop and aneurysm	5
Movement artifacts	2
Metallic artifacts	1
Extravascular clots	4
Intra-aneurysmal thrombus	1

Note that more than one indication was possible in a patient

Negative MRA result

In the 39 negative cases, IA-DSA was performed as the gold standard, which confirmed the MRA findings in 37 patients (Table 2). In one patient, IA-DSA showed an aneurysm of the posterior communicating artery, presumably the aneurysm that had bled. However, subsequent surgical intervention resulted in a negative exploration. During surgery a small loop of the posterior communicating artery was shown. Additionally, no surrounding blood or other bleeding source was seen.

In another patient, an aneurysm of the posterior communicating artery, which was not considered responsible for the SAH, was diagnosed with IA-DSA. The presence of this asymptomatic aneurysm was checked and confirmed with surgery 2 months after the SAH.

Clinical outcome of patients with an MRA-based diagnosis of ruptured aneurysm

The preoperative Hunt and Hess grades and the clinical outcome as expressed by the GOS are outlined in Table 5. In the majority of patients (n=128) the follow-up was in the University Hospital Groningen. In the remaining five patients the GOS was determined at time of discharge from the hospital, because follow-up was lost (n=3) or performed in another hospital (n=2). Most patients (77%) had been treated within 3 days after the last bleeding. At follow-up 86.5% of patients were in a favorable condition (in Table 5, indicated by "good recovery" and "moderately disabled"). The mortality rate was 4.5%, and the morbidity rate ("severely disabled" and "vegetative state"), 9.0%. There were no complications associated with the performance of 3D MRA.

Vasospasm as a postoperative complication was the main cause of serious failures in the group of patients that was severely disabled at follow-up. Six patients died: two due to fatal vasospasm; one due to arterial vasospasm and pneumonia; one due to carcinoma of the pancreas; one due to myocardial infarction and one due to pulmonary embolism. Permission for autopsy was refused in all six patients.

Table 5: Clinical outcome of 133 patients related to preoperative Hunt and Hess grade (*GR* good recovery, *MD* moderately disabled, *SD* severely disabled, *VS* vegetative state, *D* dead)

Hunt and Hess grade	GR	MD	SD	VS	D
1	45	10	4	0	2
2	16	10	3	0	1
3	16	16	4	0	3
4	0	2	0	0	0
5	0	0	1	0	0
Total cases (%)	115 (86.5%)		12 (9.0%)	0 (0)	6 (4.5%)

SUMMARY

MRA had a positive predictive value for detection of ruptured aneurysms for 99% (132/133), with surgery as the gold standard. The negative predictive value of MRA for ruling out ruptured aneurysms was 100%, with IA-DSA as the gold standard. In 16.1% (33/205) of the included patient population, the MRA was considered inconclusive, necessitating further diagnostic investigation by IA-DSA. In this category IA-DSA confirmed MRA in 73% of patients. No mortality or morbidity was associated with the performance of 3D MRA.

DISCUSSION

Imaging tools of intracranial aneurysms

IA-DSA is considered the gold standard for evaluating the intracranial vessels. However, this procedure is invasive and accompanied by radiation exposure and not without risk: cerebral embolus, dissection, rupture of cerebral arteries and hemorrhage, arterial vasospasm, or systemic complaints have been described.[13,21] The risk of complications accompanied by IA-DSA can be avoided if arteriography can be replaced by a reliable noninvasive imaging modality. The diagnostic accuracy of 3D CTA has been shown to be compatible with IA-DSA.[29-31] The results of the study of Matsumoto et al., who performed aneurysm surgery in the acute stage in patients with ruptured cerebral aneurysms by using 3D CTA, were encouraging.[26]

Recent blinded-reader studies have reported mean sensitivities of 63–93% for detection of intracranial aneurysms using 3D TOF MRA and/or MIP and mean specificities for exclusion of aneurysms of 92–100%.[32-38] When 3-5 mm was considered the critical size for detection, sensitivities increased to 86-100%.[34,35,38,39] Various reports examined the value of MRA with regard to patients with acute SAH.[40-43] The MRA in all these studies was read on an emergency basis by one or several radiologists and subsequently compared to the IA-DSA results, the latter serving as the reference standard. They established sensitivities for detection of ruptured aneurysms of between 81% and 100%. Wilcock et al. found the specificity to be 100%.[43] In the blinded multireader study of Jäger et al., IA-DSA was deliberately not chosen to represent the reference standard, and the clinical course

and surgical findings were used to explain significant differences between the readings of MRA and IA-DSA.[44] Analysis of the data showed that MRA was able to detect aneurysms not seen on IA-DSA. This finding had already been reported by Curnes et al.[45]

A distinct advantage of MRA is that views can be produced in an automated fashion by a technician after the patient has left the imager and can be supplemented by interactive viewing on a workstation, if necessary. MRA can be performed within 20 min, advancing early decision-making. At our department, where anesthetic facilities are well-organized, MRA can even be performed on critically ill patients.

MRA-based surgery of intracranial aneurysms

Unlike previous studies, we included all patients consecutively suitable for neurosurgical intervention as first treatment choice when a probable ruptured intracranial aneurysm was diagnosed by MRA. Only a few studies have been set up to establish whether satisfactory MRA images can be obtained to perform surgery on ruptured intracranial aneurysms without recurring to IA-DSA in the acute phase of illness. In the study of Keogh et al., 21 out of 30 patients for whom a diagnosis of an anterior midline aneurysm was made on MRA were selected to undergo surgery based on MRA images alone.[22] Sankhla et al. studied 51 patients presenting with SAH by MRA. The MRA results were considered satisfactory in 38 patients, and in 20 of them early surgical obliteration was possible based on MRA results.[23] Watanabe et al. performed surgery in 106 patients presenting with SAH, using 3D TOF and MIP.[24] In 48 patients (45.3%) the anatomy around the aneurysms was so typical that clipping was carried out without additional information from IA-DSA and/or computerized tomography angiography. In another study of Keogh et al., 122 patients presenting with SAH were considered for MRA studies.[25] Fifty-five of these patients showing aneurysms on MRA were clinically able to undergo early surgery, and their MRA images were considered satisfactory for surgical planning.

Implications of present study

Loop formation and overlap of vessels have been described as main causes of false-positive and false-negative interpretations.[25,35] In the present study, this diagnostic limitation of MRA led to two negative surgical explorations, of which one concerned a ruptured aneurysm. Furthermore, in five patients IA-DSA examination had to be performed, because MRA was unable to differentiate a tortuous loop or infundibular dilatation from an aneurysm. Review of source images or images from a selective (partial or target) MIP method, in which part of the source data is processed separately, may help to overcome these problems.[34] In one patient we also faced this diagnostic problem with IA-DSA examination. This has also been described earlier by others.[44,45]

In the present study MRA missed seven asymptomatic aneurysms that were smaller than 5 mm in

diameter. Two of these were discovered during surgery and subsequently clipped. Five aneurysms were diagnosed after IA-DSA examination, and three of them were also treated surgically. Decreased MRA signal intensity, which could be explained by stagnant flow near the aneurysm, may render small aneurysms invisible.[36] As mentioned before, 3 mm seems to be the threshold size for detection of aneurysms by MRA. However, asymptomatic aneurysms smaller than 3 mm are probably not important clinically.[46,47] More important, no ruptured aneurysms were missed. This result may suggest that a negative MRA in a patient presenting with acute SAH, and thus a high pre-diagnostic suspicion of ruptured aneurysm, is reliable and may replace IA- DSA.

In the present study, in 19% of patients MRA was considered inconclusive, mainly because more information was required regarding the presence or relative location and orientation of the aneurysm. This finding may be influenced by the learning curve of the neuroradiologists with the MRA technique, and, in the beginning, some uncertainty in neurosurgeons about performing surgery based on MRA results alone. In 73% of patients IA-DSA confirmed the MRA results.

The mortality (4.5%) and morbidity (9.0%) rates of the present study are beneficial and acceptable when compared with the results from the study of Edner et al., in which IA-DSA was routine in all cases.[48] In their series, favorable outcomes, as measured with the GOS at 6 months, were 82 out of 122 patients (67%), with 76% treated within 1 week after the last bleeding. The mortality and morbidity rates were16% and 17%, respectively.

Some comments can be made with regard to the present study. The prevalence of ruptured intracranial aneurysms in the total number of patients examined is 78% (160/205), which is comparable with other published data.[49] Hence, our study shows that MRA is useful for diagnosis in patients with a high suspicion of a ruptured aneurysm, i.e., in patients presenting with an SAH. The ability of MRA to correctly detect an aneurysm could change when MRA is used in patients with different pretest probabilities for an intracranial aneurysm. In our study, the radiologist had been informed of the initial CT results. CT findings, although not considered essential, can be of help in confirming the region of interest, by demonstrating the anatomical site of the intracerebral clot or concentration of subarachnoid blood.

In conclusion, in this study we included 205 patients with an SAH for MRA examination and investigated whether MRA could replace IA-DSA in the selection of patients suitable for surgical treatment of ruptured aneurysms. Only one false surgical indication was determined by MRA and no false negatives were selected by MRA. A minority of the MRA results were considered insufficient, making performance of IA-DSA necessary. We conclude, that IA-DSA can be replaced by 3D TOF MRA as the first diagnostic modality in the selection of patients suitable for clipping of ruptured aneurysms.

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Chapter 5

Time-of-flight magnetic resonance angiography in the follow-up of intracranial aneurysms treated with Guglielmi detachable coils

H. E. Westerlaan[1], A. M. van der Vliet[2], J. M. Hew[3], L. C. Meiners[1], J. D. M. Metzemaekers[4], J. J. A. Mooij[4] and M. Oudkerk[1]

[1]Department of Radiology, University Medical Center Groningen, The Netherlands
[2]Department of Radiology, University Medical Center of Nijmegen, The Netherlands
[3]Department of Radiology, Langeland Hospital, Zoetermeer, The Netherlands
[4]Department of Neurosurgery, University Medical Center Groningen, The Netherlands

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ABSTRACT

The purpose of this study was to evaluate time-of-flight magnetic resonance angiography (MRA) in the follow-up of intracranial aneurysms treated with Guglielmi detachable coils (GDCs). From January 1998 to January 2002 27 MRA and intra-arterial digital subtraction angiography (IADSA) examinations were analyzed for residual aneurysms and arterial patency following GDC placement. A total number of 33 intracranial aneurysms was analyzed, including 18 located in the posterior circulation. The MRA analysis was based on source images in combination with maximum intensity projections. The IADSA was used as the reference standard. Two aneurysms were excluded from evaluation, because of susceptibility artefacts from other aneurysms, which were clipped. Sensitivity and positive predictive values of MRA in revealing residual aneurysms were, respectively, 89% and 80%. Specificity in ruling out remnant necks and residual flow around coils was, respectively, 91% and 97%, with a negative predictive value of, respectively, 95% and 100%. Specificity and negative predictive value of MRA for arterial occlusion were, respectively, 87% and 100% for the parent arteries and, respectively, 85% and 100% for the adjacent arteries. MRA is a reliable diagnostic tool in the follow-up of GDC treatment, and it may replace IADSA in excluding residual flow around coils and aneurysmal necks and in ruling out arterial occlusion.

INTRODUCTION

In an attempt to improve the therapeutic management of patients harboring intracranial aneurysms, an endovascular occlusion technique using soft detachable platinum coils, based on two electrochemical principles: electrothrombosis and electrolysis, was introduced in 1990 by Guglielmi et al.[1-4] Since the introduction of Guglielmi detachable coils (GDCs) the endovascular method has extended its indications to include aneurysms that previously would have been treated by craniotomy and microsurgical clipping.[1,5-12] Another indication for GDC placement is treatment in the acute phase.[13-16] Early results are promising, both clinically in terms of safety and prevention of re-hemorrhage in the short term, and anatomically, in terms of obliteration of the aneurysmal lumen.[1,5,16]

Although the results with endovascular therapy appear good in the short-term follow-up period, long-term occlusion rates and protection against late rebleeding remain questionable. Results of studies on occlusion stability obtained by these coils have shown that reperfusion of the aneurysm may occur due to coil compaction or due to re-growth of a residual neck, even in cases of initial total occlusion.[17,21] In cases with neck remnants, legitimate concern regarding rebleeding exists and retreatment may be contemplated.[17,22,23]

Follow-up of intracranial aneurysms has been recommended after GDC treatment in order to evaluate the stability of the occlusion and possible subsequent need for further treatment. Usually, intra-arterial digital subtraction angiography (IADSA) is performed as follow-up examination. However, a non-invasive diagnostic modality is preferable. After embolization with GDCs there is a low risk of rebleeding (1–4%), and multiple follow-up examinations are therefore required.[7,10,16] Substitution with magnetic resonance angiography (MRA) may offer a non-invasive alternative to IADSA. Several studies have demonstrated high sensitivity of MRA in the detection of both ruptured and unruptured aneurysms.[24-32] Furthermore, MRA has a lower morbidity.[33-37] In terms of safety and image quality, GDCs have been found to be MR compatible at a static magnetic field strength of 1.5 T or less.[38] Recently, MRA has been proven to be a useful assessment modality in the identification of residual patency and recanalization of cerebral aneurysms treated with GDCs. Moreover, it may be adequate for the long-term monitoring of the stability of coiled aneurysms after concurrent primary verification of their occlusion with IADSA.[39-44]

The aim of this study was to compare three-dimensional time-of-flight (3D-TOF) MRA with IADSA, as the gold standard, in the follow-up of intracranial aneurysms that have been occluded with GDCs. At our department MRA and IADSA are performed within 3 days of first follow-up, usually 3-4 months after treatment. If the quality of the MR images is considered satisfactory at first follow-up, only MRA is performed as a subsequent follow-up examination (usually every 6-12 months).

MATERIAL AND METHODS

Patients and aneurysms

From January 1998 to January 2002, in 31 patients [four men and 27 women, mean age 52.0 years (SD 12.7)] MRA was performed after treatment with GDCs. In 26 patients the aneurysms had been accompanied by subarachnoid hemorrhage (SAH); in the remaining patients aneurysms had been discovered incidentally or because of symptoms caused by their mass effect.

A total of 37 intracranial aneurysms had been treated. Fourteen aneurysms had originated from the basilar artery (BA), 12 aneurysms from the internal carotid artery (ICA), one from the vertebral artery (VA), one from the anterior temporal artery (ATA), one from the posterior cerebral artery (PCA), one from the anterior cerebral artery (ACA), three from the superior cerebellar artery (SCA), two from the postero-inferior cerebellar artery (PICA) and two from the middle cerebral artery (MCA). Eight aneurysms had been classified as large (diameter >10 mm), 17 as medium (diameter between 4 and 10 mm) and 12 as small (<4 mm). Of the 31 patients, 28 had an IADSA examination within several days of the MRA. Three patients were not planned to have concurrent IADSA investigation, because of advanced age or complications during previous IADSA examinations. In the majority of patients (n=27) MRA was performed 3-4 months after coil placement. The remaining four patients underwent IADSA at 3 months follow-up, and, therefore, they had their first examination by MRA 6-18 months after treatment. If the MRA findings at first follow-up were considered satisfactory, further follow-up examinations were performed solely by MRA.

Image acquisition

The T_2 sequence and the MRA sequence were carried out on a 1.5-T Siemens Magnetom Vision. The T_2 TSE slices [repetition time (TR)/echo time (TE) =3,500/22-90 ms] in the transverse and/or coronal direction were obtained with a 512×512 pixel matrix, a field of view (FOV) of 220 cm² and a slice thickness of 6 mm. The following 3D-TOF MR angiogram parameters were applied: FISP 3D; TR/TE=35/6.4 ms; flip angle 20°; matrix=160×512 pixels; FOV 220 cm²; magnetization transfer (MT) pre-pulse; time for acquisition (TA) =6.44 min; 24 slices with 1.5 mm effective thickness. Postprocessing consisted of 60° maximum intensity projections (MIPs) for 360° around the head in both a left-to-right rotation and a head-to-foot rotation.

The intra-arterial DSA studies were produced on a digital angiography (Siemens Multiskop with infimed image processing) with a 512×512 pixel matrix. Selective three-vessel or four-vessel angiography, using a standard projection format (antero-posterior, lateral, peri-orbital and reverse-oblique), was performed initially, and additional views were obtained, if required, to identify the parent vessel and aneurysm neck more clearly. The amount of contrast medium (Omnipaque 300 in 1:1 dilution) was 12 ml for each series, and the injection rate 10 ml/s when the tip of the catheter was placed proximal to the carotid bifurcation. Injections into the vertebrobasilar system had a rate

of 8 ml/s to an overall amount of 8 ml.

Data analysis

The IADSA was considered the gold standard to determine the presence of complete obliteration, residual necks, residual aneurysms and patency of the parent artery and its adjacent arteries.

Angiographic results were classified as proposed by Roy et al. in 2001.[45] A class 1 result meant complete obliteration. A residual neck (class 2) was defined as the persistence of any portion of the original defect of the arterial wall as seen in any single projection but without opacification of the aneurysmal sac. Any opacification of the sac was classified as a residual aneurysm (class 3).

Adjacent arteries were (Table 1): the ipsilateral posterior communicating artery (PCoA) for ICA aneurysms located at the origin of the PCoA; ipsilateral ophthalmic artery (OA) for aneurysms located in the para-ophthalmic segment of the ICA, both PCAs for aneurysms located at the top of the BA, ipsilateral MCA and ATA for aneurysms located in the ATA, ipsilateral SCA, PCA and BA for aneurysms located in the SCA, BA and ipsilateral PCA for aneurysms located in the PCA, both the antero-inferior cerebellar artery (AICA) and the BA for aneurysms located in the VA (junction) and the ipsilateral VA and PICA for aneurysms located in the PICA.

Table 1: Details of patients, aneurysms, parent arteries, adjacent arteries and follow-up (*M* male, *F* female, *ICA(po)* para-ophthalmic segment of the ICA, *ICA(oPCoA)* origin of the PCoA, *BA(bif)* bifurcation of the BA, *P1* P1 segment, *M2* M2 segment)

Patient no.	Gender/age	Follow-up IADSA and MRA (months)	Next follow-up MRA only (months)	Aneurysm location	Parent artery	Adjacent arteries
1	M/68	4	12	ICA(oPCoA)	right ICA	right PCoA
2	F/38	3	12	BA(bif)	BA	right PCA(P1)/left PCA(P1)
3	F/41	3	12 and 36	BA(bif)	BA	right PCA(P1)/left PCA(P1)
4	F/63	3		ICA(oPCoA)	left ICA	left PCoA
5	F/64	3		BA(bif)	BA	right PCA(P1)/left PCA(P1)
6	F/48	3	12	ICA(oPCoA)	right ICA	right PCoA
				ICA(po)	left ICA	left OA
7	M/64	4	12	ICA(po)	left ICA	left OA
8	F/50	3		ATA	right MCA	right MCA, right ATA
				SCA	BA	right SCA, right PCA, BA
9	F/29	3		PCA	BA	BA, left PCA
10	F/63	3	12 and 30	BA(bif)	BA	right PCA(P1)/left PCA(P1)
11	F/42	6	30, 42 and 51	BA(bif)	BA	right PCA(P1)/left PCA(P1)

Table 1: (continued)

Patient no.	Gender/age	Follow-up IADSA and MRA (months)	Next follow-up MRA only (months)	Aneurysm location	Parent artery	Adjacent arteries
12	M/66	18	30	BA(bif)	BA	right PCA(P1)/left PCA(P1)
13	F/68	3	12	BA(bif)	BA	right PCA(P1)/left PCA(P1)
14	F/69	3	12	BA(bif)	BA	right PCA(P1)/left PCA(P1)
15	F/67	3	17	VA(junction)	VA	right VA, left VA
16	F/54	3		BA(bif)	BA	right PCA(P1)/left PCA(P1)
17	F/32	3		BA(bif)	BA	right PCA(P1)/left PCA(P1)
18	F/59	3		BA(bif)	BA	right PCA(P1)/left PCA(P1)
19	F/51	3		SCA	BA	left PCA, left SCA, BA
20	F/60	3	12	BA(bif)	BA	right PCA(P1)/left PCA(P1)
21	F/47	3		ICA(po)	right ICA	right OA
22	F/42	3		ICA(po)	left ICA	left OA
				ICA(po)	right ICA	right OA
				ICA(po)	right ICA	right OA
23	F/60	3		BA(bif)	BA	right PCA(P1)/ lPCA(P1)
				ACA	right ACA	right ACA
24	F/36	3		SCA	BA	right SCA, right PCA, BA
25	F/37	9	24	ICA(po)	left ICA	left OA
26	F/45	3		ICA(po)	right ICA	right OA
27	F/50	3		MCA	right MCA	branch M2/branch M2
				ACA	rightACA	right ACA
				PICA	right VA	right PICA, VA
28	F/42	18		MCA	right MCA	branch M2/branch M2
29	F/75	4 (MRA only)	12	PICA	right VA	right PICA, VA
30	M/46	3 (MRA only)		BA(bif)	BA	right PCA(P1)/left PCA(P1)
31	F/37	3 (MRA only)		ICA (po)	left ICA	left OA

The IADSA investigations were performed and interpreted by one of the two interventional neuroradiologists who had also done the previous endovascular treatment. Under the same criteria as IADSA, the MRA source images and standard and targeted MIP reconstructions were interpreted by one of the two neuroradiologists, without knowledge of the IADSA findings. The MRA quality was rated as informative or non-diagnostic.

RESULTS

Comparison of MR angiographic findings with IADSA findings

Twenty-eight patients underwent IADSA and MRA on the same three following days as follow-up screening. For one patient the IADSA had to be aborted, because of an adverse reaction to the contrast medium.

The imaging of 27 patients with a total of 33 treated aneurysms was used to compare MRA findings with IADSA findings. Two aneurysms were, however, excluded for evaluation, because of insufficient quality of MRA images, due to susceptibility artifacts from nearby clipped aneurysms (patients 22 and 27). The data are summarized in Table 2.

Table 2: MR angiographic performance (27 IADSA-confirmed MR angiographic studies in 31 treated aneurysms) (*TP* true positive, *FP* false positive, *TN* true negative, *FN* false negative, *D* doubtful, *PPV* positive predictive value, *NPV* negative predictive value)

		IADSA		MRA					Sensitivity	Specificity	PPV	NPV
Finding	No.	Abnormal	Normal	TP	FP	TN	FN	D	(%)	(%)	(%)	(%)
Parent artery flow	31	0	31	0	0	27	0	4	–	87	–	100
Adjacent artery flow	55	0	55	0	0	47	0	8	–	85	–	100
Residual flow in coils (class 3)	31	0	31	0	1	30	0	0	–	97	–	100
Residual neck (class 2)	31	9	22	8	2	20	1	0	89	91	80	95

Residual flow within the interstices of the coil (class 3) was absent on IADSA studies of all aneurysms (n=31). The MRA incorrectly diagnosed residual flow in one aneurysm. Flow within the aneurysmal neck (class 2) was observed with IADSA in nine aneurysms. This flow was identified correctly with MRA in eight aneurysms and was false positive in two (cases 6 and 18) (Figs. 1 and 2). The MRA initially missed the flow in the aneurysmal neck in one aneurysm (case 11).

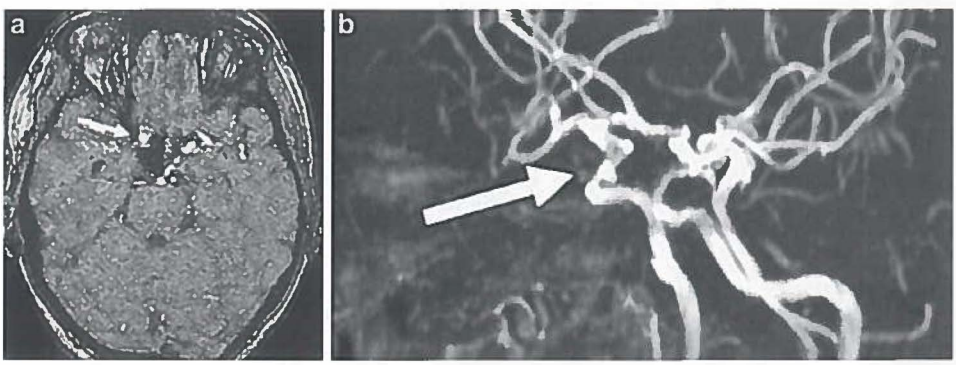


Figure 1: MRA source image, axial view (**a**) and MRA MIP reconstruction (**b**) both show false positive neck remnant of posterior communicating artery (*arrows*).

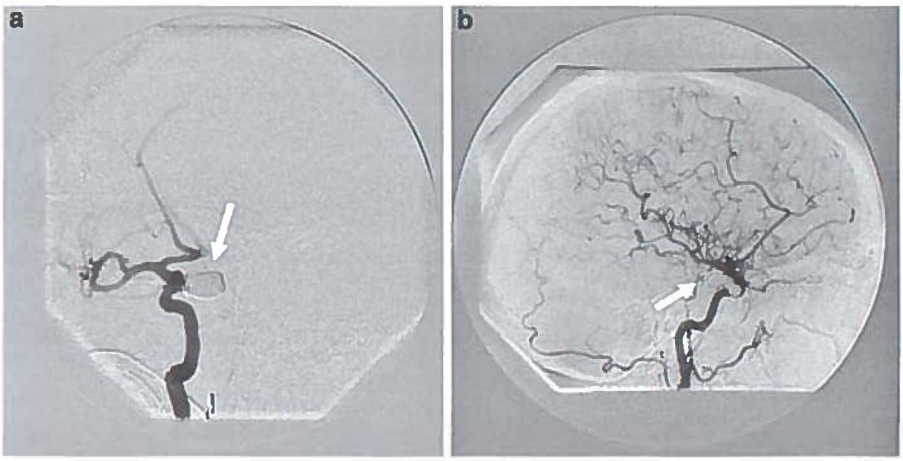


Figure 2: a,b. IADSA shows complete obliteration of the embolized aneurysm of the posterior communicating artery (*arrows*).

All parent arteries (*n*=31) were patent on IADSA. The MRA correctly identified the patency of 27 parent arteries. In four arteries (one BA, three ICAs) patency was doubtful with MRA because of segmental total loss of signal. A total of 55 branch vessels arising in proximity to the treated aneurysm was evaluated. None was occluded after GDC treatment. MRA correctly identified branch vessel patency in 47 of the 55 vessels. In the other eight arteries (three PCAs, one PCoA, three OAs and one VA), patency was doubtful with MRA because of segmental total loss of signal (Figs. 3 and 4).

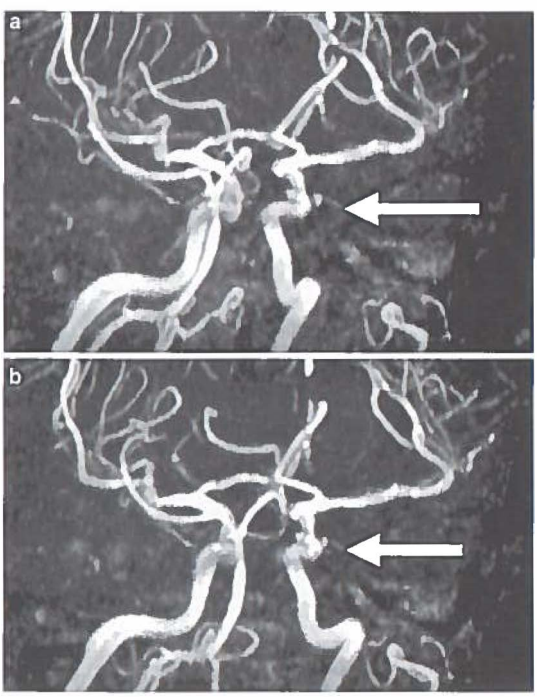
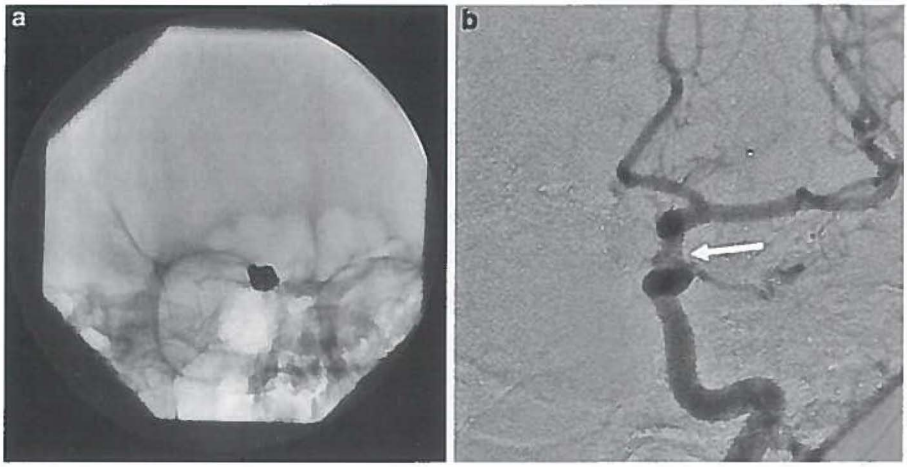


Figure 3: a,b MRA, MIP reconstructions show coil artifacts at the internal carotid artery (*arrows*).



Figue 4: **a** IADSA before subtraction. The coils within the aneurysm are shown. **b** IADSA after subtraction. Normal patency of the internal carotid artery (*arrow*)

First follow-up based on MRA

In three patients IADSA was not obtained routinely at first follow-up for reasons mentioned in the "Patients and aneurysms" section. In another patient the IADSA had to be aborted because of complications. In those patients follow-up based on MRA was considered sufficient. The MRA quality was rated as informative, and interpretation of the images was considered reliable. In one case a stable remnant neck was seen. Retreatment was not done because of the advanced age of the patient.

Further follow-up based on MRA

In 14 of the 31 patients, 18 subsequent follow-ups were performed with MRA (Table 1). In the remaining patients further follow-up examination has not yet been performed. Of the 15 intracranial aneurysms evaluated, no recurrence has developed in seven, in six a stable remnant neck was shown and in two regrowth of a remnant neck occurred. In one patient regrowth of a remnant neck of a basilar artery aneurysm was accompanied by severe headache and cranial nerve palsy. The aneurysm was occluded completely with further coiling. However, 1 month later, fatal rebleeding from the rupture of a recurrent aneurysm occurred. Permission for autopsy was refused.

DISCUSSION

The present study reports on the evaluation of 3D-TOF MRA in the follow-up of 37 aneurysms embolized recently with GDCs in 31 patients. We focused on the examination of residual aneurysms or recurrence, because, in the long term, those are the main contributors to morbidity. Residual aneurysms or recurrences may present in two different forms: either as a residual pouch between the coil mesh and the aneurysmal neck, or residual flow in the coil mesh. In our series, the first form occurred in all nine cases of remnant or recurrence.

Residual aneurysms

For detection of aneurysmal residual neck we had one false negative and two false positive MRA examinations, resulting in a sensitivity and a specificity of MRA of, respectively, 89% and 91%, considering IADSA as the reference standard. These values of MRA are comparable to the results of previous studies, which have been set up to demonstrate the potential of 3D-TOF MRA after GDC embolization. Three of those studies also examined a small number of patients, 20–49, and reported a sensitivity of MRA for detection of aneurysmal residual necks of between 90% and 100% and a specificity in ruling out a remnant cavity of between 91% and 100%, with IADSA as the gold standard.[39,42,43] In two other studies MRA had a lower sensitivity (72-83%), mostly due to the limitation of MRA in depicting aneurysmal neck remnants smaller than 3 mm or to the presence of motion or coil-induced artifacts on MRA.[40,41] One of these studies is the largest, with results based on 80 concurrent MRA and IADSA examinations in 65 patients with 70 intracranial aneurysms. In the study by Weber et al. (45 patients with 54 treated aneurysms), the sensitivity of MRA increased from 71% to 92% if the results were evaluated by experienced neuroradiologists with prior knowledge of the interventional procedures.[44]

High signal on MRA within the aneurysm is suggestive of residual flow within the interstices of the coil mass. However, susceptibility artifacts and hemorrhage can mimic residual aneurysmal flow. This occurred with low frequency in our study (one of 31 aneurysms). The MRA correctly showed the absence of flow in the remaining 30 treated intracranial aneurysms if compared with IADSA. Hence, the MRA finding of no flow within an aneurysm may be considered reliable. Brunereau et al.[41] reported an optimal specificity of MRA for excluding residual flow within the coil mass. In 18 aneurysms with evidence of complete occlusion on IADSA false persistent residual flow was diagnosed in two, which resulted in a specificity of MRA of 89% in the study by Derdeyn et al.[42]

Arterial patency

In the identification of parent artery patency, MRA demonstrated a specificity of 87% and a negative predictive value of 100%. In four of the 27 patients (15%), MRA quality was considered insufficient for diagnosing the patency of the parent artery and of the adjacent arteries, owing to the presence of a thin rim of high signal encountered in the vicinity of the coil mass and in the frequency-encoded direction. Susceptibility artifacts have been described in other publications and are a major limitation of MRA. They were reported in six of 20 patients (30%) in the study by Kähära et al., resulting in false arterial encroachment in five patients, one involving a parent artery and four affecting distal branch arteries.[43] In the study by Anzalone et al. significant artifacts, on both source images and MIP reconstructions, related to the presence of coils excluded 10.9% of the patients from accurate evaluation of parent arteries.[39] Two studies reported sensitivities of MRA for detection of parent and adjacent artery flow of, respectively, 89–96% and 83–92%.[41,42] Results concerning the identification of patency of arteries on MRA vary between different studies and may be influenced

by the location of the aneurysms. This was highlighted by Brunereau et al., who found signal loss more often in aneurysms located in the anterior communicating artery.[41] Furthermore, use of a contrast medium may have influenced the results in another publication.[39]

Follow-up based on MRA only

In the present study we were able to perform the first follow-up, 3-4 months after treatment, with MRA only in four patients. Furthermore, later follow-ups (more than 1 year after treatment) with MRA were considered sufficient in 14 patients. Subsequent endovascular retreatment based on these findings was performed in one patient.

Comments

Two comments should be made with regard to the present study. One limitation, already reported earlier by others, was the lack of arterial occlusion.[41,42] Therefore, this limitation does not allow us to evaluate the ability of MRA to depict occlusion of the parent and adjacent arteries. However, for follow-up of aneurysms treated with GDCs it is most important to be informed of the presence of residual aneurysms or recurrences. Patency of parent and adjacent arteries is usually evaluated correctly by performing IADSA postoperatively or, in cases of neurological symptoms, during the days following treatment.

Furthermore, in the present study, none of the MR angiograms were obtained with contrast medium. By limiting the effect of saturation, which can obscure signal from slow flow (such as in the residual pouches) or small vessels, enhanced MRA has been shown to be useful in evaluating residual patency in large and giant aneurysms and in better depicting the distal adjacent arteries.[39]

Summary and conclusion

Follow-up MRA and routine IADSA were performed in 27 consecutive patients with 33 aneurysms, after a median follow-up period of 3 months since treatment with GDCs. Despite three false positive cases and one false negative case in our study, 3D-TOF MRA provides a good predictive method to rule out residual flow within the aneurysmal pouch. In spite of the occurrence of susceptibility artifacts on MRA, preventing accurate evaluation of parent and adjacent arteries in a significant number of patients, our results show that MRA has an optimal positive predictive value in detection of arterial patency. Four patients had only an MRA examination at first follow-up, which yielded valuable diagnostic information. Furthermore, subsequent follow-ups based on MRA were considered sufficient in 14 patients, leading to endovascular retreatment in one. No rebleeding developed due to the lack of information gathered from MRA. We proclaim that MRA is a useful means to follow the durability of GDC treatment when assessed by an experienced neuroradiologist.

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Chapter 6

Feasibility of magnetic resonance angiography (MRA) follow-up as the primary imaging modality after coiling of intracranial aneurysms

N. A. Bakker[1], H. E. Westerlaan[2], J. D. M. Metzemaekers[1], J. M. C. van Dijk[1], O. S. Eshghi[2], J. J. A. Mooij[1] & R. J. M. Groen[1]

[1]Department of Neurosurgery, University Medical Center Groningen, The Netherlands

[2]Department of Radiology, University Medical Center Groningen, The Netherlands

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ABSTRACT

Background: Digital subtraction angiography (DSA) is still regarded as the gold standard for detecting residual flow in treated aneurysms. Recent reports have also shown excellent results from magnetic resonance angiography (MRA) imaging. This is an important observation, since DSA is associated with a risk of medical complications, is time consuming, and is more expensive.

Purpose: To determine whether MRA could replace conventional DSA and serve as the primary postinterventional imaging modality in patients with coiled intracranial aneurysms.

Material and Methods: We studied a prospectively enrolled cohort of 190 patients treated endovascularly for a first-ruptured and/or unruptured intracranial aneurysm between January 2004 and December 2008. The imaging protocol included a 1.5T time-of-flight (TOF) MRA and a DSA at 3 months (on the same day) and, depending on comparability, a 1.5T TOF-MRA or DSA 1 year after treatment. All images were evaluated by a multidisciplinary panel.

Results: In 141/190 patients, both an MRA and DSA were performed after 3-month follow-up. In 2/141 patients (1.4%), (small) neck remnants gave false-negative MRA results. In one patient (0.7%), this led to additional neurosurgical clipping of the aneurysm. In 25/141 patients, future follow-up (>3 months) consisted of DSA because of various reasons. In 24/25 of these patients, primary MRA images alone would invariably have led to additional DSA imaging.

Conclusion: The present study shows that 1.5T TOF-MRA is a feasible primary follow-up modality after coiling of intracranial aneurysms. Given our data, we now suggest that, in every patient with a coiled intracranial aneurysm, the first follow-up, 3 months after coiling, should be an MRA study. Only when this MRA is inconclusive (e.g., because of coil artifacts), or in the case of suspicion of recanalization, should DSA be performed additionally.

INTRODUCTION

Endovascular treatment of intracranial aneurysms has become a widespread and approved technique over the past 15 years.[1,2] One of the disadvantages of this technique, however, is the relatively frequent occurrence of recanalization after treatment due to coil impaction or due to regrowth of a residual neck.[1,3-5] It is therefore recommended that a post-treatment follow-up be performed in order to treat those patients at risk for a (repeated) subarachnoid hemorrhage in a timely fashion. This follow-up protocol differs among centers, not only with regard to time interval but also in the techniques used. Most centers perform at least one postinterventional intra-arterial digital subtraction angiography (IADSA) 3 or 6 months after treatment, frequently accompanied by a contrast-enhanced (CE) magnetic resonance angiography (MRA) or a time-of-flight (TOF) MRA. With regard to these MRA techniques, it is not clear which technique should be favored; however, the results seem reasonably comparable.[6]

Although DSA is regarded as the gold standard for detecting residual flow in treated aneurysms, recent reports have shown excellent results with MRA imaging.[7-10] This is an important observation, since DSA is associated with a risk of neurological complications in 0.5–2.0% of cases in various studies.[11,12] Moreover, this method exposes patients to ionizing radiation or potentially nephrotoxic iodinated contrast media, and is more time consuming, more expensive, and requires hospitalization.

Evaluation by MRA of the results of coiling is noninvasive, does not carry the risk of complications, is radiation free, less expensive, and can be performed in an outpatient-clinic setting. For these reasons, follow-up of endovascularly treated intracranial aneurysms using MRA as the only imaging modality is preferable. Recently, FERRE et al. reported on the utility of TOF-MRA at 3T compared with DSA in 51 cases and concluded that TOF-MRA was at least as efficient as DSA for the evaluation of intracranial aneurysm occlusion.[8] URBACH et al. shared their conclusions in a prospective series of 50 patients.[9] In contrast, LUBICZ et al. recently suggested, after evaluating a group of 55 patients with 67 aneurysms, that a single DSA should remain mandatory during imaging follow-up, since they missed one major recanalization on CE-MRA.[13] However, due to the small numbers involved, no definitive conclusions can be drawn from these studies. In particular, because of these small numbers, it is not yet known whether a single case of recanalization missed on MRA outweighs the risks associated with DSA imaging. In view of this, our aim was to determine whether MRA (1.5T TOF-MRA) could serve as the primary postinterventional imaging modality in a prospectively enrolled cohort of 190 patients treated endovascularly at our center for a first-ruptured and/ or unruptured intracranial aneurysm between January 2004 and December 2008.

MATERIALS AND METHODS

Patients

Between January 2004 and December 2008, 190 consecutive patients harboring 235 intracranial

aneurysms were prospectively enrolled in our follow-up program for endovascularly treated intracranial aneurysms. This follow-up program was standard medical care for all patients with endovascularly treated intracranial aneurysm. For this reason, no institutional review board (IRB) approval or informed consent was considered necessary.

All patients were treated using endovascular coil embolization at the University Medical Center Groningen, the Netherlands, because of a first-ruptured or unruptured intracranial aneurysm. Characteristics for all patients are shown in Table 1. The median age at the time of endovascular treatment was 54 years (range 14–84 years), 128 patients were female (67%), the median aneurysm size was 6 mm (range 3–29 mm), and 41 patients (22%) harbored multiple aneurysms. A total of 164 patients (86%) were symptomatic (i.e., ruptured) and were treated in an acute setting (i.e., <72 hours from bleeding). In general, the localization of the aneurysms was comparable with the figures usually found, with a predominance of anterior communicating artery aneurysms, posterior communicating artery aneurysms, and basilar artery aneurysms (Table 1). Middle cerebral artery aneurysms were underrepresented, since, in our center, neurosurgical clipping is favored.

Table 1: Patient characteristics

	Number (median)	% (range)
Total	190	100
Age, years	(54)	(14–84)
Female	128	67
Aneurysm location	190	100
ACOM	80	42
PCOM	39	21
Basilar	32	17
PICA	12	6
ICA	8	4
ACM	8	4
Other	11	6
Aneurysm size, mm	(6)	(3–29)
Multiple aneurysms	41	22
Symptomatic/acute	164	86
Aneurysm obliteration*	190	100
Class 1	171	90
Class 2	8	4
Class 3	11	6
Use of stent/balloon	9	5

Endovascular treatment

Endovascular treatment was performed under general anesthesia and systemic heparinization. All patients were treated by selective embolization with Guglielmi detachable coils (GDC; Boston Scientific/Target, Fremont, Calif., USA). The endovascular procedure consisted of endosaccular coiling of 201 aneurysms in 190 patients. In patients with ruptured aneurysms who harbored

additional asymptomatic aneurysms, only the symptomatic aneurysm was treated initially, unless otherwise indicated. In nine patients (5%), balloon- or stent-assisted coiling took place. At the end of the procedure, all patients were evaluated using angiography to document baseline aneurysm obliteration.

Follow-up

A multidisciplinary therapeutic protocol has been established in our institution for the management of patients with ruptured or unruptured intracranial aneurysms. For the follow-up of patients treated by endovascular coiling, our imaging protocol includes a 1.5T TOF-MRA and DSA at 3 months (on the same day) and, depending on how these imaging modalities compare, a TOF-MRA or DSA 12 months after treatment. When the aneurysm continues to be completely obliterated after 1 year, patients are discharged from follow-up. Only very young patients are offered follow-up imaging after 5 years.

All images of these patients were evaluated by a multidisciplinary panel consisting of an interventional neuroradiologist, a vascular neurosurgeon, and a vascular neurologist, all with >10 years' experience in this field. Depending on the panel's opinion, follow-up then continued with either MRA (preferably) or DSA. Patients were followed up with MRA only if DSA and MRA images completely correlated at 3-month evaluation.

MRA

The three-dimensional (3D) TOF-MRA was carried out on a 1.5T Siemens Sonata system (Siemens AG, Erlangen, Germany). The following 3D TOF-MR angiogram parameters were applied: 3D fast imaging with steady-state precession (FISP); repetition/echo time (TR/TE) 38/5.09 ms; flip angle 25°; matrix 640 × 384 pixels (voxel size 0.6 × 0.4 × 0.8 mm); bandwidth 181 Hz/pixel; field of view (FOV) 230 cm^2; magnetization transfer (MT) pre-pulse; time for acquisition (TA) 5 min 30 s; 72 slices with 0.83 mm effective thickness and a distance factor of –50% (contiguous sampling with 50% overlap of slices). Postprocessing consisted of 60° maximum intensity projections (MIPs) for 360° around the head in both a left-to-right rotation and a head-to-foot rotation. For evaluation, both source images and MIPs were viewed, with particular emphasis on the source images. The source images were loaded in AquariusNET Viewer (TeraRecon, Inc. San Mateo, Calif., USA).

DSA

Angiography was performed according to the Seldinger technique, using either a 4- or a 5-French introducer in the common femoral artery. Angiograms included selective injection of internal carotid or vertebral arteries with intracranial views (frontal, lateral) completed using 3D rotational angiography and/or additional embolization views when necessary (contrast material: Visipaque [iodixanol] 270; GE Healthcare BV, Eindhoven, The Netherlands).

Inclusion

For a reliable comparison, only patients who underwent an MRA as well as a DSA after 3 months were included. As a result, a total of 49 patients were excluded from the analysis (Figure 1). Twenty-four patients (13%) did not receive any follow-up imaging, in most cases because they passed away within 3 months after coiling ($n = 10$, all related to initial subarachnoid hemorrhage) or because of the presence of severe disabilities ($n = 14$, only patients with symptomatic aneurysms). Another 15 patients (8%) only underwent MRA imaging due to severe disabilities, adverse reactions to contrast material, or because patients refused a DSA. Finally, 10 patients (5%) underwent DSA imaging only after 3 months due to claustrophobia, implants, a previous neurosurgical clipping procedure, or additional aneurysms. In the end, 141 patients (74%) fulfilled the criteria.

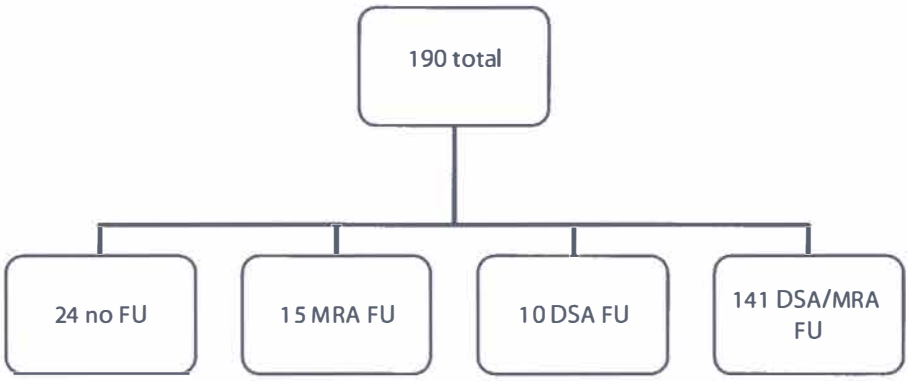

Figure 1: Initial follow-up (FU). MRA: magnetic resonance angiography; DSA: digital subtraction angiography.

Data analysis

IADSA was considered the gold standard for determining the presence of complete obliteration, residual necks, residual aneurysms, and patency of the parent artery and its adjacent arteries. Angiographic results were classified as proposed by ROY et al. in 2001.[14] A class 1 result meant complete obliteration. A residual neck (class 2) was defined as the persistence of any portion of the original defect of the arterial wall as seen in any single projection but without opacification of the aneurysmal sac. Any opacification of the sac was classified as a residual aneurysm (class 3).

Statistics

Continuous variables were expressed as mean with standard deviation or median with range, and categorical variables as counts and percentages. The Shapiro-Wilk test, together with normality plots, was used to assess normal distribution of the continuous variables. Differences between groups were evaluated by Student's *t* test or by the Mann-Whitney U test for continuous data, and by Fisher's exact test or the chi-square test for categorical data. A two-tailed *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, Ill., USA).

RESULTS

Of the 141 patients with both an MRA and DSA at 3-month follow-up, 115 patients (82%) eventually received a 1-year follow-up with MRA, since DSA and MRA images correlated completely. Of the 26 remaining patients, 25 patients (96%) received 1-year follow-up with DSA instead of MRA for various reasons (Figure 2): artifactual signal loss because of nearby coils (11 patients, 44%), poor visibility of the aneurysm neck (seven patients, 28%), additional aneurysms not adequately visualized on MRA (five patients, 20%), missed neck remnant on MRA (one patient, 4%, no consequences), and development of claustrophobia in one patient (4%). One patient (4%) did not receive a 1-year follow-up because of additional neurosurgical clipping of a significant neck remnant of a previously coiled posterior communicating artery (PCOM) aneurysm (the patient favored clipping over additional coiling).

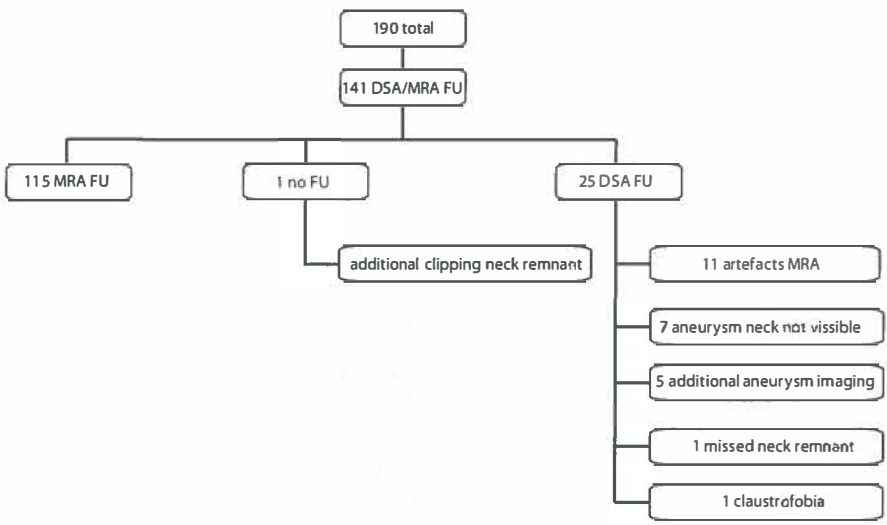

Figure 2: Follow-up (FU) after imaging at 3 months. MRA: magnetic resonance angiography; DSA: digital subtraction angiography.

From the aforementioned, it can be concluded that, in two out of 141 patients (1.4%), neck remnants were not identified with MRA. In one, this did not lead to additional intervention because of the very minor nature of the recanalization. In the second patient (0.7%), DSA imaging led to additional neurosurgical clipping of the aneurysm (see above). In the remaining 24 patients with DSA follow-up, the primary MRA images alone would invariably have led to additional DSA imaging.

Age ($P = 0.23$), sex ($P = 0.66$), aneurysm location ($P = 0.28$), size ($P = 0.08$), presence of multiple aneurysms ($P = 0.58$), symptomatic vs. asymptomatic aneurysms ($P = 1.00$), aneurysm obliteration at baseline ($P = 0.45$), and the use of a stent or balloon ($P = 0.59$) were not associated with future DSA follow-up after a 3-month comparison (Table 2).

Table 2: Predictors of DSA follow-up.

	MRA FU		DSA FU/no FU		
	Number	(%)	Number	(%)	P
Total	115	(100)	26	(100)	
Age, years (mean)	54		51		0.23
Female	73	(64)	18	(69)	0.66
Aneurysm location					0.28
ACOM	53	(46)	9	(35)	
PCOM	20	(17)	7	(27)	
Basilar	20	(17)	2	(8)	
PICA	8	(7)	3	(12)	
ICA	4	(4)	0	(0)	
ACM	4	(4)	1	(4)	
Other	6	(5)	4	(15)	
Aneurysm size, mm (mean)	8		6		0.08
Multiple aneurysms	20	(17)	6	(23)	0.58
Symptomatic/acute	97	(84)	22	(85)	1.00
Aneurysm obliteration*	115	(100)	26	(100)	0.45
Class 1	105	(91)	24	(92)	
Class 2	5	(5)	2	(8)	
Class 3	5	(5)	0	(0)	
Use of stent/balloon	5	(4)	0	(0)	0.59

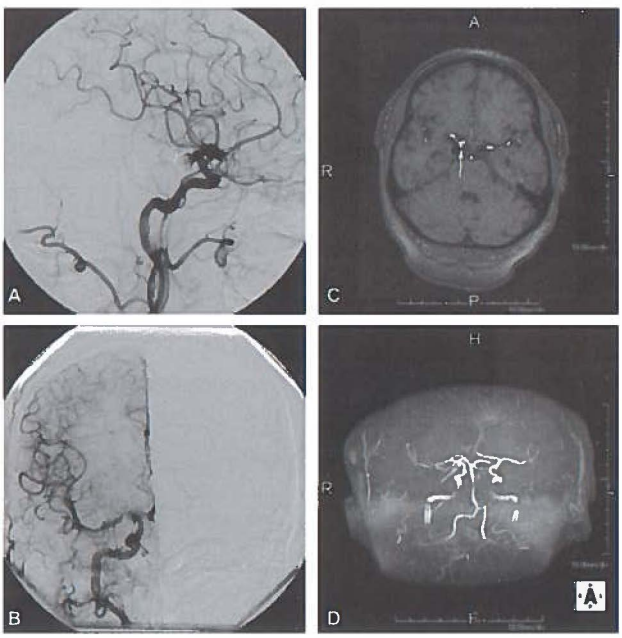

Figure 3: DSA after selective catheterization of the right internal carotid artery: right oblique view (A) and coronal view (B). MRA source image of the same case in the axial plane (C) and the MIP reconstruction in coronal view (D). A neck remnant of the coiled aneurysm at the origin of the posterior communicating artery is revealed with both imaging modalities.

Figure 3 shows an example of concordant findings on both MRA and DSA of a coiled PCOM aneurysm with a neck remnant.

DISCUSSION

In this study, we aimed to determine whether follow-up imaging of coiled intracranial aneurysms with 1.5T TOF-MRA as the primary imaging modality would have been sufficient to detect recurrent or residual flow. Since no guideline currently exists proposing MRA as the follow-up method of first choice, the gold standard in follow-up diagnostic imaging is still intraarterial DSA, associated with an inherently small rate of permanent neurological deficit. In view of this, our most important finding is that, in 139/141 patients studied (98.6%), initial MRA findings would have been sufficient as primary follow-up. In that case, 115 patients (82%) would not have needed to undergo DSA imaging, with its accompanying risks. In our large case series, one missed neck remnant (0.7%) led to additional treatment. This percentage seems to be less than the reported risk of permanent neurological complications from diagnostic DSA imaging.[11,12] Moreover, when the risk of not acutely treating the one patient with a neck remnant is taken into account, it is unclear what the real percentage is that would indeed have led to a repeated subarachnoid hemorrhage, which would obviously be significantly lower than 100% a year.

In the available literature, several studies have already suggested that follow-up of coiled intracranial aneurysms with MRA might be sufficient. FERRE et al. reported on the utility of TOF-MRA at 3T compared with DSA in 51 patients, and concluded that TOF-MRA was at least as efficient as DSA for the evaluation of intracranial aneurysm occlusion.[8] URBACH et al. shared their conclusions in a prospective series of 50 patients.[9] In contrast, LUBICZ et al. recently suggested, after evaluating a group of 55 patients with 67 aneurysms, that a single DSA remains mandatory during follow-up, since they missed one major recanalization on CE-MRA.[13] The question now remains of whether a missed neck remnant outweighs the risks associated with DSA imaging. Of course, this would depend not only on the percentage of missed neck remnants, but also on the risk of rehemorrhage after incomplete coil embolization. From the CARAT study, we learned that, in cases of partial coiling (i.e., <70%), a 25% annual risk of rehemorrhage was present.[5] In the worst-case scenario, with a 25% chance of rehemorrhage in 1/141 patients with a significant neck remnant, this would lead to a bleeding risk of approximately 0.2%. This is far below the reported risks of (possibly permanent) neurological complications associated with DSA imaging.[12] Moreover, every patient receives a follow-up MRA *1 year* after coil embolization, and, in the eventuality of a growing neck, it can then be detected.

In various studies, 3TTOF-MRA had been used as the imaging modality. One could question whether our findings could be compared with those findings in groups of patients evaluated with 3T TOF-MRA. The recent report by BUHK et al., however, shows that both imaging modalities (1.5T and 3T)

have approximately the same results in terms of residual flow detection.[15]

None of the characteristics of the aneurysms—for example, their size, location, or presence of multiple aneurysms—was associated with poorer visibility of residual flow on an MRA in our series. Recently, DEUTSCHMANN et al. showed, in a group of 127 patients with 136 aneurysms, that small aneurysms, that is those <5 mm, might be visualized less accurately on MRA when compared with DSA imaging.[16] We cannot confirm these data in our patients, although there was a trend (P=0.08, n.s.) for smaller aneurysms to be located in the group of patients with DSA follow-up.

To date, this is the largest cohort in which postinterventional DSA and MRA have been compared for their ability to detect residual flow in endovascularly treated aneurysms. Our data have some important implications. Not only can a significant proportion of patients be spared the per-procedural risks of DSA imaging, but the patients will also not be exposed to ionizing radiation or potentially nephrotoxic iodinated contrast media, and will not need to undergo hospitalization. Also, in case of doubt, re-coiling can be planned during the additional DSA, thereby again sparing the patient additional DSA imaging. Finally, the costs of the procedure (i.e., MRA) are significantly lower than in the case of follow-up with DSA.

In conclusion, the present study shows that 1.5T TOF-MRA is a feasible modality for primary follow-up following coiling of intracranial aneurysms. Given our data, we now suggest that, in every patient with a coiled intracranial aneurysm, the first follow-up, 3 months after coiling, should be an MRA study. Only when this MRA is inconclusive (e.g., because of coil artifacts), or in the case of suspicion of recanalization, should DSA be performed additionally. In this way, a significant number of patients with coiled intracranial aneurysms will not need to undergo a (expensive) DSA and also will not be exposed to the potential risks involved with this procedure.

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Chapter 7

Main findings

Part 1:

Noninvasive imaging of intracranial aneurysms in patients with acute subarachnoid hemorrhage at presentation

Part 2:

Noninvasive imaging of intracranial aneurysms after endovascular treatment

Part 1: Noninvasive imaging of intracranial aneurysms in patients with acute subarachnoid hemorrhage at presentation

Subarachnoid hemorrhage (SAH) is a bleeding into the subarachnoid space - the area between the arachnoid membrane and the pia mater surrounding the brain. This usually occurs from a ruptured intracranial aneurysm. SAH is a devastating disorder with a poor prognosis for many patients. Rapid diagnostic evaluation and treatment are crucial for the patient's outcome.

Although selective cerebral angiography is considered the reference standard for the detection of intracranial aneurysms, it is invasive, time-consuming and carries a small but definitive risk. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are readily available and less invasive alternatives to selective cerebral angiography.

In chapter 2 we found in a systematic review and meta-analysis of 42 studies that CTA had a very high diagnostic value for the detection of ruptured intracranial aneurysms (pooled sensitivity of 98% and pooled specificity of 100%). The studies were of good methodological quality. There was evidence for publication bias. Studies using selective cerebral angiography as gold standard had higher heterogeneity in sensitivity and specificity and lower sensitivity and specificity than studies using findings at treatment or autopsy as gold standards. Most studies used a 4-detector scanner. Specificity and sensitivity for 4- or 16/64 detector scanners were comparable, although studies with 16- or 64-detector scanners showed minimal heterogeneity in sensitivities compared to the 4-detector scanner. CTA had a relatively high false negative rate in the detection of small aneurysms near the central skull base, i.e. aneurysms of the internal carotid artery and the posterior communicating artery. A substantial number of false negative aneurysms could be shown retrospectively on CTA.

In chapter 3 we assessed that CTA is clinically useful in treatment stratification of ruptured intracranial aneurysms, especially in the acute phase, without recourse to selective cerebral angiography. In CTA-negative patients selective cerebral angiography provided no or marginal added value. The remaining true indication for selective cerebral angiography was in patients with inconclusive CTA results, most often due to difficulties in the differentiation between infundibulum, vessel loop and aneurysm and insufficient information regarding location and orientation of the aneurysm. In more than half of those selective cerebral angiography provided relevant new diagnostic information.

In chapter 4 we showed that 3 dimensional time-of flight (3D TOF) MRA at 1.5 Tesla (T) is feasible as a first diagnostic modality in the selection of patients suitable for surgical treatment of ruptured intracranial aneurysms in the acute phase. No morbidity or mortality was associated with a MRA-based diagnosis of ruptured aneurysm. No false negatives were selected by MRA and in a majority selective cerebral angiography confirmed MRA findings initially classified as inconclusive due to insufficient information regarding location and orientation of aneurysm, presence of arterial

vasospasm and difficulties in the differentiation between infundibulum, vessel loop and aneurysm.

Part 2: Noninvasive imaging of intracranial aneurysms after endovascular treatment

Endovascular treatment with coils has become an established treatment modality for both ruptured and unruptured intracranial aneurysms. Coiling has several shortcomings. Not all aneurysms can be occluded completely at first treatment, leaving the patient at risk for early recurrent hemorrhage in case of a recently ruptured aneurysm. It has been shown that reperfusion of even initially adequately occluded aneurysms may occur due to coil compaction, aneurysm growth or dissolution of an intraluminal thrombus. Follow-up imaging after endovascular treatment is therefore recommended in order to evaluate the stability of the occlusion and possible subsequent need for further treatment. The standard follow-up imaging modality after coiling is selective cerebral angiography, but this diagnostic procedure is invasive, uses ionizing radiation, and exposes the patient to a small risk of serious complications. Substitution with MRA may offer a noninvasive alternative to selective cerebral angiography.

In chapter 5 we compared 3D TOF MRA at 1.5T with selective cerebral angiography. We demonstrated that non-invasive 3D TOF-MRA at 1.5 T is feasible in the follow-up of coiled intracranial aneurysms, for the detection of reopening and remnants. In chapter 6 we showed that 3D TOF MRA at 1.5 T can serve as the primary follow-up imaging modality after coiling in the majority of patients. We demonstrated that TOF MRA a 1.5 T had a high negative predictive value for aneurysm recurrence. Hence, there is only a very small probability of finding incomplete occlusion of an aneurysm at selective cerebral angiography when MRA shows total occlusion. Major indications for follow-up with selective cerebral angiography were magnetic susceptibility effects in coil masses and insufficient delineation of aneurysm necks.

Practical implications of the thesis and future directions

CTA has evolved to become the diagnostic standard imaging modality in patients with SAH and enables rapid assessment and treatment stratification of ruptured intracranial aneurysms. Its diagnostic performance has surpassed 2D selective cerebral angiography performed by experienced angiographers. Its false negative rate nearly equals the complication risk of selective cerebral angiography in some studies. While selective cerebral angiography remains the basis of endovascular treatment CTA may improve workflow and enables endovascular treatment to be more focused and less time consuming. CTA is minimally invasive, can immediately follow the unenhanced CT demonstrating SAH, only takes 10-15 seconds of scan time, and has a lower radiation exposure and is cheaper than selective cerebral angiography.

To be cost effective, a clinical guideline may be that selective cerebral angiography can be omitted if CTA results are positive and that a negative CTA result should be confirmed with a second reevaluation by a radiologist; at that point, a negative CTA should be accepted as the final diagnosis.

Further prospective data collection should be performed to test this clinical practice guideline we recommend. The remaining true indication for selective cerebral angiography is in patients with inconclusive CTA results, mostly due to insufficient experience with or confidence in the modality. It is very likely that with improved technical acquisition and postprocessing techniques with isotropic voxel resolutions of up to 0.4 mm for 64-section CTA experience will further improve the sensitivity of CTA.

Both CTA and selective cerebral angiography continue to improve and new fields are open for future studies, such as the additional value of 3D rotational angiography and bone-subtraction CTA or dual-energy direct bone removal CTA in patients with SAH. Further research is required into whether these methods and information improve decision making.
Although the results of 3D TOF MRA at 1.5 T as a first diagnostic modality in the selection of patients suitable for surgical treatment of ruptured intracranial aneurysms in the acute phase were promising, meanwhile a shift in the management of ruptured intracranial aneurysm from surgery to endovascular means has appeared. This shift in treatment management demands the imaging modality not only to identify the source of bleeding but also to provide a pre-treatment assessment of the detected aneurysm. 3D TOF MRA is considered inadequate for the characterization and therefore for the pretreatment assessment of intracranial aneurysms. The main limitation of 3D TOF MRA in the assessment of aneurysm morphology is the fact that high signal represents flow rather than the real boundaries of the aneurysm. At 3D TOF MRA slow flow within the aneurysm may escape detection and provide false impression of aneurysm morphology. Furthermore, signal inhomogeneities due, for example, to spin dephasing may lead to an imprecise depiction of the aneurysm neck. The decision as to whether an aneurysm is suited for coil embolization or surgery can usually be based on multidetector CTA. Furthermore, the 3D information of multidetector CTA can be used to support treatment planning by assessing aneurysm morphology and the relationship to the parent vessels, and by finding a suited working projection. Concerning neurosurgical clipping, an increasing number of neurosurgeons rely on CTA as the sole preoperative imaging. At present, CTA is better suited than MRA in the acute stage of SAH: unenhanced CT to demonstrate SAH may be combined with CTA in the same session and MRA is often impractical in severely affected patients. The rapid development of faster MR scan techniques and the benefits of MR imaging with higher magnetic fields enable MRA to date to be a good screening method for detecting unruptured aneurysms.

Documentation of good diagnostic performance of 3D TOF MRA at 1.5 T represents an important step toward replacing selective cerebral angiography with MRA in the follow-up of patients with aneurysms treated with coils. MRA evolution has increased the utility of this modality in investigating the circle of Willis. MRA at 3 T may potentially be superior to MRA at 1.5 T because of higher spatial resolution, more efficient suppression of the background tissue, and higher signal-to-noise ratio.

In addition, using parallel imaging on higher magnetic field strength scanners, a combination with a multi-channel phased-array head coil, greater spatial and temporal resolution can be achieved. Turbulent and complex flow patterns within aneurysms and tortuous vascular segments can result in significant signal-intensity loss on 3D TOF-MRA. This can be largely overcome with a contrast-enhanced MRA (CE-MRA) technique. More 3T MRA and CE-MRA studies are required to explore their exact value in the follow-up of coiled aneurysms.

Summary in Dutch

Deel 1:

Niet-invasieve beeldvorming van intracraniële aneurysmata bij patiënten met een acute subarachnoidale bloeding

Deel 2:

Niet-invasieve beeldvorming van intracraniële aneurysmata na endovasculaire behandeling

Deel 1: Niet-invasieve beeldvorming van intracraniële aneurysmata bij patiënten met een acute subarachnoidale bloeding

Een subarachnoidale bloeding (SAB) is een bloeding rond of in de hersenen onder het spinnenwebvlies (arachnoidea). Meestal treden deze bloedingen op vanuit een aneurysma (uitstulping van de wand) van een slagader die onder de hersenen loopt, vlakbij of deel uitmakend van de cirkel van Willis. Een SAB is een ernstige aandoening met een slechte prognose voor veel patiënten. Snelle diagnostiek en behandeling zijn cruciaal voor de prognose van de patiënt. Ofschoon selectieve cerebrale angiografie wordt beschouwd als de gouden standaard in de diagnostiek van intracraniële aneurymata, is deze techniek invasief, tijdsintensief en niet zonder risico op complicaties. Magnetische resonantie angiografie (MRA) en computertomografie angiografie (CTA) zijn minder invasieve beschikbare alternatieven voor selectieve cerebrale angiografie.

In hoofdstuk 2 hebben we een systematische literatuurstudie en meta-analyse uitgevoerd naar de resultaten van CTA bij patiënten met een subarachnoidale bloeding. Er werden 42 studies geïncludeerd van goede methodologische kwaliteit. Er was sprake van publicatiebias (dit is de vertekening die ontstaat als positieve resultaten van een nieuwe modaliteit of behandeling wel, maar negatieve of onduidelijke resultaten niet gepubliceerd worden). CTA bleek een hoge diagnostische waarde te hebben in het vaststellen van geruptureerde intracraniële aneurysmata (gepoolde sensitiviteit 98% en gepoolde specificiteit 100%). Studies die de selectieve cerebrale angiografie als gouden standaard gebruikten, waren heterogener (de studies kwamen minder goed met elkaar overeen wat betreft onderzochte populatie, onderzoeksopzet en methode van analyseren) en hadden een lagere sensitiviteit en specificiteit dan studies die de bevindingen tijdens behandeling (chirurgisch of endovasculair) of obductie als gouden standaard gebruikten. In de meeste studies werd een 4-detector scanner gebruikt. Specificiteit en sensitiviteit voor 4- of 16/64-detector scanners waren vergelijkbaar, hoewel studies met 16- of 64-detector scanners minimale heterogeniteit in sensitiviteit hadden vergeleken met de 4-detector scanner. De meeste aneurysmata die met CTA gemist werden (fout-negatieve CTA) bevonden zich vlakbij de centrale schedelbasis (aneurysmata van de arteria carotis interna en de arteria communicans posterior). Wanneer (na detectie met de gouden standaard) de CTA nogmaals werd bekeken, kon een aanzienlijk aantal gemiste aneurysmata alsnog worden aangetoond.

In hoofdstuk 3 stelden we vast dat de behandeling van patiënten met een aneurysmatische SAB kan worden bepaald met alleen CTA. De selectieve cerebrale angiografie had geen of slechts een minimale toegevoegde waarde bij patiënten met een negatief CTA resultaat. Alleen bij patiënten met een inconclusief CTA-resultaat (meestal door moeilijkheden met de differentatie tussen infundibulum, vaatlus en aneurysma en onvolledige informatie omtrent locatie en oriëntatie van het aneurysma) was de selectieve cerebrale angiografie geïndiceerd. In meer dan de helft van deze patiënten gaf de selectieve cerebrale angiografie relevante nieuwe diagnostische informatie.

In hoofdstuk 4 toonden we aan, dat de 1,5 Tesla 3 dimensionale time-of-flight MRA (3D TOF MRA) toepasbaar is als eerste diagnostische modaliteit bij de selectie van patiënten die geschikt zijn voor chirurgische behandeling van geruptureerde aneurysmata in de acute fase. Deze strategie veroorzaakte geen morbiditeit of mortaliteit. Er waren geen fout-negatieve MRA resultaten. De inconclusieve MRA resultaten werden meestal veroorzaakt door moeilijkheden met de differentiatie tussen infundibulum, vaatlus en aneurysma, onvolledige informatie omtrent locatie en oriëntatie van het aneurysma en de aanwezigheid van arteriële vaatspasmen. Uiteindelijk bleek de initieel als inconclusief geclassificeerde diagnose met MRA in de meerderheid van de patiënten overeen te komen met de bevindingen van de selectieve cerebrale angiografie.

Deel 2: Niet-invasieve beeldvorming van intracraniële aneurysmata na endovasculaire behandeling

Endovasculaire behandeling met platina spiraaltjes (coils) van daarvoor geschikte geruptureerde of ongeruptureerde intracraniële aneurysmata is effectief en veilig, maar kent enkele tekortkomingen. Niet alle aneurysmata kunnen volledig geoccludeerd worden tijdens de eerste behandeling. Patiënten met een recent geruptureerd aneurysma hebben in deze gevallen kans op een vroege recidief bloeding. Ook aanvankelijk volledig geoccludeerde aneurysmata kunnen na verloop van tijd openen als gevolg van inklinking van coils, groei van het aneurysma of oplossen van intraluminale stolsels. Om de stabiliteit van de occlusie en de noodzaak voor nieuwe behandeling te beoordelen wordt vervolgonderzoek met beeldvorming uitgevoerd. Selectieve cerebrale angiografie wordt hiervoor als de gouden standaard beschouwd. Dit onderzoek is echter invasief, maakt gebruik van röntgenstraling en heeft een kleine kans op complicaties. MRA is een niet-invasieve beeldvormende techniek, waarbij geen röntgenstraling wordt gebruikt.

In hoofdstuk 5 vergeleken we 1.5 Tesla 3D TOF MRA met selectieve cerebrale angiografie. We toonden aan dat de niet-invasieve 3D TOF MRA geschikt is als follow-up onderzoek van gecoilde intracraniële aneurysmata om de mate van occlusie van het aneurysma vast te stellen. De invasieve selectieve cerebrale angiografie kan hiermee in de meeste gevallen komen te vervallen. In hoofdstuk 6 concludeerden we dat 1.5 Tesla 3D TOF MRA bij de meerderheid van de patiënten als eerste diagnostische modaliteit na coiling gebruikt kan worden. MRA had een hoge negatief voorspellende waarde voor aneurysma recidieven. Dit betekent dat er slechts een kleine kans is dat een aneurysma recidief wordt gevonden met selectieve cerebrale angiografie als de MRA volledige occlusie van het aneurysma toont. De belangrijkste indicaties voor follow-up met selectieve cerebrale angiografie zijn magnetische susceptibiliteitsartefacten in het gecoilde aneurysma en onvoldoende afbeelding van de aneurysmahals.

Praktische aanbevelingen

CTA heeft zich ontwikkeld tot de nieuwe standaard in de diagnostische beeldvorming bij patiënten met een SAB. CTA maakt snelle diagnostiek en behandelingskeuze van geruptureerde intracraniële aneurysmata mogelijk. De diagnostische kwaliteit van CTA heeft die van 2D selectieve cerebrale angiografie overtroffen. De kans op een fout negatieve uitslag met CTA is vergelijkbaar met de kans op complicaties met selectieve cerebrale angiografie in sommige studies. Selectieve cerebrale angiografie blijft nodig voor de endovasculaire behandeling van intracraniële aneurysmata. CTA kan de workflow verhogen en de endovasculaire behandeling doelgerichter en tijdsbesparend maken. CTA is minimaal invasief, kan aansluitend volgen op de standaard CT scan waarop een SAB is aangetoond, kost slechts 10-15 seconden scantijd, heeft een lagere stralingsbelasting en is goedkoper dan selectieve cerebrale angiografie. Selectieve cerebrale angiografie kan worden overgeslagen als de CTA positief is en een negatieve CTA moet worden bevestigd met een tweede herbeoordeling door een radioloog; in dat geval zou een negatieve CTA als uiteindelijke diagnose geaccepteerd moeten worden. Dit advies zou verder getest moeten worden met prospectief onderzoek. Selectieve cerebrale angiografie is alleen nog geïndiceerd bij inconclusieve CTA resultaten, vaak als gevolg van onvoldoende ervaring met of vertrouwen in de modaliteit. Met verdere verbeteringen in de technische acquisitie en postprocessing technieken en met het toenemen van de ervaring zal de sensitiviteit van de CTA nog hoger worden.

Nieuwe ontwikkelingen op het gebied van zowel subtractie CTA of dual-energy direct bone removal CTA als 3D rotatie angiografie openen de weg voor verder onderzoek naar de toegevoegde waarde van deze technieken bij patiënten met SAB. Verder onderzoek is nodig om te bepalen in welke mate deze technieken de besluitvorming zullen verbeteren.

De resultaten van 1,5 Tesla 3D TOF MRA als eerste diagnostische modaliteit bij de selectie van patiënten die geschikt zijn voor acute chirurgische behandeling van geruptureerde aneurysmata waren veelbelovend. Echter, sindsdien is een verschuiving in de behandeling van cerebrovasculaire aneurysmata van chirurgie naar coiling opgetreden. Dezewijziging in het behandelbeleid heeft ertoe geleid, dat de beeldvormende techniek niet alleen de bloedingsbron moet kunnen aantonen, maar ook in staat moet zijn om de vereiste informatie voor de behandelingskeuze van het gedetecteerde aneurysma te leveren. 3D TOF MRA is minder goed toepasbaar in het afbeelden van de morfologie van het aneurysma. De belangrijkste beperking van 3D TOF MRA is gelegen in het feit, dat hoog signaal overeenkomt met flow en niet met de werkelijke begrenzingen van het aneurysma. Met 3D TOF MRA kan trage flow in het aneurysma gemist worden, wat kan leiden tot een onjuiste weergave van de morfologie van het aneurysma. Ook kunnen signaalinhomogeniteiten bijvoorbeeld als gevolg van "spin dephasing" leiden tot onnauwkeurige afbeelding van de aneurysmahals. Met multidetector CTA is het doorgaans wél goed mogelijk om te besluiten of een aneurysma geschikt is voor embolisatie met coils of voor chirurgie. De 3D informatie van multidetector CTA kan

gebruikt worden om de planning van de behandeling te ondersteunen. Voor de neurochirurgische behandeling geldt, dat een toenemend aantal neurochirurgen vertrouwt op de preoperatieve beeldvorming met CTA. Momenteel is CTA geschikter dan MRA in het acute stadium van SAB: de standaard CT om de SAB aan te tonen kan gecombineerd worden met CTA in dezelfde sessie en MRA is soms onuitvoerbaar bij ernstig zieke patiënten (gezien langere scantijd, onrustige patiënt, eventuele beademing etc). De ontwikkeling van snellere MR scantechnieken en de voordelen van MR beeldvorming met hogere magneetveldsterktes maken MRA een geschikte modaliteit voor het screenen op niet-geruptureerde aneurysmata bij een coöperatieve patiënt.

Door het aantonen van de hoge diagnostische kwaliteit van 1,5 Tesla 3D TOF MRA in de follow-up van endovasculair behandelde intracraniële aneurysmata is een belangrijke stap voorwaarts gemaakt. Hierdoor kan in de meeste gevallen selectieve cerebrale angiografie worden vervangen door MRA. Door de verdere technische ontwikkeling van MRA is de bruikbaarheid van deze modaliteit bij het onderzoeken van de cirkel van Willis toegenomen. Beeldvorming met 3 Tesla MRA is mogelijk beter dan met 1,5 Tesla MRA, vanwege hogere spatiële resolutie, betere onderdrukking van achtergrondweefsel en hogere signaalruis verhouding. Door het gebruik van parallel imaging bij sterkere magneetvelden kunnen hogere spatiële en temporele resolutie bereikt worden. Turbulente flow in aneurysmata en kronkelige vaatsegmenten kunnen leiden tot signaalverlies op 3D TOF MRA. Contrastversterkte-MRA kan hierbij uitkomst bieden. Meer 3 Tesla- en contrastversterkte-MRA studies zijn noodzakelijk om hun precieze waarde in de follow-up van endovasculair behandelde intracraniële aneurysmata te bepalen, maar de vooruitzichten zijn veelbelovend.

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Curriculum vitae

Henriëtte Ellen Westerlaan was born on February 11th 1975 in Oosterwolde, the Netherlands. She graduated from secondary school in 1993 (Stellingwerf College, Oosterwolde). In 1993 she started Medical School at the University of Groningen, where she obtained her medical degree in 1999. She then became a resident in Pulmonology and Internal Medicine at the Medisch Spectrum Twente, Enschede. In November 2001 she started a research position at the Department of Radiology at the University Medical Center Groningen, which resulted in the beginning of this thesis. In July 2002 she became resident in Radiology at the University Medical Center Groningen. She completed five years of training as a radiologist, under supervision of Prof. Dr. M. Oudkerk and Prof. Dr. E.J. van der Jagt, and two years of a fellowship in Neuroradiology and Head and Neck Radiology, under supervision of Dr. L.C. Meiners. In September 2009 she obtained a European Board Certification in Diagnostic Neuroradiology. During her residency and fellowship she continued her research, culminating in this thesis. Since July 2007 she is staff member of the Department of Radiology at the University Medical Center Groningen.

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