Intracranial Aneurysms and Subarachnoid Hemorrhage

Clinical studies on diagnosis and treatment

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Cover design
Victor Loop (aged *4*, when he made the drawing)

Layout
Matthijs de Sain-Groen

Printed by
Optima Grafische Communicatie

ISBN-10: 90-9020366-4
ISBN-13: 978-90-9020366-9

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Further financial support for the publication of this thesis was provided by
Siemens Medical Solutions, Boston Scientific, Sanofi-Aventis, Boehringer, UCB Pharma, Bristol-Myers Squibb, Biogen Idec

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Clinical studies on diagnosis and treatment

Intracraniële aneurysmata en de subarachnoïdale bloeding

Klinische studies betreffende diagnostiek en behandeling

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 7 juni 2006 om 11.45 uur

door

Mathieu van der Jagt

geboren te Oud-Beijerland

Promotiecommissie:

Promotoren	**:**	Prof.dr. P.J. Koudstaal Prof.dr. C.J.J. Avezaat
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The mind of the most rational among us
may be compared to a stormy ocean of passionate convictions based upon desire,
upon which float perilously a few tiny boats carrying a cargo of scientifically tested beliefs.
Bertrand Russell, The Scientific Outlook (1931)

Dedicated to those who have suffered from aneurysmal subarachnoid hemorrhage
and their families

Table of Contents

1

General introduction

1.1. General aspects of aneurysmal subarachnoid hemorrhage

Epidemiology

Spontaneous subarachnoid hemorrhage (SAH) is caused in 85% of cases by rupture of an intracranial – mostly saccular – aneurysm, located at the junction of two or more arteries at the base of the brain.[27,28] In the remaining patients with SAH who do not have an aneurysm either another cause such as an arteriovenous malformation, or no cause at all is found. Reported incidence rates of SAH vary between 5 and 10 per 100.000 persons per year.[28] Therefore the estimated incidence of SAH in the Netherlands amounts to between 800 and 1600 cases. Mortality after aneurysmal SAH is at least 30%, which equals mortality after ischemic stroke, but SAH strikes younger patients, on average in the sixth decade.[8,28,29] The most important causes of death after aneurysmal SAH are the direct effects of the initial bleed, rebleeding and delayed cerebral ischemia.[30,31] Patients in whom no cause is found usually have an excellent prognosis.

Signs and symptoms

Sudden and severe headache, commonly described by patients as "the worst headache ever", frequently accompanied by nausea and vomiting, should always raise the suspicion of aneurysmal SAH.[32] Unfortunately, both patient's and doctor's delay are common because the typical clinical presentation with headache of acute onset is often misinterpreted as a less devastating disorder, such as migraine.[34] Furthermore, the initial symptoms may not always be easily elicited, for instance when the patient's consciousness is impaired and history taking is impossible, or in case of concurrent traumatic brain injury that may be wrongly considered as the primary cause of SAH. Another reason for misinterpretation is that SAH usually occurs in patients who have been relatively healthy in terms of cardiovascular co-morbidity compared with patients with ischemic stroke or intracerebral hemorrhage, and that focal neurological deficits are typically absent at onset. Finally, SAH may present with atypical symptoms, for instance with coma and fever mimicking meningitis, with delirium or with signs and symptoms of myocardial infarction due to neurogenic myocardial dysfunction.[32,33] Delayed diagnosis may have serious consequences in terms of outcome and cerebral complications and therefore early diagnosis and immediate referral to hospital are essential.[34]

Recent advances

Several recent advances in the diagnosis and treatment of patients with aneurysmal subarachnoid hemorrhage have contributed to a more optimistic outlook for patients with this devastating disease. Computerized tomography angiography (CTA) has become a potential alternative for conventional digital

subtraction angiography (DSA) with the Seldinger technique to assess presence and localization of intracranial aneurysms and allow decisions on the best mode of treatment.[1] CT-angiography confers substantial advantage over DSA in these patients, because it can be performed much quicker, in unstable or agitated patients, and with fewer resources and less risk for the patient. However, it is still uncertain whether the diagnostic accuracy of CTA equals that of DSA. On the other hand, because of the widespread availability of CT angiography, many hospitals have already implemented CTA in the diagnostic work-up of SAH patients.[25,26]

Endovascular treatment has been shown to improve outcome compared with surgical treatment of ruptured aneurysms,[2,3] at least on the short term, and most physicians nowadays consider endovascular treatment the preferred treatment when feasible. Intravenous magnesium,[4] intrathecal urokinase (after endovascular occlusion of the ruptured aneurysm[5]) and statins[6] all have been found to prevent vasospasm and cerebral ischemia. Further clinical studies on clinical efficacy of these drugs are underway. However, although declining mortality has been reported after aneurysmal SAH, mortality after aneurysmal subarachnoid hemorrhage remains high (around 30%).[7,8,9] Therefore, further improvements in diagnostic and therapeutic management of this disease are needed.

1.2. Background and aim of the thesis

Clinical significance of the amount of blood and blood distribution on CT

High amount of cisternal blood on initial CT after aneurysmal SAH and the presence of localized blood clot in de subarachnoid cisterns have been associated with the occurrence of vasospasm and delayed cerebral ischemia.[17,18-20] Different methods have been described to assess the amount of blood on CT.[15,18-20] In only one of these studies interobserver agreement was elaborately tested and proved reliable.[15] However, in this study the investigators were familiarized with the method of assessment of the amount of blood on CT in advance. Therefore, in clinical practice the assessment of the amount of blood on CT by physicians unfamiliar with the methods used in these studies may not yield the high interobserver agreement that was found previously. This may have consequences for the reproducibility of the method of assessment of the amount of blood on CT. Furthermore, the high correlation between the scores assigned by different observers as has been found previously may negate the fact that individual assessments may differ to a great extent.[16] The importance of the prognostic value of the amount of blood on CT for the development of cerebral ischemia lies in the fact that statistical models such as multivariate logistic regression analyses have to include the amount of blood when this is considered an independent prognostic factor. Further, a high amount of blood on CT may be used as a clinical selection criterion when studying the efficacy of new treatment modalities for cerebral ischemia or prophylactic treatments in patients at risk for cerebral ischemia.

Intuitively, it seems plausible that subarachnoid blood from a ruptured aneurysm is localized around the ruptured aneurysm. Therefore, the blood distribution on CT may predict the localization of the ruptured aneurysm. The localizing value of blood on CT may be important in patients with SAH in whom more than one aneurysm is found with angiographic studies, as is the case in approximately 20% of patients, especially when the aneurysms cannot be treated simultaneously in one surgical procedure. In that case identification of the ruptured aneurysm is of great importance. In case of a localized intracerebral hematoma with a flame-like configuration originating from the place where the anterior communicating artery or middle cerebral artery runs, identification of the location of the ruptured aneurysm will be easy. However, false localization of the ruptured aneurysm and treatment of another unruptured aneurysms have been reported in SAH patients with multiple aneurysms because cisternal blood distribution on CT apparently did not correspond with the location of the ruptured aneurysm or the ruptured aneurysm was missed on angiography.[21,22] Anatomic characteristics of intracranial aneurysms as found on angiographic studies, such as the size of the aneurysm and irregularities of the aneurysmal wall, have been associated with rupture.[23,24] On the other hand, smaller aneurysms are not excluded from causing SAH,[21] and not all ruptured aneurysms show wall irregularities. The localizing value of the blood distribution on CT for the ruptured aneurysm has not been studied systematically.

Risk of re-rupture and timing of aneurysm surgery

Re-rupture of an intracranial aneurysm, causing a rebleed, has a mortality of 80%. The risk of re-rupture after conservative treatment is 15-25% in the first two weeks, 40-50% up to 6 months after the bleed and 2-3% annually thereafter.[35-38] Therefore occlusion of a ruptured aneurysm should be performed as soon as possible, preferably within the first days after SAH. Currently, endovascular treatment is generally considered the preferred treatment for ruptured aneurysms that are technically suitable for this treatment.[2,3] When endovascular treatment is not feasible, surgical treatment is indicated. In the 1960s and 1970s, many neurosurgeons preferred delayed surgery, because early surgery within the first few days after the bleed posed significant technical difficulties to successful occlusion by means of clipping of the ruptured aneurysm.[39] Impaired access to and visibility of the ruptured aneurysm is caused by a tightly swollen brain in the acute phase after bleeding and the presence of abundant subarachnoid blood clots. The tendency of cerebral arteries surrounded by fresh subarachnoid blood clot to easily develop extensive vasospasm, which is considered an important contributor to the development of cerebral ischemia, was considered to be another disadvantage of surgery within the first two weeks after the bleed.[18] Therefore, delaying surgery at the cost of increased risk of re-rupture of the aneurysm seemed more attractive. After this period, most neurosurgeons adopted a strategy of early surgery (most frequently defined as surgery within 72 hours after the initial bleed),

mostly in patients with good clinical grades, because microsurgical techniques had advanced and technical difficulties with surgical occlusion had subsided.[40,41] Moreover, successful reversal of ischemic deficits by means of hypervolemic hypertensive hemodilution therapy had been reported extensively and the consequences of vasospasm seemed, at least in some cases, treatable.[42] However, conclusive evidence from controlled trials in favor of early surgery is lacking. Further, many studies on the timing of aneurysm surgery seem to affirm that early surgery can prevent re-rupture at the cost of increased rate of cerebral ischemia, thereby negating the potential beneficial effect of prevention of re-ruptures on overall outcome.[39,40,41]

Computerized tomography angiography (CTA)

Digital subtraction angiography has been the reference standard for the evaluation of the presence, and feasibility and selection of treatment of ruptured intracranial aneurysms for many years. However, DSA is an invasive procedure with a risk of neurological complications of 0.9-2.3% and a risk of permanent neurological deficit of 0.3%.[25] Recently, the shift from surgical therapy as first line treatment of ruptured aneurysms to endovascular treatment in many centers in Europe since publication of the ISAT trial[2,3] increased pressure on angiographic resources. The introduction of CTA in the diagnosis of ruptured aneurysms has alleviated the increased pressure to some extent, whilst it has also improved time to diagnosis and planning of definitive treatment. The advent of multidetector row CT scanners has steadily improved diagnostic accuracy of CT scanners due to improved spatial and temporal resolution.[1,25] Only very recently, equivalent diagnostic accuracy both in terms of sensitivity and specificity and pre-treatment evaluation of the best mode of treatment – endovascular or surgical - has been reported with 16-detector row CT angiography as compared with DSA. This was also the first study to report on 16- instead of 4-detector row CT angiography in a clinical setting with a reference standard that included not only the DSA but also other available clinical information such as perioperative findings.[26] In this study, some aneurysms were more clearly depicted with 3D-CTA than with DSA. When the neurosurgeon required additional DSA because of doubt on the CTA results, no clear additional information regarding surgical anatomy was provided by DSA except in one patient with an anterior communicating artery aneurysm in whom CTA did not reveal whether the anterior communicating artery was filling from the right or left side. Furthermore, the shift to endovascular treatment may have altered the requirements posed on angiographic visualization of intracranial aneurysm, because surgical and endovascular approaches probably differ with respect to the required level of anatomical detail of the aneurysm and its surrounding arteries. Finally, implementation of CTA in the pre-treatment evaluation of cerebral aneurysms is subject to a learning curve. All together, the high diagnostic accuracy of 16-detector row CT scanners in the evaluation of ruptured intracranial aneurysms needs confirmation and the diagnostic value of these high resolution multidetector row CT

scanners with respect to the clinical assessment regarding the feasibility of endovascular treatment of the ruptured aneurysm should be studied.

Rupture rate of unruptured intracranial aneurysms

Patients with unruptured intracranial aneurysms are at risk of suffering from SAH in the future. These unruptured –or incidental- intracranial aneurysms (UIAs) may be found when these patients have a CTA or Magnetic Resonance Angiography (MRA) or DSA for reasons unrelated or related to the presence of an UIA, for instance ischemic stroke, primary intracerebral hemorrhage or oculomotor nerve palsy. Observational studies have reported annual rupture rates of UIAs varying between 0.7 and 7%.[10] This is too wide an interval to be able to perform an unequivocal decision analysis to decide whether the risk of treatment of the UIA is less than the risk of watchful waiting, because the decision to treat or not to treat greatly depends on the estimated life time rupture risk of the UIA and the sequelae. The estimations of annual rupture rates vary widely in different observational studies because of differences in methodological quality.[11] Most decision analyses use rupture risk estimates based either on the most frequently reported annual rupture risk or based on studies in which relatively many subjects were included.[12,13] However, although precision of estimated rupture risk increases with increasing number of subjects included in the study, internal and external validity is hampered when lack of methodological quality causes biased estimates.[14]

The aim of this thesis is to provide answers to the following questions:

1. Does the blood distribution on initial CT after aneurysmal subarachnoid hemorrhage help to determine the location of the ruptured aneurysm?
2. To what extent is the assessment of the amount of cisternal blood on initial CT subject to interobserver variability?
3. What is the diagnostic accuracy of the recently introduced 16-detector row CT angiography for the detection of intracranial aneurysms, when compared with a reference standard that includes all available clinical and radiological information?
4. Does a treatment strategy that includes early aneurysm surgery (within 72 hours after the initial bleed) in patients in good clinical condition after aneurysmal subarachnoid hemorrhage improve outcome when compared to a treatment strategy aimed at postponed surgery in all patients?
5. Can 16-detector row computerized tomography angiography (CTA) replace digital subtraction angiography (DSA) as sole diagnostic investigation in the acute phase after aneurysmal subarachnoid hemorrhage for the assessment of feasibility of endovascular treatment?

6. What is the annual rupture rate of unruptured intracranial aneurysms based on observational studies primarily aimed at determining rupture rate, when these studies are systematically assessed taking into account methodological quality?

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2

Aneurysmal subarachnoid hemorrhage: diagnosis

2.1

Validity of prediction of the site of ruptured intracranial aneurysms with CT

Abstract

Objective

We studied the diagnostic power of blood distribution on CT scan (performed within 72 hours after the bleed) for the site of ruptured aneurysm in 168 consecutive patients with SAH with either a single aneurysm or no aneurysm on the four-vessel angiogram or postmortem examination.

Methods

A neurosurgeon and a neuroradiologist blind to the results of the angiography independently scored the distribution of blood on the CT and predicted the site of the ruptured aneurysm.

Results

Overall agreement among raters was 52% and chance-adjusted agreement (kappa) was 0.42 (weighted kappa-value 0.47). A parenchymal cerebral hematoma was an excellent predictor for the site of a ruptured aneurysm but was present only in a minority of cases (15%). The next most valid predictor was blood distribution on CT in patients with a ruptured anterior cerebral artery aneurysm or anterior communicating artery aneurysm (sensitivity 0.79, specificity 0.96, and positive predictive value 0.79 for rater 1; sensitivity 0.77, specificity 0.97, and positive predictive value 0.90 for rater 2). The validity of the predictive value of blood distribution on CT in patients with a ruptured aneurysm of the middle cerebral artery, internal carotid artery, or posterior circulation arteries was either inconsistent between raters or low.

Conclusion

With the exception of the presence of a parenchymal hematoma, the site of the ruptured aneurysm can be predicted by CT only in ruptured anterior cerebral artery or anterior communicating artery aneurysms.

Introduction

In patients with multiple aneurysms (12% to 45% of patients with aneurysmal SAH[1,2,3,4,5,6,7,8,9,10,11]) that cannot be clipped in one surgical session, accurate identification of the ruptured aneurysm followed by clipping of the ruptured aneurysm as soon as possible after the bleeding is of vital importance. Misjudgment in the determination of the site of the ruptured aneurysm may result in clipping of the wrong aneurysm.[12]
Angiography is the principal investigation for the determination of the site of a ruptured intracranial aneurysm after subarachnoid hemorrhage (SAH).[13] The sensitivity of this diagnostic procedure for the detection of the site of ruptured aneurysm in cases with a single aneurysm is more than 95%.[13] But in multiple aneurysms, the diagnostic power of angiographic features for the ruptured aneurysm has not been established.[3,14,15,16] Others claim that it is possible to determine the site of the ruptured aneurysm in case of multiple aneurysms by means of the distribution of blood on the initial CT scan, but sensitivity in those studies varies widely from 45% to 86%.[6,10]
Therefore, we investigated the diagnostic power of the blood distribution on CT scan (performed within 72 hours after the bleed) for the site of the ruptured aneurysm.

Patients and Methods

Between January 1989 and December 1992, a total of 308 consecutive patients with signs and symptoms of aneurysmal SAH were admitted to the Intensive Care Unit of the Departments of Neurology and Neurosurgery of the Academisch Ziekenhuis Rotterdam Dijkzigt. The diagnosis was confirmed by CT scanning on admission or, in case of negative CT scanning, by spectrophotometric evidence of xanthochromia in the cerebrospinal fluid (CSF). Thirty-four patients were admitted beyond 72 hours following the initial bleed. Another 71 patients did not undergo angiography because of the bad clinical condition. In 34 other patients more than one aneurysm was found and the CT scan of one patient was missing. In the remaining 168 patients, a four-vessel angiogram had been performed (157 patients) or an aneurysm had been confirmed by postmortem examination (11 patients). These patients were included in this study.
Two experts (a neurosurgeon and a neuroradiologist), who were unaware of the results of the angiography or postmortem examination, independently reviewed the CT scans. The amount of cisternal blood (14 cisterns) and ventricular blood was scored (no blood, partially filled with blood or completely filled with blood) as described previously[17] and the site of an intracranial hematoma was reported when present. On the basis of these findings, the raters predicted the site of the ruptured aneurysm. Diagnostic categories (predicted sites of aneurysm rupture) are: 1) non-aneurysmal SAH (non-aneurysmal perimesencephalic hemorrhage or

angionegative aneurysmal type SAH[18]); 2) right internal carotid artery (ICA); 3) left ICA; 4) anterior cerebral artery (ACA) or anterior communicating artery (ACoA); 5) right middle cerebral artery (MCA); 6) left MCA; 7) posterior circulation arteries; and 8) unknown site of rupture.

Table 1. Characteristics of 168 patients with subarachnoid hemorrhage (SAH).

	Patients with SAH n=168	
	no.	%
Sex		
male	60	36
female	108	64
mean age (in years)	51.2	
age		
≤40 years	40	24
41-60 years	83	49
>60 years	45	27
Loss of consciousness at ictus	80	48
Time interval between SAH and CT scan		
≤1 day	153	91
2 days	9	5
3 days	6	4
Sum score of Glasgow Coma Scale		
≤12	58	35
>12	110	65
Aneurysm site		
no aneurysm	39	23
right carotid artery	25	15
left carotid artery	7	4
anterior cerebral artery	48	29
right middle cerebral artery	19	11
left middle cerebral artery	13	8
posterior circulation	17	10

We calculated the agreement, the expected agreement, and chance-adjusted agreement (kappa) between raters.[19] In addition, we calculated weighted kappa-values. A weight of 1 indicates that the observations are in perfect agreement. The lower the weights the more serious the expected consequences are in case of disagreement.[20] A weight of 0 is given if raters disagree on the side (left or right) of the ruptured aneurysm or if there is disagreement on whether the aneurysm has supratentorial or infratentorial localization. Disagreement on an ICA and an MCA aneurysm located on the same side is not counted as full disagreement but rather as a 75% agreement and a weight of 0.75 is given. Disagreement on an ACA or ACoA aneurysm

and an ICA or MCA aneurysm is given a weight of 0.5. Thereafter, we calculated sensitivity, specificity, and positive predictive value of CT scan for the site of rupture in a 2x2 table with the results of the angiogram as the disease and the predictions by rater 1 or rater 2 as the test results.[21]

Results

Characteristics of the 168 patients with SAH are presented in *table 1*. We detected an aneurysm in 77% and in the remaining 23% the angiogram was negative. Time interval between SAH and CT scan was less than 24 hours in 91% of the patients. The frequency of right internal carotid artery aneurysms is much higher than that of left internal carotid artery aneurysms (*table 1*).

Agreement between raters is 52% (weighted agreement is 65%) and the expected agreement is 17% (weighted expected agreement is 35%). The kappa value is 0.42; 95% confidence interval 0.35-0.49 (weighted kappa value 0.47; 95% confidence interval 0.39-0.55). If analysis is restricted to patients with an ACA or ACoA aneurysm, agreement between raters is 67%, expected agreement is 62%, and kappa value is 0.12. On the other hand, if analysis is restricted to all other patients, agreement is 47%, expected agreement is 18%, and kappa value is 0.35.

In cases where raters agreed on the rupture of ACA or ACoA aneurysms, right MCA aneurysms, and left MCA aneurysms, the prediction proved to be correct in a high proportion of patients (31 of 32 [97%] for ACA or ACoA aneurysms, 14 of 19 [74%] for right MCA aneurysms, and 6 of 7 [86%] for left MCA aneurysms). Raters agreed on the prediction ruptured ICA aneurysm only once. Thus, in 51 (86%) of the 59 cases in which raters had agreed on the rupture of a supratentorial aneurysm the prediction was correct. In contrast, the proportion of correctly predicted ruptured aneurysm was low (eight of 20 cases, 40%) when the raters agreed on a ruptured posterior circulation artery aneurysm.

Raters were unable to predict the site of rupture (unknown site of rupture) in 25 patients (rater 1) and in 23 patients (rater 2) (*table 2*). In a few patients a contralateral supratentorial aneurysm was wrongly predicted (two patients by rater 1 and five patients by rater 2) (*table 2*). The difference between the two raters in the prediction of MCA aneurysms in case of a left MCA aneurysm on the angiogram is probably caused by inaccurate predictions of rater 2 in four of the five cases. Retrospectively, we found that rater 2 reported that cisternal blood in these four patients was located on the left side but then predicted the aneurysm to be located on the right side. Clearly, rater 2 mistook right for left in these patients. We did not correct these results. In addition, rater 2 predicted less patients with right ICA aneurysm rupture (two versus 16 patients, *table 2*) and more patients with ruptured right MCA aneurysm (48 versus 22 patients, *table 2*) than rater 1. This is explained by the fact that rater 2 often mistook right ICA aneurysms for right MCA aneurysms.

Table 2. Diagnostic power of predictions of the site of ruptured aneurysm by means of blood distribution on CT scan by the two raters in 168 patients with SAH admitted within 72 hours after onset of symptoms.

Site of ruptured aneurysm depicted by angiography		Site of ruptured aneurysm predicted by rater, n													
		Unknown		Non-aneurysmal		Right ICA		Left ICA		ACA or AcoA		Right MCA		Left MCA		Posterior circulation			
		No.		No.		No.		No.		No.		No.		No.		No.		Sensitivity	Specificity	Positive predictive value
No aneurysm	Rater 1	7		0		6		4		3		1		0		18		0.00	0.99	0.00
	Rater 2	7		3		0		1		1		6		3		18		0.08	0.98	0.60
Right ICA	Rater 1	7		0		6		0		6		4		0		2		0.24	0.95	0.38
	Rater 2	3		0		1		0		3		17		0		1		0.04	0.99	0.50
Left ICA	Rater 1	1		1		0		2		0		0		1		2		0.29	0.95	0.20
	Rater 2	0		1		0		2		0		0		2		2		0.29	0.99	0.50
ACA or ACoA	Rater 1	5		0		2		0		38		0		0		3		0.79	0.96	0.79
	Rater 2	4		1		0		0		37		3		2		1		0.77	0.97	0.90
Right MCA	Rater 1	0		0		0		0		1		17		1		0		0.89	0.97	0.77
	Rater 2	3		0		0		0		0		15		0		1		0.79	0.78	0.31
Left MCA	Rater 1	1		0		1		1		0		0		10		0		0.77	0.99	0.83
	Rater 2	2		0		0		0		0		5		6		0		0.46	0.95	0.46
Posterior Circulation	Rater 1	4		0		1		3		0		0		0		9		0.53	0.85	0.26
	Rater 2	4		0		1		1		0		2		0		9		0.53	0.85	0.28
Totals	Rater 1	25		1		16		10		48		22		12		34				
	Rater 2	23		5		2		4		41		48		13		32				

ICA = internal carotid artery
ACA = anterior cerebral artery
ACoA = anterior communicating artery
MCA = middle cerebral arteryaneurysm

In other patients a ruptured posterior circulation artery aneurysm was mistaken for an ICA aneurysm (four patients by rater 1 and two patients by rater 2) or for an MCA aneurysm (two patients by rater 2) (*table 2*). In addition, ruptured supratentorial aneurysms were mistaken for a posterior circulation artery aneurysm in seven patients by rater 1 and in four patients by rater 2 (*table 2*).

Non-aneurysmal SAH was predicted only in one patient by rater 1 (appeared to be an ICA aneurysm on the angiogram) and in five patients by rater 2 (correct prediction in three patients, one patient had an ACA or ACoA aneurysm, and one patient an ICA aneurysm). On the other hand, in many patients with a non-aneurysmal hemorrhage, a ruptured posterior circulation artery was predicted to have caused the bleed (18 of 39 patients by rater 1 and rater 2) (*table 2*). Parenchymal cerebral hematoma had always occurred in the immediate proximity of the site of rupture, but this was present only in 15% of the patients. The presence of ventricular blood had no localizing value.

Rupture of aneurysms of the ACA or ACoA (illustrated by *figure 1*) and right MCA were predicted with the highest sensitivity and specificity by both raters (*table 2*). Ruptured left MCA aneurysm was predicted with high sensitivity only by rater 1. Sensitivity of the prediction of ruptured posterior circulation artery aneurysm was 0.53 for both raters, and sensitivity of the prediction of ruptured ICA aneurysm was lower than 0.30 for both raters (illustrated by *figure 2*). Sensitivity was lowest for the prediction non-aneurysmal SAH. With the exception of the prediction of ruptured posterior circulation artery aneurysm and that of right MCA for rater 2, specificity was above 90% (*table 2*). The positive predictive value of CT was highest for ruptured ACA or ACoA aneurysm by both raters (0.79 and 0.90) and for ruptured right and left MCA by rater 1 (0.77 and 0.83). Predictions of rupture of the remaining aneurysms had a positive predictive value of 0.6 or lower (*table 2*). These results did not change when we restricted the analysis to patients who were admitted within 24 hours after SAH (data not shown).

Discussion

In this study, 91% of all CT was performed within 24 hours after the initial bleed. The proportion of negative angiograms was 23%. A posterior circulation artery aneurysm was found in 10%, and the remaining 67% of the patients had a supratentorial aneurysm. Surprisingly, the frequency of right internal carotid artery aneurysms, as depicted by angiography, by far exceeded that of left internal carotid artery aneurysms (15% versus 4%). In the interrater analysis, both raters agreed on the site of the ruptured aneurysm in 52%. As a result of the low expected agreement (17%), kappa value was moderate (0.42). If analysis is restricted to patients with an ACA or ACoA aneurysm agreement is even higher (67%), but because the expected agreement was not much lower (62%) kappa value was low (0.12).

Figure 1. An example of the computed tomogram of a patient with a ruptured aneurysm of the anterior communicating artery. In this patient, both raters made the correct prediction.

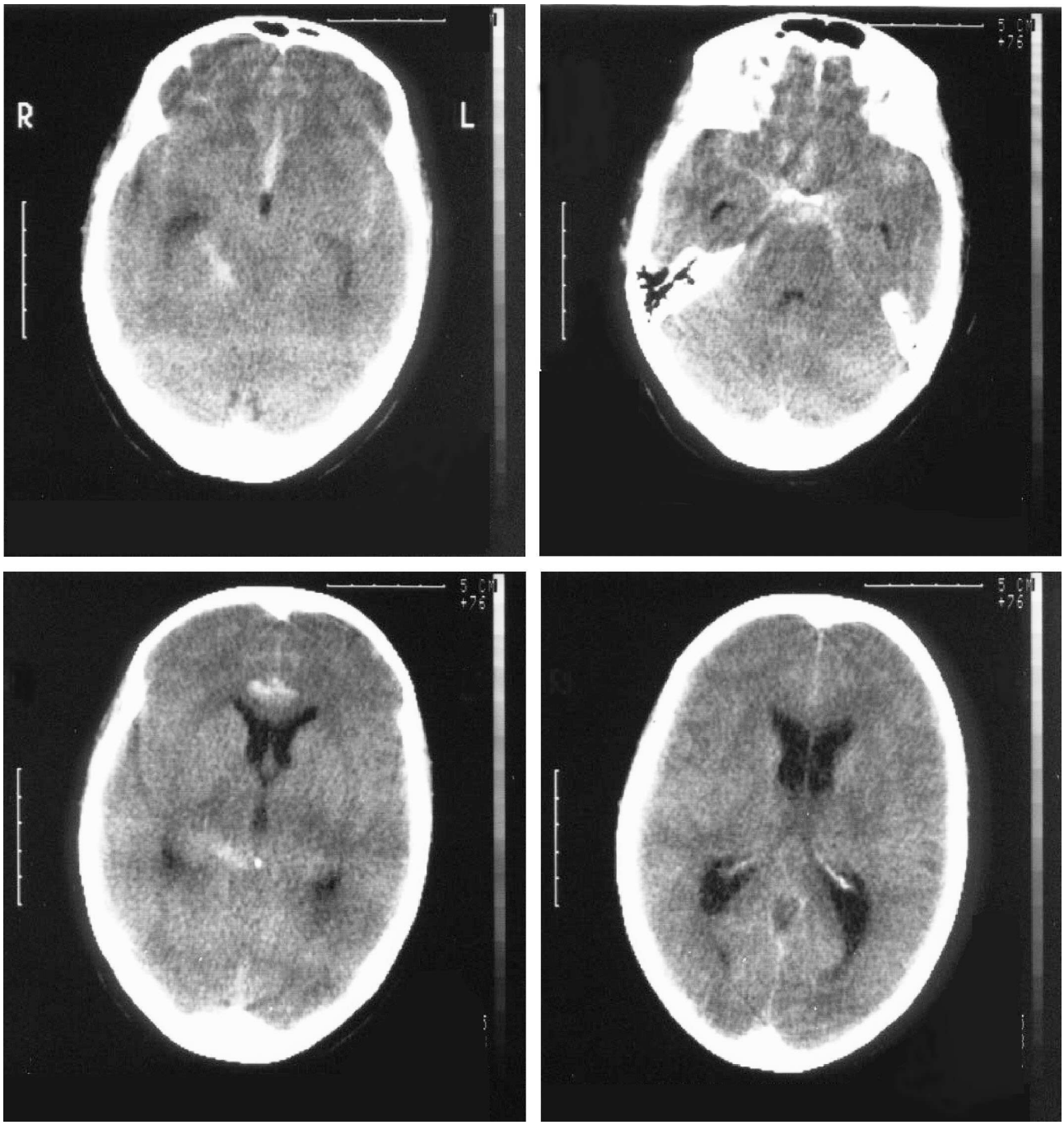
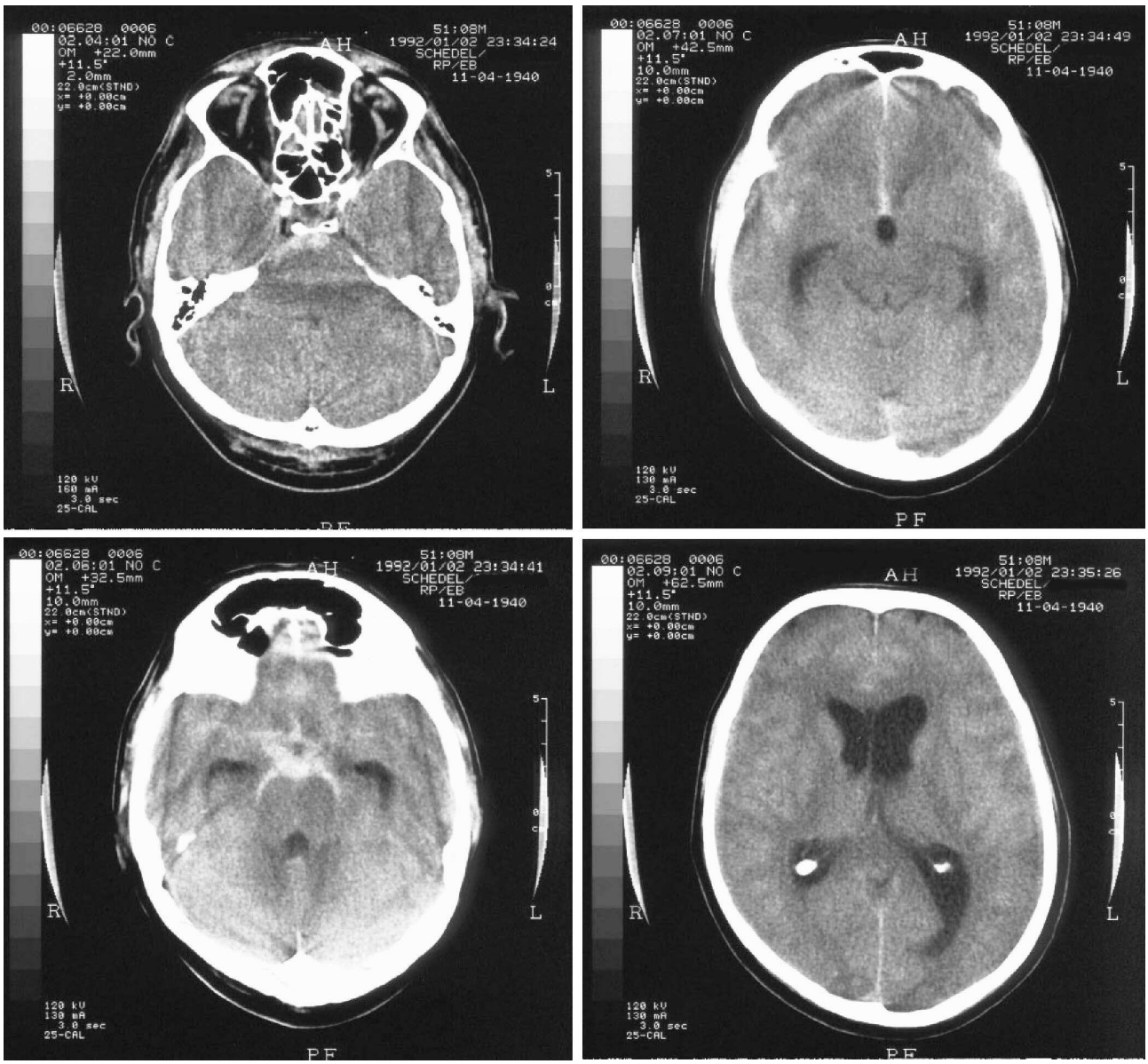


Figure 2. The computed tomogram of a patient with a ruptured aneurysm of the internal carotid artery at the origin of the right posterior communicating artery on the angiogram. In this patient, rater 1 predicted a ruptured aneurysm of the anterior communicating artery and rater 2 predicted a ruptured aneurysm of the basilar artery



In other words, a relatively high kappa value does not necessarily indicate high agreement between raters and low kappa value does not necessarily indicate low agreement between raters. Although agreement and expected agreement were slightly higher when weights for disagreement are applied, weighted kappa-value was similar to the original kappa-value.
In 86% of the cases in which raters had agreed on the rupture of a supratentorial aneurysm, the prediction was correct. However, the validity of CT for the prediction of ruptured ICA aneurysm is low. In addition, the proportion of correct predictions in cases where raters had agreed on the site of ruptured posterior circulation artery aneurysms was also low (40%).

The high proportion of patients with a negative angiogram and with perimesencephalic blood pattern in this group had caused the latter. It is clear that both raters had difficulties in distinguishing SAH caused by a ruptured posterior circulation artery aneurysm from non-aneurysmal SAH: both raters predicted the presence of a ruptured aneurysm in most cases where no aneurysm could be found by angiography (*table 2*). Furthermore, it may be quite difficult to distinguish ICA from MCA aneurysms on one side, because rater 2 often mistook a right ICA for a right MCA aneurysm. In patients with an SAH caused by a ruptured supratentorial aneurysm, both raters predicted a ruptured posterior circulation artery aneurysm, or could not make a prediction of the site of rupture, or suspected a non-aneurysmal SAH in nearly one-fifth of the cases. On the other hand, when a posterior circulation artery aneurysm has ruptured, the raters predicted a ruptured supratentorial aneurysm to have caused the bleed or they could not make a prediction of the site of rupture in half of the cases. As a consequence, in patients who have multiple aneurysms on these sites, it is not always possible to accurately determine which of the aneurysms had caused the bleed.
A valid and invariable prediction of the site of ruptured aneurysm (high and invariable sensitivity, specificity, and positive predictive values for both raters) can be performed only in case of a ruptured ACA or ACoA aneurysm. In addition, parenchymal cerebral hematoma was always found in the immediate proximity of the ruptured aneurysm, but this was present only in 15% of the patients.

The proportion of aneurysms located on the ICA, ACA, ACoA, MCA, and posterior circulation artery in earlier reports corresponds with that of this study.[6,11,22,23] However, a difference in the frequency of lateral aneurysms located on the right and on the left side has not been reported before. This may be explained by the fact that most studies do not differentiate between right and left lateral aneurysms, probably because of the presumption that there will be no difference in the frequency of right and left-sided aneurysms.[6,11,15,22,23,24,25,26]
Interrater variability of the diagnostic power of the distribution of cisternal blood on CT for the site of a ruptured supratentorial aneurysm has not been investigated. Only one author reported the interrater

variability in a study to differentiate patients with non-aneurysmal perimesencephalic SAH from selected cases with a ruptured aneurysm of the posterior circulation artery.[18]

In general, the sensitivity and positive predictive value of CT scan for the prediction of the site of the ruptured aneurysm in patients with aneurysmal SAH varies widely in other studies (sensitivity from 45%[6] to 86%[26] and positive predictive value from 70%[27] to 100%[10]). In our study, the sensitivity of the CT scan for the prediction of the site of a ruptured aneurysm depends on the location of the aneurysm. Differentiation by the location of an aneurysm was done in two other studies.[22,25] The sensitivity values in these studies are generally higher than in our study. The large variability in sensitivity and positive predictive value in the literature and the differences between these values and that of our study may be explained by several factors: 1) the use of contrast enhanced CT scan for a direct visualization of intracranial aneurysms[24,26]; 2) the use of CT for the differentiation between aneurysmal SAH and an intracranial bleed by other causes[25,27]; 3) the restriction to patients with aneurysms at one particular site[28] or to those with a non-aneurysmal perimesencephalic SAH[18,29]; 4) the inclusion of patients with multiple aneurysms[11,15]; 5) time lapsed between SAH and CT was more than 3 days[6,10,22,28] or was unknown[15,23,24,25,30,31]; 6) the omission of a complete four-vessel angiography[3,8,9,22].

The assumption that one may safely perform selective angiography depending on blood distribution on the CT scan[22] and restrict clipping to the aneurysm or aneurysms located at the same side of the highest amount of cisternal blood is incorrect and may be hazardous.[3,7,12,32,33] But, one may debate whether one should recommend early surgery for all aneurysms in case of multiple aneurysms in those who are in good clinical grade if the aneurysm cannot be clipped in one stage and in whom one is not certain about the site of aneurysm rupture.[1,4,7,34] In many centers, early surgery (<72 hours after SAH) will not be performed in case of a ruptured posterior circulation artery aneurysm.[33,35] The presence of a supratentorial aneurysm (for example an ICA aneurysm) and a distal basilar artery aneurysm in one patient is a problem in these centers. Endovascular treatment of the aneurysms by means of Guglielmi's detachable coils may be an option to eliminate the aneurysms in these patients.[36]

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2.2

Interobserver variability of cisternal blood on CT after aneurysmal subarachnoid hemorrhage

Summary

Interobserver variability in the prediction of delayed cerebral ischemia by means of blood on CT was investigated in 159 patients with aneurysmal SAH, admitted within 72 hours after the bleed. We found a considerable interobserver variability in the assessment of the amount of blood in the individual cisterns. A high sum score was an independent predictor for DCI only for rater 1 (hazard ratio 3.26, 95% CI = 1.14 to 7.75 for rater 1 and hazard ratio 1.72, 95% CI = 0.72 to 4.09 for rater 2). We conclude that interobserver variability limits the predictive power of the amount of blood on CT for the occurrence of cerebral ischemia.

Introduction

Delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (SAH) is a serious complication that occurs in 20% to 30%.[1,2] Amount of blood on initial CT scan, presence of ventricular blood and treatment with tranexamic acid have been found to be significantly associated with the development of DCI after aneurysmal SAH.[1,2,3,4] However, the validity of the predictive value of the amount of blood on the initial CT for the development of DCI depends on the method of assessment[4,5] and is probably subject to interobserver variability.[5,6] We investigated the impact of interobserver variability on the predictive value of blood on the initial CT for the development of DCI in 159 consecutive patients with aneurysmal SAH.

Patients and Methods

A total of 308 consecutive patients with signs and symptoms of aneurysmal SAH were admitted to the Neurology and Neurosurgery Intensive Care Unit. The diagnosis was confirmed by CT scanning on admission or, in case of negative CT scanning, by spectrophotometric evidence of xanthochromia in the cerebrospinal fluid (CSF). We excluded 149 patients: 34 admitted beyond 72 hours from the bleed, 71 did not undergo angiography, 39 had no aneurysm on the four-vessel cerebral angiography, four patients had a bad quality CT, and the CT scan of one patient was missing. In the remaining 159 patients, a four-vessel angiogram or postmortem examination confirmed the presence of at least one aneurysm.

CT scans of the 159 patients were performed within 72 hours after the initial bleed. Two expert raters independently scored the amount of cisternal blood on CT, blinded for the results of the angiography and clinical information. The amount of blood in 13 individual cerebral cisterns (the different cisterns are mentioned in *table 2*) on each CT was scored as described previously:[5] a score of 0= no blood; 1=cistern partially filled with blood; and 2=completely filled with blood. Thereafter, the sum score (ranging from 0 to 26) for each CT was calculated. A sum score greater than 13 was regarded as a “high cisternal blood score”. Ventricular blood and cerebral hematoma were reported when present.

Hydrocephalus detected on CT on admission was referred to as "hydrocephalus on the initial CT". Hydrocephalus was defined as the bicaudate index on the CT exceeding the 95th percentile for age. Clinical events occurring during the observation period were defined as follows: 1) *deterioration from hydrocephalus* was defined as deterioration of the level of consciousness with no detectable cause other than hydrocephalus confirmed by a repeat CT; 2) *probable delayed ischemia:* gradual development of focal neurologic signs with or without deterioration of the level of consciousness, without confirmation by CT or autopsy; 3) *definite DCI*: development of focal neurologic signs or deterioration of the level of consciousness, or both, with CT or autopsy evidence of cerebral infarction; 4) *probable rebleeding*: sudden deterioration of the level of

consciousness and death, without CT confirmation or if autopsy is refused; 5) *definite rebleeding:* sudden deterioration of the level of consciousness, with or without focal signs, with an increase in the amount of blood on a repeat CT or at autopsy when compared with a previous CT. We counted definite and probable DCI as DCI and definite, and probable rebleeding as rebleeding in the analysis.

Table 1. Characteristics of 159 patients with subarachnoid hemorrhage (SAH).

	Patients with SAH n=159	
	No.	%
Sex		
Male	56	35
Female	103	65
Mean age (in years)	50.3	
Age		
≤60 years	120	75
>60 years	39	25
History of hypertension		
Unknown	2	1
No	128	81
Yes	29	18
History of cerebrovascular disease		
Unknown	2	1
No	138	87
Yes	19	12
Loss of consciousness at ictus		
Unknown	5	3
No	62	39
Yes	92	58
Time interval between SAH and CT scan		
≤1 day	149	94
2 days	4	3
3 days	6	4
Sum score of Glasgow Coma Scale		
≤12	60	38
>12	99	62
Aneurysm site		
Carotid artery	40	26
Anterior cerebral artery	57	36
Middle cerebral artery	39	24
Posterior circulation	23	14

The agreement of the sum scores for cisternal blood between raters was analyzed by plotting the difference between the two raters' sum scores, as a function of the mean sum scores of both raters (Altman plot). Limits of agreement are defined as mean of the difference ± 2SD.[7] Thereafter, we computed the hazard ratio for the occurrence of DCI in two separate multiple regression models using the Cox proportional hazard method with stepwise forward selection of the variables. Each model contained the 3 covariates as scored by one of the two raters (high cisternal blood score on CT, presence of ventricular blood and presence of cerebral hematoma) and additional covariates: age >60; loss of consciousness at ictus; history of cerebrovascular diseases; history of hypertension; GCS on admission of >12; deterioration from hydrocephalus and rebleeding (time-dependent variables).

Results

The characteristics of the 159 patients with SAH are presented in *Table 1*. In 149 of the 159 patients (94%) CT was performed within 24 hours after SAH. Crude interobserver agreement for the presence of cisternal blood, presence of ventricular blood, and presence of parenchymal hematoma varied between 68% and 90% and kappa-values varied between 0.34 and 0.66 for the different cisterns. The agreement of the sum scores for cisternal blood between raters is presented in the Altman plot (*Figure*).

The proportion of patients with high cisternal sum score who developed cerebral ischemia is presented in *Table 2*. Multivariate analysis by means of the two separate Cox proportional hazard models showed that the only variable that significantly predicted DCI was a high sum score by rater 1 (hazard ratio 2.87, 95% CI = 1.26 to 6.51 for rater 1 and hazard ratio 1.86, 95% CI = 0.79 to 4.37 for rater 2).

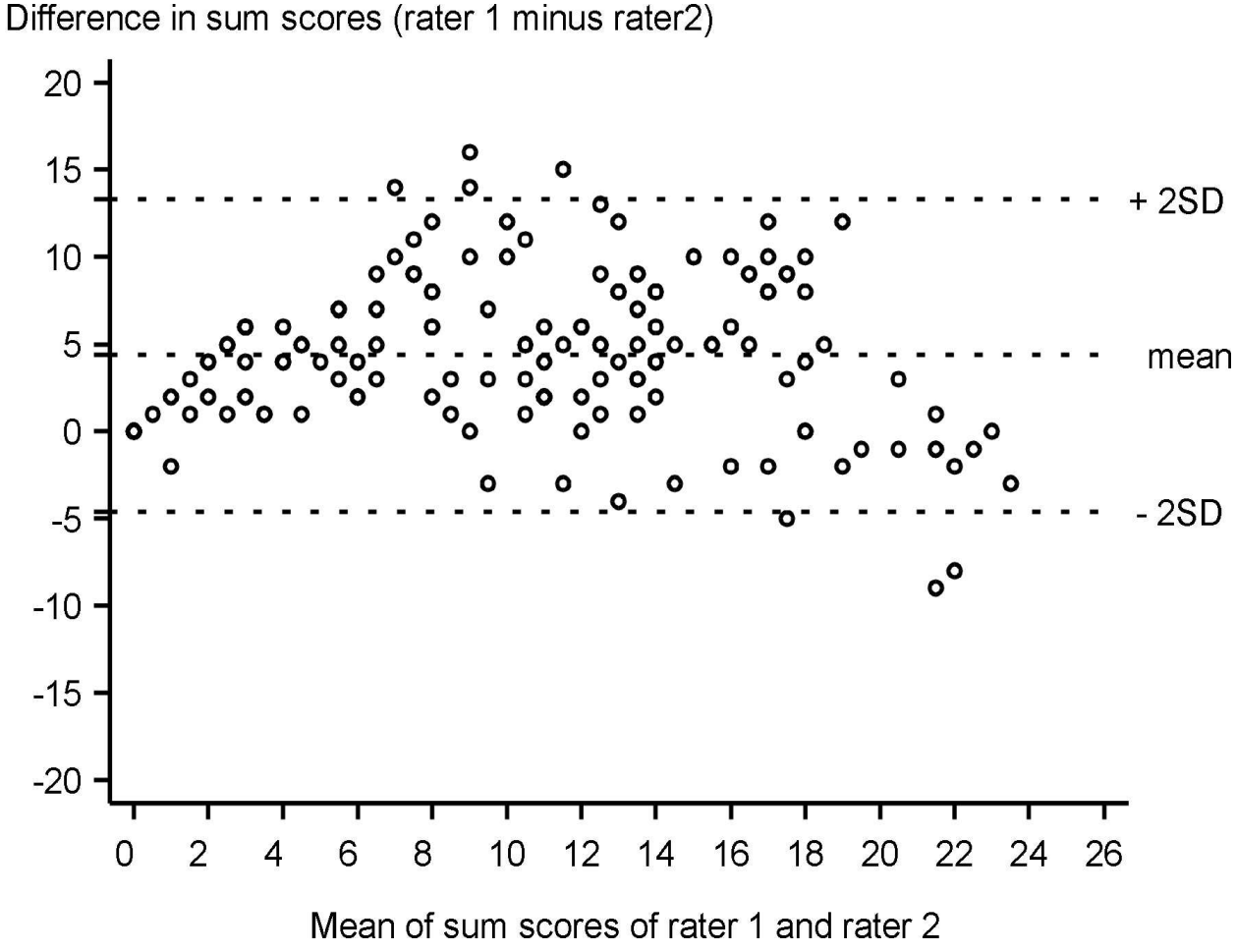
Table 2. Relationship between amount of blood on the initial CT as scored by both observers and the occurrence of delayed cerebral ischemia in159 patients with SAH.

	Rater 1			Rater 2		
	Cerebral ischemia		Totals	Cerebral ischemia		Totals
Sum score	No.	%	No.	No.	%	No.
0 – 6	3	10	30	8	12	69
7 – 13	5	10	52	13	20	55
14 – 20	12	22	54	3	20	15
21 – 26	8	35	23	4	40	10
Totals	28	18	159	28	18	159

Discussion

In this study, we have found considerable interobserver variability for the assessment of the amount of cisternal blood on CT after aneurysmal SAH. The analysis of the agreement of the sum scores by means of the Altman plot showed that the mean value of the difference in sum scores was 4.4. This means that rater 1 tended to give a 3.7 to 5.1 points (95% confidence interval) higher score than rater 2. Furthermore, the limits of agreement (−4.6 to 13.3) were very wide (up to half of the total sum score of 26 points) and therefore unacceptable for clinical purposes.[7] A high sum score independently and significantly predicted the occurrence of DCI for rater 1 and not for rater 2. In our study, as in most studies in which all patients had an angiogram, an inevitable selection bias towards patients in good clinical grades will have occurred, because performing angiography requires a reasonable clinical condition. Therefore, a subgroup of patients suffering from DCI has not been included in the analysis.

Figure. Altman plot representing the difference between the sum scores of the two rates, as a function of the mean sum scores of both raters in 159 patients with SAH. Mean value for the difference in sum score (rater 1 minus rater 2) was 4.4 points (95% confidence interval = 3.7 to 5.1 points), limits of agreement (mean ±2SD) were –4.6 to 13.3, and range was –9 to 16 points.



There are many methods for the estimation of the amount of cisternal blood following SAH.[2,4,5] Two types of grading methods have been used repeatedly.[4,5] Interobserver analysis on scores of the individual cisterns has been performed only in one of the two methods.[5] Although the reported kappa values were moderate, the authors did not report the actual agreement data. A general problem is that kappa values reflect the ratio between agreement and expected agreement rather than the extent of agreement between raters. In other words, a relatively high kappa value does not necessarily indicate a high agreement and a low kappa value not a low agreement between raters. Several studies reported the predictive factors for the occurrence of DCI following SAH.[2,3,8,9,10] With the exception of some studies, a high amount of cisternal blood on CT significantly predicted the occurrence of DCI after SAH.[2,8,9] Despite the fact that the prognostic factors for DCI are interdependent, multivariate analysis was not performed in many studies. The inclusion of characteristics on admission as well as time dependent variables, which can have multiplicative effect on DCI in patients after SAH, necessitates the use of a multiple regression model that employs both types of covariates. The omission of such a complex analysis may lead to erroneous conclusions.
Apparently grading of the amount of blood in many individual cisterns leads to considerable interobserver variability. Perhaps other methods such as the detection of the presence of localized intracranial clots after aneurysmal SAH[4] may have a better predictive value for the occurrence of DCI.

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2.3

Diagnostic accuracy of 16-detector row CT angiography for the detection of intracranial aneurysms

Abstract

Objective

To assess diagnostic accuracy of 16-detector row CT angiography (CTA) for the detection of both ruptured and unruptured intracranial aneurysms in patients after subarachnoid hemorrhage (SAH).

Methods

We included 108 consecutive patients with SAH who were referred to our university center between 2002 and 2004 and who underwent both CTA and DSA. Two experienced interventional neuroradiologists independently evaluated 3D-CTA and –immediately thereafter- DSA hard-copies with respect to the presence and location of the ruptured aneurysm and additional aneurysms. We determined diagnostic accuracy of CTA for the detection of intracranial aneurysms and all aneurysms. We also assessed interobserver agreement.

Results

Interobserver agreement for the presence of a target aneurysm on CTA was excellent, (Kappa=0.97). Interobserver agreement on the presence of all aneurysms was lower (Kappa=0.80, weighted Kappa=0.82). For reader 1, sensitivity of CTA for the detection of the target aneurysm was 99% (CI 96-100%), and specificity was 92% (CI 81-100%). Negative predictive value (NPV) was 97% (CI 87-100%) and positive predictive value (PPV) was 98% (CI 94-100%). For reader 2, sensitivity was also 99% (CI 96-100%), specificity was 96% (CI 88-100%), NPV 96% (CI 88-100%) and PPV 99% (CI 96-100%). For the detection of all aneurysms with CTA alone sensitivity was 88% (CI 82-94%) and 91% (CI 86-96%) and specificity was 84% (CI 70-98%) and 92% (CI 81-100%) for reader 1 and 2 respectively. Viewing DSA after CTA improved diagnostic accuracy only with regard to additional aneurysms.

Discussion

16-Detector row CTA without DSA is a reliable investigation to assess the presence of ruptured intracranial aneurysms, with excellent interobserver agreement. However, diagnostic accuracy for additional aneurysms improves when DSA is performed in addition to CTA.

Introduction

Computed tomography angiography (CTA) is applied in many centers for the diagnostic evaluation of ruptured intracranial aneurysms, mostly in addition to digital subtraction angiography (DSA).[1,2] The reported sensitivity of single and 4-detector CT has been reviewed in several meta-analyses and a recent review, that reported a sensitivity of 85% to 99% and specificity of 72% to 100%.[3-5] However, several studies calculated accuracy per aneurysm and not per patient or ruptured aneurysm. The large variation that has been reported can partly be explained by a learning curve effect because more recent studies generally reported better diagnostic accuracy than earlier studies. Although the accuracy of CTA was high in more recent studies, it was concluded that replacement of DSA by CTA was not advised yet. Especially the accuracy in the detection of small aneurysm (≤ 3mm) was low.

With the introduction of multidetector CT technology it is expected that the accuracy of CTA will be good enough to make this imaging modality the first choice in the diagnostic evaluation of patients with non-traumatic subarachnoid hemorrhage.

The value of DSA as reference test can be questioned, however, since aneurysms may be detected with CTA that have, on occasion, been missed with DSA.[6,7] The ultimate reference test, or "gold standard", should ideally incorporate all clinical information and imaging findings. Furthermore, a new development is the advent of 16-detector row CT scanners.[3,8] One recent study has found equivalent diagnostic accuracy in comparison with DSA.[9]

In this study, we assessed the diagnostic accuracy of 16-detector row CT angiography for the detection of intracranial aneurysms compared with all available radiological and clinical information as the reference test.

Methods

Patients

The study was a single-center observational study with prospective inclusion of patients with subarachnoid hemorrhage (SAH). Patients were recruited from October 1st, 2002, to September 10th, 2004 in a University Hospital. During the inclusion period, it was standard clinical practice to perform both CTA and DSA in all patients with SAH of presumed aneurysmal origin, provided that their clinical condition permitted performance of both procedures. In our hospital, endovascular treatment (EVT) is considered as preferred treatment option for ruptured intracranial aneurysms, in accordance with the results of the ISAT trial. Inclusion criteria were: 1) clinical diagnosis of non-traumatic subarachnoid hemorrhage, confirmed by CT or CSF spectrophotometric analysis, 2) age 18 years or over, 3) written informed consent by the patient or relative to review the patient's clinical record and imaging data, 4) performance of both CTA and DSA. The

protocol was approved by the hospital's Medical Ethics Committee. For the conduct and reporting of this study, we adhered to the STARD criteria.[10]

CTA data acquisition

Studies were performed with a 16-detector row CT scanner (Somatom X-32 Sensation 16; Siemens Medical Solutions, Erlangen, Germany). The scan volume started from the upper limit of the posterior arch of the atlas and extended cephaled with coverage of 100 mm. The lower limit was chosen to include a proximal origin of the posterior inferior cerebellar artery; the upper limit was chosen to include the callosomarginal artery. 80 ml of contrast material (Iodixanol 320 mg/ml – Visipaque – Amersham Health, Little Chalfont, UK) was injected. The CTA scan was synchronized with the contrast material injection with a bolus tracking technique. The time-interval between DSA and 3D-CTA was at least 6 hours to prevent contrast intoxication.

DSA data acquisition

Diagnostic DSA was performed in all patients being standard clinical strategy, with 3D imaging when necessary. Four vessel DSA was done according to the Seldinger technique. A 4–5-F catheter was selectively placed in the internal carotid and the vertebral arteries, injecting 6 cc (4 cc/s; internal carotid) or 7 cc (5 cc/s; vertebral artery) of contrast material (Iomeron 350, Bracco, Milan). In all patients, frontal, lateral and oblique views were obtained (matrix 1,024×1,024; image intensifier 20–28 cm). Images that yielded the clearest spatial projections of detected aneurysms were printed on hardcopies to be used for this study.

Data scoring and evaluation

Two experienced interventional neuroradiologists (ZF and HLJT) independently scored the 3D-CTA images. Both readers were familiar with the clinical use of 3D-CTA. Both readers were unaware of the actual treatment. 3D-CTA images were examined at a work station. A standardized evaluation was performed with maximum intensity projections (MIPs) with a thickness of 6–8 mm and an overlap of 3–4 mm in axial, sagittal, and coronal planes for the anterior circulation, and in the sagittal plane and a plane parallel to the clivus for the posterior circulation. MIP planes and thickness could be adjusted and source images were available for additional evaluation. The readers were aware of the results of the unenhanced diagnostic CT regarding the blood distribution in the subarachnoid cisterns and presence and distribution of intraventricular blood, but were not aware of the clinical condition of the patient. The 3D-CTA images were masked for patient identification.

The readers scored the 3D-CTA on the work station blinded to all other clinical data and DSA results. A standard form had to be filled out by both readers. The CTA was evaluated with respect to the presence and location of the target aneurysm, which was defined as the aneurysm that had ruptured as judged by the reader. The location of the target aneurysm was noted as being at one of the 29 locations as previously described by Yasargil.15 Furthermore, presence and location of additional aneurysms were assessed.
The size of the target aneurysm was measured by one of the neuroradiologists (ZF). Size of the target aneurysm was scored by dome width (maximal diameter of the aneurysm), length (from fundus to base) and neck size in millimeters (mm).
A subgroup analysis was performed for patients with a proven aneurysm in whom we evaluated the value of CTA in assessing the feasibility of endovascular treatment and the additional value of DSA (reported separately).11 Both readers therefore also scored the DSA on the standard form. The DSA was viewed directly after the CTA in all cases.

Interobserver agreement with respect to the presence of a target aneurysm and all aneurysms (i.e. including additional aneurysms) was assessed by means of Cohen's Kappa and weighted Kappa's respectively.[12]
Next, the presence and location of a target aneurysm and additional aneurysms detected with CTA and DSA was compared with the reference standard. The reference standard was the presence and location of a ruptured aneurysm and all other aneurysms as determined by evaluating all available clinical information. This information included clinical (for instance an oculomotor palsy in case of posterior communicating artery aneurysm), diagnostic (blood distribution on CT in combination with angiography), surgical and follow-up information. Two investigators (AvdL, MvdJ) assessed the reference standard by consensus. We assessed diagnostic accuracy of CTA alone and of DSA with CTA (i.e. the additional value of DSA compared with CTA alone) by calculating sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) and corresponding 95% confidence intervals (CI's) for the detection of the target aneurysm and all aneurysms.

Results

Of 122 consecutive patients assessed for eligibility, 14 were excluded for the following reasons: two patients had traumatic SAH, one patient had SAH caused by an arteriovenous malformation, in seven patients either CTA or DSA was not performed, for one patient one of the readers had not filled out the scoring form and from three patients or their relatives informed consent could not be obtained. The remaining 108 patients were included.

The female to male ratio was 2 (72/36) and the mean age 53 years (range 19 to 80 years). The relative frequencies of the locations of target aneurysms by vascular territory corresponded with those previously reported[13]: 24 patients had no aneurysm on the angiogram (22%), 37 patients (34%) had an anterior cerebral artery (ACA) aneurysm, 23 had an internal carotid artery (ICA) aneurysm (21%), 18 a middle cerebral artery (MCA) aneurysm (17%) and 6 patients had a posterior circulation aneurysm (6%). Size (length, from fundus to base) distribution of the target aneurysms was as follows: 10 aneurysms were ≤ 3mm (12%), 18 were >3 and ≤ 5mm (21%), 47 were >5 and ≤ 10mm (55%) and 10 were >10mm (12%).
In 38 patients, the CTA and the DSA were performed at the same day (median of the difference in days for all 108 patients: 0, range: 0 to 46 days). CTA was performed after DSA in 20 patients (median: 1 day later, range: 1-4 days). DSA was performed after CTA in 50 patients (median: 1 day later, range: 1 to 46 days). On average DSA was performed 1.5 day later than CTA.

Interobserver agreement for the presence of a target aneurysm on CTA was excellent, with a Kappa of 0.97 (*Table 1*). The two readers disagreed on the presence of a target aneurysm on CTA in only one patient. Viewing DSA after CTA resulted in slightly lower agreement, with a Kappa of 0.92 (*Table 2*). Interobserver agreement on the presence of all aneurysms was lower. Kappa was 0.80 and weighted Kappa was 0.82 with CTA alone (*Table 3*). Interobserver agreement improved only slightly after viewing the DSA after CTA. Kappa was 0.81 and weighted Kappa was 0.85 (*Table 4*).

Table 1. Interobserver agreement on the presence of a target aneurysms by CTA

CTA		Reader 2		
		Absent	Present	Total
Reader 1	Absent	23	0	23
	Present	1	84	85
	Total	24	84	108

Kappa=0.97

Table 2. Interobserver agreement on the presence of a target aneurysms by CTA and DSA

CTA and DSA		Reader 2		
		Absent	Present	Total
Reader 1	Absent	22	1	23
	Present	2	83	85
	Total	24	84	108

Kappa=0.92

Table 3. Interobserver agreement on the presence of all aneurysms with CTA

CTA		Number of aneurysms by reader 2					
		0	1	2	3	≥ 4	Total
Number of aneurysms by reader 1	0	23	0	0	0	0	23
	1	1	60	6	0	0	67
	2	0	3	12	1	0	16
	3	0	1	0	0	0	1
	≥ 4	0	0	0	0	1	1
	Total	24	64	18	1	1	108

Kappa=0.80, weighted Kappa=0.82

Table 4. Interobserver agreement on the presence of all aneurysms with CTA and DSA

CTA and DSA		Number of aneurysms by reader 2					
		0	1	2	3	≥ 4	Total
Number of aneurysms by reader 1	0	22	1	0	0	0	23
	1	2	57	3	0	0	62
	2	0	4	15	0	0	19
	3	0	0	2	1	0	3
	≥ 4	0	0	0	0	1	1
	Total	24	62	20	1	1	108

Kappa=0.81, weighted Kappa=0.85

For reader 1, sensitivity of CTA for the detection of the target aneurysm was 99% (CI 96-100%), and specificity was 92% (CI 81-100%, *Table 5*). The target aneurysm was missed with CTA by both readers in one

patient with a left sided anterior choreoideal artery aneurysm with a length of 2 mm. In this patient, the blood distribution on the diagnostic CT may have suggested a perimesencephalic hemorrhage but the presence of frank intraventricular blood in the 4th ventricle precluded this diagnosis (*Appendix 1a and 1b*).[14] NPV was 97% (CI 87-100%) and PPV was 98% (CI 94-100%) for reader 1. The diagnostic accuracy for reader 1 was similar after viewing the DSA (*Table 5*). For reader 2, sensitivity was also 99% (CI 96-100%), specificity was 96% (CI 88-100%), NPV 96% (CI 88-100%) and PPV 99% (CI 96-100%). With DSA after CTA, sensitivity, specificity, NPV and PPV were 100% (*Table 5*).
For the detection of all aneurysms with CTA alone sensitivity was 88% (CI 82-94%) and 91% (CI 86-96%) and specificity was 84% (CI 70-98%) and 92% (CI 81-100%) for reader 1 and 2 respectively. With both CTA and DSA, sensitivity improved to 92% (CI 88-97, reader 1) and 94% (CI 90-98%, reader 2) and specificity was 78% (CI 62-93%) and 100% for reader 1 and 2 respectively (table not shown).

Discussion

In this study of 108 patients with acute subarachnoid hemorrhage, cerebral CT angiography with a 16-detector row scanner detected almost all ruptured aneurysms except for one very small ruptured aneurysm (sensitivity 99%) compared with our reference standard that consisted of all available radiological and clinical information. The specificity was more than 90% which means that CTA may falsely suggest the presence of an aneurysm in some patients. Negative predictive value was more than 95% by the two readers and positive predictive value 98% or higher. Diagnostic accuracy improved after viewing the DSA only for one of the readers yielding a sensitivity, specificity, and positive and negative predictive value of 100%.

Interobserver agreement was excellent with regard to the detection of the ruptured aneurysm by CTA and did not improve with additional DSA. Finally, we found that diagnostic accuracy of CTA is far less than perfect for the detection of additional aneurysms and that DSA conferred a consistent additional benefit compared with CTA alone.

Before our results can be accepted some methodological issues should be discussed. We included only patients who underwent both CTA and DSA, and whose clinical condition allowed for endovascular or surgical treatment. However, detection rate of ruptured aneurysms is unlikely to be influenced by the clinical condition of the patients and therefore our results probably also apply to those in poorer clinical condition. On the other hand, detection of ruptured aneurysms is clinically important only in patients that would be expected to benefit from treatment.

Table 5. Diagnostic accuracy of CTA and both CTA and DSA for two readers (*see also: Appendix 2a* & *b)*

		Target aneurysm by reference standard		
		Absent	Present	Total
Target aneurysm by CTA	Absent			
	Reader 1	22	1	23
	Reader 2	23	1	24
	Present			
	Reader 1	2	83	85
	Reader 2	1	83	84
Target aneurysm by CTA and DSA	Absent			
	Reader 1	22	1	85
	Reader 2	24	0	84
	Present			
	Reader 1	2	83	85
	Reader 2	0	84	84
	Total	24	84	108

Reader 1 (CTA and both CTA and DSA): sensitivity 99% (95% CI 96-100%), specificity 92% (95% CI 81-100%), NPV 97% (95% CI 87-100%), PPV 98% (95% CI 94-100%)
Reader 2 (CTA): sensitivity 99% (95% CI 96-100%), specificity 96% (95% CI 88-100%), NPV 96% (95% CI 88-100%), PPV 99% (95% CI 96-100%)
Reader 2 (CTA and DSA): sensitivity, specificity, NPV and PPV 100%

The interpretation of our results on the detection rate of additional unruptured aneurysms, which was clearly inferior to the detection of ruptured aneurysms, requires some caution. This is a substudy of a study primarily aimed at evaluating the diagnostic value of CTA alone for the judgment of feasibility of endovascular treatment. Therefore the detection of the ruptured aneurysm had the highest priority, and detection of additional aneurysms did not affect the treatment decisions by both readers. On the other hand, the possibility to score the presence of one or more additional aneurysms was clearly reflected in the standard scoring form. In some cases of angionegative SAH with an aneurysmal type of blood distribution on the unenhanced diagnostic CT an angiography was not repeated. Theoretically, this may have resulted in undetected ruptured aneurysms. However, this did not influence the results of our reference test in these cases because no aneurysm was found both by the reference test and the CTA. Furthermore, it should be noted that the diagnostic accuracy of DSA was not studied independently of CTA and therefore our results do not address the diagnostic accuracy of DSA alone. Therefore, although DSA conferred additional information regarding both ruptured and unruptured aneurysms in this study, our results can not be taken as evidence that 16-detector row CTA is inferior to DSA.

The strengths of this study are the strict clinical setting where clinical practice was combined with this investigation in eligible patients for treatment. Furthermore, we included a consecutive series of patients with ruptured aneurysms who were representative by demographic parameters and distribution of locations of ruptured aneurysms compared with most consecutive series including patients with non-traumatic subarachnoid hemorrhage.13 Also, small ruptured aneurysms were included and our results therefore also apply to these aneurysms. Therefore, we think that external validity of our study is good.

Only one recent study reported the diagnostic accuracy of 16-detector row CT angiography in ruptured intracranial aneurysms including an evaluation of its value for treatment decisions.9 The reference standard used in that study was comparable to ours because it consisted of the DSA results in conjunction with the findings at surgery and endovascular treatment or both. However, the authors did not use 3D-DSA in patients who were included, but instead judged the 2D-DSA results (hard-copy films) as part of the reference standard. In our hospital, 3D-DSA is performed in many patients and the results are available during the diagnostic and therapeutic procedure, in case of endovascular treatment and included in the final diagnostic evaluation. This has a clear advantage over 2D-DSA as a reference standard, because of superior anatomical detail as has been shown previously.16,17 The 3D-DSA results are therefore included in our reference standard, when performed. In the previous study, a sensitivity of 96% (95% CI 88-99%) of CTA was found per aneurysm and sensitivity was similar per patient (n=44). Specificity was 100% both per aneurysm and per patient. Two readers missed one different causative aneurysm that the other reader detected with CTA. The slightly lower sensitivity and superior specificity may be due to the fact that the readers in our study also had to make a treatment decision for the ruptured aneurysm. This may have influenced sensitivity positively and specificity negatively. High sensitivity is preferred over high specificity after aneurysmal subarachnoid hemorrhage to detect the ruptured aneurysm, because the consequences of not detecting this aneurysm may be much worse than the consequences of false positive results, especially when endovascular treatment is feasible. An intraprocedural DSA will then be performed as part of the procedure before the actual treatment takes place.

We conclude that 16-detector row CT angiography is a reliable investigation for the detection of ruptured intracranial aneurysms with a very high sensitivity. The additional value of digital subtraction angiography for the detection of ruptured intracranial aneurysms is restricted mainly to the detection of additional aneurysms. However, when an aneurysm is not detected with 16-detector row CTA, DSA may provide additional information especially when the blood distribution on CT strongly suggests the presence of an aneurysm. However, we can not exclude that repeating the CTA provides equivalent diagnostic accuracy as DSA in such cases.

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3

Aneurysmal subarachnoid hemorrhage: treatment

3.1

Impact of early surgery on the outcome of patients after aneurysmal subarachnoid hemorrhage

Abstract

Objective

We investigated whether a treatment strategy aimed at early aneurysm surgery (<72 hours) in patients with subarachnoid hemorrhage (SAH) was beneficial and which patients benefited most.

Methods

We studied two consecutive series of patients with aneurysmal SAH from a prospective registry (postponed surgery [PS] cohort, n=118, 1989-1992: surgery was planned on day 12 and early surgery [ES] cohort, n=85, 1996-1998: early surgery was performed only in patients with Glasgow Coma Scale [GCS] > 13). We used multivariate logistic regression analysis to assess outcome at three months.

Results

In the PS cohort, 91 patients underwent surgery. In the ES cohort, 47 patients underwent early surgery and 27 postponed surgery. Favorable outcome (Glasgow Outcome Scale 4 or 5) was similar in both cohorts. Cerebral ischemia occurred significantly more often in the ES cohort. The occurrence of rebleeds was similar in both cohorts. External CSF drainage was performed more often in the ES cohort (51% versus 19%). Patients with cisternal sum score of subarachnoid blood <15 on admission benefited from the strategy including early surgery (adjusted OR for favorable outcome: 6.4, 95% CI 1.0-39.8). In patients with both cisternal sum score <15 and GCS >12 on admission this OR was 10.5, 95% CI 1.1-99.4.

Conclusions

Patients with low amount of cisternal blood on CT and good clinical condition on admission probably benefit from an early surgery strategy. Active CSF drainage to improve clinical condition prior to early surgery might have precipitated more rebleeds.

Introduction

Decision making in the treatment of ruptured intracranial aneurysms has been significantly changed by the advent of endovascular coiling as alternative to surgical clipping.[17,24,47]In the International Subarachnoid Aneurysm Trial (ISAT), after one year, a relative risk reduction of 22.6% and an absolute risk reduction of 6.9% for death or dependency were found with endovascular treatment versus surgical treatment.[17] However, 80% of patients with aneurysmal subarachnoid hemorrhage (SAH) were excluded and of these patients 50% were surgically treated. In addition, there is some evidence that short-term risk of rebleeding after endovascular coiling may exceed the risk of rebleeding after clipping.[4,17,25,45] Moreover, incomplete direct occlusion or recanalization after endovascular treatment of ruptured aneurysm is reported in up to 50% and 34% respectively. [4,6,17,24,33,37,38] Finally, not all ruptured aneurysms are suitable for endovascular treatment.[17,37] A comparison of the long term results of endovascular and surgical treatment has to be awaited. Consequently, surgery must still be considered an important treatment option for ruptured aneurysms and the issue of the timing of surgery therefore is still relevant in clinical practice today.

The timing of surgery in aneurysmal subarachnoid hemorrhage and the selection of patients for either early or delayed surgery is still subject to considerable controversy. [2,7,12,19-22,28,31,32,35,41,43,49,50] In a recent systematic review of studies on the timing of aneurysm surgery,[7] it was concluded that observational studies on timing of aneurysm surgery should contain (among other criteria for methodological quality) data on neurological condition on admission and amount of blood on CT, and that outcome should be related to prognostic factors. The authors were unable to identify a prospective study that met these criteria. It was suggested that early aneurysm surgery (within 7 days after the bleed) may benefit patients with a Glasgow Coma Scale of 13 or more on admission. However, this was based on data of only three prospective studies with different inclusion criteria, in which nimodipine and hypervolemic hemodilution therapy were not standard therapy. It has been suggested that, ideally, a randomized trial should solve the issue of the best timing of surgery, but this would lead to considerable logistic problems in a time when endovascular treatment is accepted as an effective alternative to surgery.

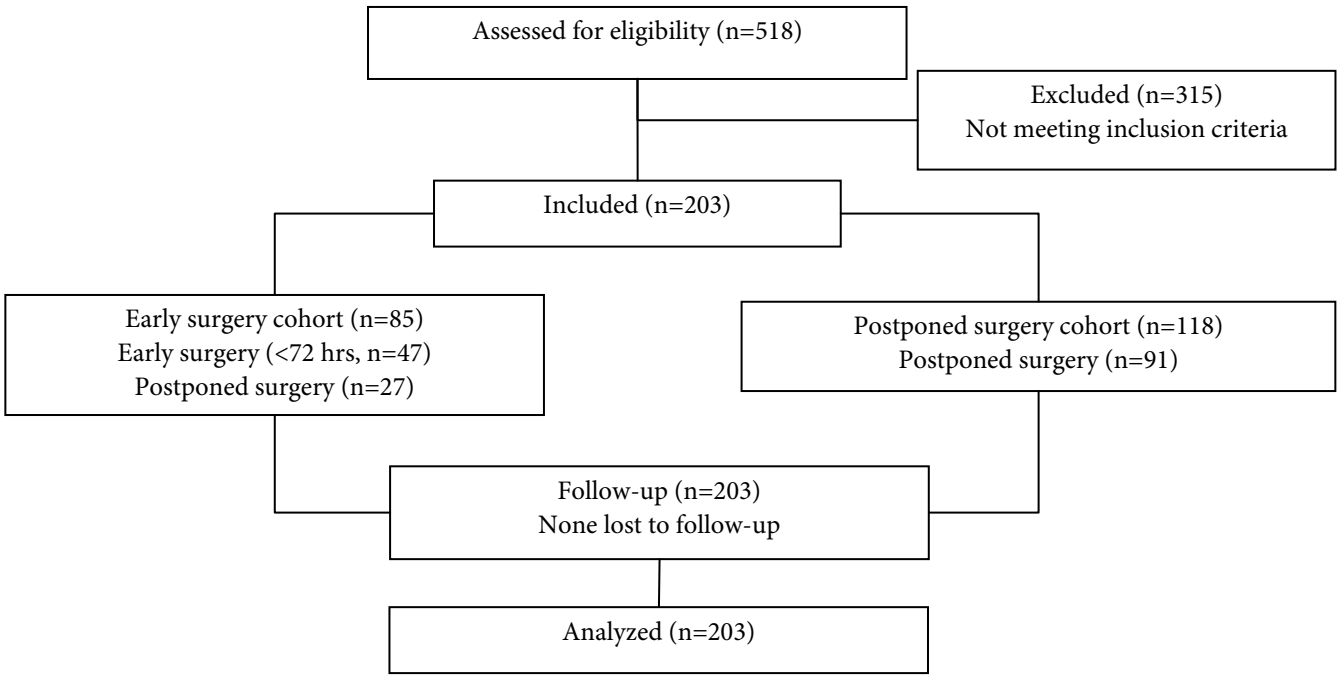
In a previous study on the impact of changes in medical treatment on outcome after aneurysmal SAH in our center,[48] we suggested that further improvement of outcome may be achieved if the efficacy of preventive measures against rebleeding is increased by performing early aneurysm surgery. In the present study, we investigated the impact of two treatment strategies on the outcome of patients after SAH in two historical cohorts. The first included delayed aneurysm surgery in patients who were in a good clinical condition to undergo surgery. The second strategy included early aneurysm surgery when the patients were admitted in a good clinical condition and delayed surgery when the patient improved after admission. Our hypothesis was that the second strategy would improve outcome.

Material and Methods

Patient Population and Study Design

We selected 203 consecutive patients with aneurysmal subarachnoid hemorrhage (SAH) admitted to the Neurological and Neurosurgical ICU within 72 hours after the bleed from a prospective registry of 518 aneurysmal SAH patients (*Figure 1*). Participants had to be potential candidates for early aneurysm surgery (within 72 hours after the initial bleed) based on their clinical characteristics on admission ("intention-to-treat" rather than "on-treatment"). These clinical characteristics were: 1) SAH from a confirmed anterior circulation aneurysm, 2) admission within 72 hours after the initial bleed, 3) Glasgow Coma Scale (GCS) on admission ≥ 5 and 4) age >18. The cut point of a GCS of 5 was chosen because some patients with a GCS of 5 on admission eventually were fit enough to undergo early aneurysm surgery.

Figure 1. Patient flow chart. Exclusion criteria were: death appeared imminent, posterior circulation aneurysm or no aneurysm, age ≤ 18, admission beyond 72 hours after initial bleed and Glasgow Coma Scale on admission<5



The 203 included patients originated from two different periods in time. The first 118 patients were admitted in the period from 1989 through December 1992. During that period the treatment strategy included aneurysm surgery on day 12 or later after the initial bleed (postponed surgery [PS] cohort). Because of the inclusion of subjects on an intention-to-treat basis not all patients underwent surgery (in both cohorts) and not all patients eligible for early surgery actually received this treatment. The other 85 patients were admitted between April 1996 and April 1998. In that period early aneurysm surgery was restricted to patients with a

GCS of 14 or 15 and a motor score of 6, no clinical signs of cerebral ischemia, and inclusion within the first 72 hours after the bleed. Patients that did not comply with these criteria were scheduled for postponed surgery (early surgery [ES] cohort). Patients in whom death appeared imminent on admission were excluded. During the study period, endovascular treatment was not yet performed in patients who had bled from an anterior circulation aneurysm.

Clinical Monitoring, Treatment, and Outcome

SAH was confirmed in all patients by CT, revealing a distribution of blood compatible with aneurysmal SAH,[46] or, when the CT revealed no blood, by spectrophotometric analysis of the CSF.

Angiography was performed as soon as possible when patients were considered fit for surgery or when immediate surgery was planned in case of a life threatening space occupying intracranial hematoma. Amount of cisternal blood was scored for all initial CT scans as described earlier.[15]

Patients were kept at the ICU as long as they were at risk for hydrocephalus, cerebral ischemia and rebleeding. The level of consciousness was assessed by means of the Glasgow Coma Scale.[44] When deterioration of the patient's clinical condition occurred, physical examination, and if possible CT was repeated. Hydrocephalus detected by CT was defined as the bicaudate index (width of the frontal horns at the level of the foramina of Monro, divided by the corresponding diameter of the brain) on the CT exceeding the 95th percentile for age.[8,30] Clinical events occurring during the observation period were defined as follows: 1) deterioration from hydrocephalus was defined as deterioration of the level of consciousness with no detectable cause other than hydrocephalus confirmed by a repeat CT; 2) probable delayed ischemia: gradual development of focal neurological signs with or without deterioration of the level of consciousness, without confirmation by CT or autopsy; 3) definite cerebral ischemia: development of focal neurological signs or deterioration of the level of consciousness, or both, with CT or autopsy evidence of cerebral infarction; 4) probable rebleeding: sudden deterioration of the level of consciousness and death, without CT confirmation or if autopsy is refused; 5) definite rebleeding: sudden deterioration of the level of consciousness, with or without focal signs, with an increase in the amount of blood on a repeat CT or at autopsy when compared with a previous CT. We counted definite and probable cerebral ischemia as cerebral ischemia and definite and probable rebleeding as rebleeding in the analysis.

From 1989 until1992 (PS cohort), all patients were treated with tranexamic acid and nimodipine (6x60 mg/d orally or 2 mg/h intravenously) during the first 21 days or until aneurysm surgery (tranexamic acid). Daily fluid intake was at least 3 L, unless cardiac failure was present. Fludrocortisone (2x0.2 mg/d) was administered in all patients as preventive measure against hyponatremia.[13] Diuretic agents and other antihypertensive drugs were avoided, unless the patient was on these drugs on admission. Hydrocephalus was treated with external lumbar CSF drainage or serial lumbar puncture in the absence of intracerebral

hematoma with mass effect or obstruction of the third or fourth ventricle by localized blood clot, or else with external ventricular drainage. When cerebral ischemia occurred, patients were treated with vigorous plasma volume expansion under intermittent monitoring of pulmonary wedge pressure, cardiac output, pulmonary arterial pressure, systemic vascular resistance and arterial blood pressure, aiming at a hematocrit of 0.29 to 0.33.

From 1996 to 1998 (ES cohort), all patients received similar standard treatment and treatment of complications compared with the PS cohort with the exception of fludrocortisone. In the ES cohort, fludrocortisone was administered only when hyponatremia did not respond adequately to sodium chloride administration.

All surviving patients were followed up until at least 3 months after SAH. Outcome was assessed at 3 months after the bleed at the outpatient clinic or, if the patient was not able to attend the outpatient clinic, by means of a questionnaire to be filled in by the patient, his or her relatives or general practitioner. Outcome was rated on the 5-point Glasgow Outcome Scale (GOS).[18] Favorable outcome was defined as GOS 4 or 5 at three months.

Statistical Analysis

Differences in entry characteristics were assessed by two sided $\chi 2$ test or Fishers' exact test. We calculated crude and adjusted Odds Ratio's (OR) and 95% confidence intervals (CI) for favorable outcome in the ES cohort versus the PS cohort by means of logistic regression. We adjusted for the following prognostic variables: GCS on admission, cisternal sum score, location of target aneurysm, sex, age, loss of consciousness at ictus, and presence of ventricular blood.[1,3,5,7,10,19,26] We categorized GCS on admission in GCS ≤ 12 and GCS>12, cisternal blood sum score (CSS) in CSS<15 and CSS≥ 15 and age in ≤ 40, 41-60 and >60. The same method was applied to calculate risk of cerebral ischemia, adjusted for: age, sex, CSS, presence of ventricular blood, loss of consciousness at ictus, GCS on admission, use of tranexamic acid, and location of target aneurysm. In an exploratory analysis in the entire population of patients with aneurysmal SAH from the prospective registry, we found that GCS and cisternal sum score on admission were the most important prognostic variables in selecting patients that would benefit from a treatment strategy including early surgery. Therefore, we did a subanalysis to examine whether patients with one or both of these favorable prognostic factors (GCS>12 and/or cisternal sum score<15) had better chances for a favorable outcome. Missing data were handled with standard imputation methods.[9]

To test the stability of the multiple logistic regression model for the outcome analyses, additional models were tested, with inclusion of patients with posterior circulation aneurysms, and inclusion of continuous rather than categorical dependent variables.[42]

Results

Most entry characteristics were similar in both cohorts, except for GCS on admission, cisternal sum score on initial CT and location of target aneurysm that are shown in *Table 1*. In the ES cohort, 35% of subjects were male and in the PS cohort this percentage was 28%. Age distribution was as follows: ≤40: 24%, 41-60: 47% and >60: 29%. Clinical characteristics on admission were more favorable in the ES cohort (*Table 1*).

Table 1. Differences in entry characteristics on admission between the postponed and early surgery cohort

Prognostic factors on admission	Postponed surgery cohort (n=118)	Early surgery cohort (n=85)
GCS on admission > 12	84 (71%)	73 (86%)§
CSS (range 0-30) < 15	34 (29%)	49 (58%)#
Location of target aneurysm		
Carotid artery	35 (30%)	28 (33%)¶
Middle cerebral artery	37 (31%)	12 (14%)¶
Anterior cerebral artery	46 (39%)	45 (53%)¶

§ P<0.02 # P<0.001 ¶ P<0.02
GCS=Glasgow Coma Scale, CSS=cisternal sum score

Aneurysm surgery was performed in 74 of the 95 patients (87%) in the ES cohort and in 91 of 118 patients (77%) in the PS cohort. From the 74 patients in the ES cohort that underwent surgery, 47 (65%) had early surgery (*Figure 1*).

Outcome assessment at three months follow-up was complete. No difference was observed between the two cohorts. In the PS cohort, 70% of subjects had favorable outcome versus 75% in the ES cohort (adjusted OR for favorable outcome in ES versus PS cohort was 1.2; 95% CI 0.5-2.5, *Table 2*).

Cerebral ischemia occurred more often in the ES cohort, compared with the PS cohort (41% versus 16% respectively, adjusted OR 5.9; 95% CI 2.5-13.7 [*Table 2*]).

Rebleeding rate was similar in both cohorts: 12% in the ES cohort versus 17% in the PS cohort (unadjusted OR 0.7; 95% CI 0.3-1.5, *Table 2*). External CSF drainage was performed more often in the ES cohort (51% in the ES cohort versus 19% in the PS cohort). This difference is due to more frequent CSF drainage in the first three days after the initial bleed. External CSF drainage in patients who underwent early surgery was started before surgery in all except one patient who had drainage the day after surgery. Adjustment for increased

pre-operative external CSF drainage, resulted in significant preventive effect of ES on the rate of rebleeding (adjusted OR for rebleeding 0.3, 95% CI 0.1-0.8). On the other hand, 48% of patients without a rebleed in the ES cohort versus 11% of patients in the PS cohort were treated with external CSF drainage (P<0.001 with $\chi 2$ test) and in patients with a rebleed these percentages were 70% (ES cohort) and 55% (PS cohort) (P>0.5 with Fishers' exact test). External CSF drainage had no effect on the other outcomes when it was added to the logistic regression models.

Table 2. Odds Ratio's for favorable outcome at 3 months and incidences of cerebral ischemia and rebleeding in the early surgery cohort compared with the postponed surgery cohort

Outcome at 3 months	Postponed surgery cohort (n=118)	Early surgery cohort (n=85)	Crude OR (95% CI)	Adjusted OR (95% CI)
Favorable outcome (GOS 4-5) at 3 months	82 (70%)	64 (75%)	1.3 (0.7-2.5)	1.2 (0.5-2.5)[1]
Incidence of cerebral ischemia	19 (16%)	35 (41%)	3.6 (1.9-7.0)	5.9 (2.5-13.7)[2]
Incidence of rebleeding	20 (17%)	10 (12%)	0.7 (0.3-1.5)	0.3 (0.1-0.8)[3]

[1]*Adjusted for: GCS on admission, cisternal sumscore, location of target aneurysm, sex, age, loss of consciousness at ictus, presence of ventricular blood*
[2]*Adjusted for: age, sex, cisternal sumscore, presence of ventricular blood, loss of consciousness at ictus, GCS on admission, tranexamic acid, location of target aneurysm*
[3]*Adjusted for external CSF drainage*

When we restricted the analysis to patients with a GCS>12 on admission they did not fare better in the ES cohort than the patients in the PS cohort (adjusted OR 1.2; 95% CI 0.5-2.9, *Table 3*). However, patients with a low cisternal sum score on initial CT of less than 15 (adjusted OR for favorable outcome 6.4; 95% CI 1.0-39.8) and patients with both a low cisternal sum score on CT *and* a high GCS of more than 12 on admission had better chances for a favorable outcome (adjusted OR 10.5; 95% CI 1.1-99.4, *Table 3*). In additional multiple regression models, with inclusion of patients with posterior circulation aneurysms (total number of patient 293) or inclusion of continuous rather than categorical fixed variables, the results of the analyses were virtually the same. The average proportion of missing data for all analyses was 3% (range 0-5%). Imputation of missing data did not change the results.

Table 3. Subgroup analysis of patients with favorable prognostic factors on admission

Subgroup	Favorable outcome at 3 months in the early surgery cohort (GOS 4-5)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
GCS on admission>12 (n=157)	1.4 (0.7-2.9)	1.2 (0.5-2.9)[1]
Cisternal sum score (CSS)<15 (n=83)	1.3 (0.4-4.1)	6.4 (1.0-39.8)[2]
Both GCS>12 and CSS<15 (n=71)	1.7 (0.4-6.3)	10.5 (1.1-99.4)[3]

[1,2,3] *Adjusted for: location of target aneurysm, sex, age, loss of consciousness at ictus, presence of ventricular blood,* [2]*GCS on admission,* [1]*cisternal sumscore*

Discussion

We found that a treatment strategy that included early aneurysm surgery in all SAH patients who were eligible for this treatment, combined with delayed surgery did not improve outcome or reduce rebleeds compared with a treatment strategy of delayed surgery only. Furthermore, with the combined early or delayed surgery strategy cerebral ischemia occurred more often and external CSF drainage was performed more frequently. However, the strategy of combined early and delayed surgery showed a strong trend for improved outcome at 3 months in patients who were admitted with either a low cisternal blood sumscore on CT, indicating a minor bleed, or both a high level of consciousness and a minor bleed.

Before our results can be accepted, some methodological issues need to be discussed. The strengths of our study are the inclusion of patients from a prospective registry and similar standard treatment and identification of neurological complications of all patients with aneurysmal SAH over time in both cohorts on a neuro-intensive care unit in a single institution. This supports the assumption that only the treatment with respect to the timing of surgery differed between both cohorts. Our study is a non-randomized cohort study with historical controls aimed to test whether treatment of combined early and delayed surgery improves outcome in patients with SAH when compared to treatment with delayed surgery alone. Our study is one of the few on the subject to use a method that allows for comparison of two treatment strategies without confounding by indication because the timing of surgical treatment was prespecified in both cohorts, in contrast to most other observational studies on the effect of early surgery on outcome that did not have a control group. Furthermore, we stratified the patients by the most powerful prognostic factors on admission for the development of cerebral ischemia and for outcome, i.e. amount of cisternal blood on the initial CT and level of consciousness on admission,[3] among other factors. In addition, we tested these variables in several multiple logistic regression models to assess its stability, but found that the results of the different analyses remained essentially the same.

Some limitations have to be addressed that may influence external validity of our study. First, our study is a single center study. Therefore, our results may not apply to clinical settings in which the standard treatment of aneurysmal SAH and its complications differs from our protocol. Second, the number of subjects in this study is relatively small which decreases the precision of the estimates of clinical outcomes in the subgroup analyses. Third, because this is not a randomized study, the distribution of known and unknown confounders was not necessarily balanced between both cohorts. It is difficult to exclude that other confounders than the ones we included in the logistic regression analysis have influenced the results of our study. For instance, we cannot exclude that medical treatment on the ICU has improved over time, diagnostic possibilities such as CT have become more accurate or that neurosurgical techniques and experience and anesthesiological support have improved. On the other hand, most of these changes have been minimized by the fact that the medical and nursing staff was relatively constant over time and all patients were treated in the same hospital.

In a systematic review on the timing of surgery after aneurysmal SAH, De Gans et al.[7] reported that patients with World Federation of Neurological Surgeons scale (WFNS) I-III on admission, which equals GCS>12, had a lower risk of poor outcome (death or severe disability), i.e. a risk ration of 0.41 (95% CI 0.34-0.51). Among 269 studies on this subject, only one study used randomization between a strategy of early versus delayed surgery. This study yielded inconclusive results.[35] None of the 268 observational studies included prognostic factors for outcome of patients with SAH in the analysis with the exception of clinical condition on admission. One study adjusted mortality for prognostic factors by means of proportional hazards modelling,[12] but the effect of individual prognostic factors applied in their analysis could not be extracted from the article. Moreover, the studies that were reviewed were published in a period when prophylactic hypervolemic therapy and nimodipine were not standard medical treatment. Therefore, comparison with our results is difficult.

In a more recent observational study,[34] it was found that the timing of surgery was not a major factor determining outcome in patients in good clinical condition on admission, but that patients with poor clinical condition on admission that underwent early surgery had an adjusted OR for poor outcome (GOS 1-3) of 0.1, 95% CI 0.0-0.6. This finding is counter-intuitive, as the authors noticed themselves. No explanation for this finding was given by the authors, except for the fact that other authors have reported that early surgery may be of benefit for patients in poor condition.[11,32,40] These studies lacked controls and the outcome was not better than patients in our study who were admitted with unfavorable prognostic factors. In our study with a historical control group, we observed that poor clinical condition on admission was associated with increased risk for poor outcome in the early surgery cohort (analysis not shown). Further, we could not find other observational studies on the timing of surgery that have associated poor initial clinical grade with benefit from early surgery. Therefore, we think that confounding factors are more likely to explain these very

significant results than the timing of surgery. On the other hand, we cannot exclude that early surgery can benefit some poor grade patients.

We found that low amount of cisternal blood on initial CT is associated with improved outcome in case of a strategy of combined early and late surgery and that concurrent good clinical grade on admission seems to be an additive factor with this treatment strategy. This supports the policy to perform early surgery in good grade patients, adhered to by many neurosurgeons.[14,16,20,35] However, to our knowledge, the amount of cisternal blood on CT has not been investigated in relation to the timing of surgery and outcome.

We found that the strategy that included early aneurysm surgery failed to prevent rebleeding when compared with the group with postponed surgery only. In addition, we observed an increase in the frequency of delayed cerebral ischemia in the early surgery cohort although the most important prognostic factors for cerebral ischemia (GCS on admission and cisternal sum scores on initial CT) were more favorable in the early surgery cohort. This suggests a causal relation between early surgery and increased risk of cerebral ischemia.

Although cerebral ischemia occurred more frequently in the early surgery cohort, overall outcome was not worse compared with the postponed surgery cohort. This finding suggests improved outcome after cerebral ischemia, which may have several explanations. First, early aneurysm surgery may have allowed for more aggressive triple-H therapy without the risk of a rebleed after early occlusion of the aneurysm. Second, tranexamic acid was administered less often in the early surgery cohort, probably because it was given less often to patients that were scheduled for immediate surgery, and administration of tranexamic acid has been shown to result in poor outcome more often once cerebral ischemia has occurred.[39] Third, it has recently been found that lumbar CSF drainage may have a protective effect on the occurrence of cerebral ischemia,[23] and this procedure was performed more often in the early surgery cohort.

Contrary to our expectation, patients in the early surgery cohort did not experience less rebleeds, as has been found by others.[20,35] This may be explained by more frequent external CSF drainage, which has been found previously to precipitate rebleeding.[36] This notion seems to be supported by the fact that the adjusted OR for rebleeding for the increased application of external CSF drainage in the early surgery cohort (adjusted OR 0.3, 95% CI 0.1 to 0.8) indicated a protective effect of the early surgery strategy against rebleeding. On the other hand, external CSF drainage was performed only slightly more often in the ES cohort in those with a rebleed compared with the PS cohort. However, in the ES cohort external CSF drainage may not only have been applied to treat hydrocephalus, but also to try and improve consciousness which may have lead to more aggressive CSF drainage and a further increase of the risk of rebleeding.[29] Another reason for a lack of effect on rebleeds in the ES cohort may be that rebleeding often occurs within the first 24 hours especially in poor grade patients.[27] In our study, poor grade patients mostly did not have early aneurysm surgery and early surgery was not performed within the first 24 hours for logistic reasons.

Conclusions

A treatment strategy that included early aneurysm surgery does not improve outcome at three months in all eligible patients with aneurysmal SAH. However, it may benefit patients who are admitted with a high level of consciousness and a minor bleed. More aggressive external CSF drainage with the aim to allow early surgery may result in more rebleeds in the first 72 hours in the early surgery cohort, thereby negating the decreased rebleeding rate in the period from the third to the twelfth day after the bleed. Furthermore, delayed cerebral ischemia occurs more frequently in the early surgery cohort, but without affecting outcome. The advantage of early surgery in selected patients may increase when better treatments for cerebral ischemia will become available. Our results do not allow definite recommendations regarding early surgery in patients in poor clinical grades on admission. Studies on the timing of aneurysm surgery are not likely to be performed in the future, because endovascular treatment is the preferred treatment in many centers. Future studies on treatment strategies in the early phase after aneurysmal SAH should include both endovascular and neurosurgical treatment and should be stratified by cisternal blood score and clinical status. Timing and effect of endovascular treatment in poor grade patients also deserves further study.

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3.2

Assessment of feasibility of endovascular treatment of ruptured intracranial aneurysms with 16-detector row computed tomographic angiography

Abstract

Background

The value of computed tomography angiography (CTA) in the assessment of feasibility of endovascular treatment (EVT) of ruptured intracranial aneurysms is unknown. We therefore investigated whether 16-detector row CTA was sufficient as pretreatment investigation to assess feasibility of EVT of ruptured intracranial aneurysms, and whether digital subtraction angiography (DSA) had additional value compared with CTA alone.

Methods

We included 80 consecutive patients with aneurysmal subarachnoid hemorrhage who were referred to our university center between 2002 and 2004 and who underwent both CTA and DSA. Two experienced interventional neuroradiologists independently scored 3D-CTA and –immediately thereafter- DSA hard-copies with respect to feasibility to treat the ruptured aneurysm endovascularly. We determined whether CTA alone was sufficient for a definite judgment. We also assessed interobserver agreement with respect to feasibility judgments based on CTA alone or the combination of CTA and DSA.

Results

Reader 1 and 2 were able to make a definite judgment on feasibility of EVT with CTA alone in 58 (73%) and 57 (71%) of the patients, respectively. DSA results never changed definite judgments by CTA alone, except in one patient who underwent DSA later than CTA when vasospasm had subsided. DSA yielded additional or affirmative anatomical information in 21% (reader 1) and 12% (reader 2), whereas in 33% and 12% DSA was considered inferior to CTA. Interobserver agreement on feasibility of EVT both before and after viewing DSA was just fair (kappa is 0.35 and 0.39, respectively).

Discussion

16-Detector row CTA without DSA is a reliable pretreatment investigation to assess feasibility of EVT of ruptured intracranial aneurysms. However, interobserver disagreement on feasibility of EVT is considerable.

Introduction

In patients with subarachnoid hemorrhage (SAH) digital subtraction angiography (DSA) is still considered as the reference test ("gold standard") for the evaluation of the presence of ruptured intracranial aneurysms as well as the selection and feasibility of treatment. However, DSA is an invasive procedure with a risk of neurological complications of 0.9-2.3% and a risk of permanent neurological deficit of 0.3%.[1] Computed tomography angiography (CTA) confers substantial advantage over DSA because it is non-invasive, is associated with few complications and it can be performed in unstable or agitated patients. Furthermore, it diminishes demands on conventional angiographic resources and is less dangerous for the patient. The advent of multidetector row CT scanners has steadily improved the diagnostic accuracy of CT scanners due to improved spatial and temporal resolution.[1,2] Equivalent diagnostic accuracy has been reported with 4 and 16-detector row CT angiography as compared with DSA.[3-6] The diagnostic value of CTA depends not only on the accuracy in detecting and localizing ruptured aneurysms but also on the ability to select the treatment and assess the feasibility of treatment.[1] The recent shift from surgical therapy as first line treatment of ruptured aneurysms to endovascular treatment[7] may have altered the requirements posed on angiographic visualization of intracranial aneurysm, because surgical and endovascular approaches probably differ with respect to the required level of anatomical detail of the aneurysm and its surrounding arteries. The diagnostic value of the more recently developed high resolution multidetector row CT scanners with respect to the clinical assessment regarding the feasibility of endovascular treatment of the ruptured aneurysm has not been studied. Therefore, we investigated the diagnostic value of 16-detector row CTA compared with conventional DSA for the assessment of feasibility of endovascular treatment of ruptured intracranial aneurysms in the acute phase after aneurysmal subarachnoid hemorrhage.

Methods

Patient inclusion

The study was a single-center, non-randomized observational study with prospective inclusion of subjects. Patients were recruited from October 1st, 2002, to October 1st, 2004 in a University Hospital. During the inclusion period, it was standard clinical practice to perform both CTA and DSA in all patients with spontaneous subarachnoid hemorrhage (SAH) of presumed aneurysmal origin, provided that their clinical condition permitted performance of both procedures. In our hospital, endovascular treatment (EVT) is considered the preferred treatment option for ruptured intracranial aneurysms, in accordance with the results of the ISAT trial.[7] Inclusion criteria for this study were: 1) clinical diagnosis of subarachnoid hemorrhage, confirmed by CT or CSF spectrophotometric analysis, 2) age 18 years or over, 3) written

informed consent by the patient or relative to review the patient's clinical record and imaging data, 4) performance of both CTA and DSA and 5) an aneurysm was found on CTA and DSA. The protocol was approved by the hospital's Medical Ethics Committee.

CTA data acquisition

Studies were performed with a 16-detector row CT scanner (Somatom X-32 Sensation 16; Siemens Medical Solutions, Erlangen, Germany). The scan volume started from the upper limit of the posterior arch of the atlas and extended cephaled with coverage of 100 mm. The lower limit was chosen to include a proximal origin of the posterior inferior cerebellar artery; the upper limit was chosen to include the callosomarginal artery. 80 ml of contrast material (Iodixanol 320 mg/ml – Visipaque – Amersham Health, Little Chalfont, UK) was injected. The CTA scan was synchronized with the contrast material injection with a bolus tracking technique. The time-interval between DSA and 3D-CTA was at least 6 hours to prevent contrast intoxication.

DSA data acquisition

Diagnostic DSA was performed in all patients being standard clinical strategy, with 3D imaging when necessary. Four vessel DSA was done according to the Seldinger technique. A 4–5-F catheter was selectively placed in the internal carotid and the vertebral arteries, injecting 6 cc (4 cc/s; internal carotid) or 7 cc (5 cc/s; vertebral artery) of contrast material (Iomeron 350, Bracco, Milan). In all patients, frontal, lateral and oblique views were obtained (matrix 1,024×1,024; image intensifier 20–28 cm). Images that yielded the clearest spatial projections of detected aneurysms were printed on hardcopies to be used for this study.

Data scoring and evaluation

Two experienced interventional neuroradiologists (ZF and HLJT) independently scored the 3D-CTA images and –immediately thereafter- the DSA images. The readers worked in the same hospital and had cooperated during many endovascular procedures. Both readers were familiar with the clinical use of the 3D-CTA. Reader 1 had performed over 100 endovascular procedures in patients with ruptured aneurysms and reader 2 had performed more than 40 procedures. Both readers were unaware of the actual treatment. 3D-CTA images were examined at a work station. A standardized evaluation was performed with maximum intensity projections (MIPs) with a thickness of 6–8 mm and an overlap of 3–4 mm in axial, sagittal and coronal planes for the anterior circulation, and in the sagittal plane and a plane parallel to the clivus for the posterior circulation. MIP planes and thickness could be adjusted and source images were available for additional evaluation.

DSA images were examined on hard-copy films. The readers were aware of the results of the unenhanced diagnostic CT regarding the blood distribution in the subarachnoid cisterns and presence and distribution of intraventricular blood, but were not aware of the clinical condition of the patient and the actual treatment. Both the 3D-CTA images and the DSA hard-copies were masked for patient identification.

CT-angiography

First, the readers scored the 3D-CTA on the work station blinded to the DSA results. The CTA was evaluated with respect to the location and size of the target aneurysm, which was defined as the aneurysm that had ruptured according to the reader. The location of the target aneurysm was noted as being at one of the 29 locations as previously described by Yasargil.[18]

The size of the target aneurysm and the presence of vasospasm were measured by one of the neuroradiologists (ZF). Size of the target aneurysm was scored by dome width (maximal diameter of the aneurysm), length (from fundus to base) and neck size in millimeters (mm).

Next, both readers chose one of the following three options with regard to suitability of the target aneurysm for endovascular occlusion based on CTA: 1) aneurysm can be treated with endovascular occlusion (with or without balloon remodeling technique) and DSA is not necessary, 2) aneurysm can not be treated with endovascular treatment and for this judgment DSA is not necessary, or 3) CTA yields insufficient information to make a definite judgment and DSA is needed to make a treatment decision. When option 2 or 3 was chosen, the reason for this choice was also specified.

Digital Subtraction Angiography

Immediately following the evaluation of the CTA, the DSA was examined. Therefore, the second evaluation was based on the results of both CTA and DSA. Again, the location of the target aneurysm was noted. Thereafter, a choice was made based on both CTA and DSA with regard to the feasibility of endovascular treatment, from the following options: 1) aneurysm can be treated with endovascular occlusion (with or without balloon remodeling technique), 2) aneurysm can not be treated with endovascular occlusion, or 3) both the results of CTA and DSA do not allow for a treatment decision. Finally, we compared the treatment decision based on CTA alone versus on both CTA and DSA. Both readers chose one of the following options: 1) same judgment, and DSA not necessary, 2) same judgment, but DSA was still considered to provide additional information or 3) same judgment and DSA was considered inferior to CTA. When option 2 or 3 was chosen the reason was given.

Outcomes

The main outcome was the proportion of target aneurysms for which 16-detector row CT angiography as judged on the work station was regarded as sufficient by each reader separately to make a definite judgment on feasibility of endovascular treatment. In addition, we assessed interobserver agreement with respect to judgment of feasibility of endovascular treatment based on CTA only and on both CTA and DSA. Further, we assessed: 1) how often and for what reason examination of DSA changed a definite judgment on feasibility of endovascular treatment with CTA, 2) the additional information, if any, provided by DSA after a definite judgment with CTA, 3) reasons for requiring DSA when CTA was regarded as insufficient for a definite judgement, 4) the relation between the size and location of the target aneurysm and the proportion of definite judgments that could be made with CTA and 5) whether the presence of vasospasm influenced the likelihood that a definite feasibility judgment was possible.

Statistics

Statistical analysis was performed with SPSS 12.0.1. Interobserver agreement between readers regarding feasibility of endovascular treatment of the ruptured aneurysms were assessed with Cohen's Kappa (K). Agreement is comsidered poor if $K \leq 0{,}20$, fair if $0{,}21 \leq K \leq 0{,}40$, moderate if $0{,}41 \leq K \leq 0{,}60$, substantial if $0{,}61 \leq K \leq 0{,}80$ and good if $K > 0{,}80$.[8] The proportion of patients in whom definite judgments regarding feasibility of endovascular treatment could be made with CTA alone, and next after viewing DSA, were tabulated in 2x2 tables. The relationship between the readers' judgments and characteristics of the aneurysms were tested with Pearson's X2 test.

Results

From 111 consecutive patients with SAH who underwent both CTA and DSA, 31 were excluded for the following reasons: 2 patients had traumatic subarachnoid hemorrhage, in 8 patients the DSA was not available for analysis, in 1 patient one of the readers doubted the target aneurysm on CTA although an infundibular dilatation near the posterior communicating artery that was confirmed to be the ruptured aneurysm at surgery was described by the reader on CTA. Twenty patients were excluded because the angiographic studies did not reveal an aneurysm. This study is based on the remaining 80 patients in whom both readers readily identified the target aneurysm on either CTA or DSA or both.

The relative frequencies of the locations of target aneurysms by vascular territory corresponded with those previously reported[7]: 35 patients (44%) had an anterior cerebral artery (ACA) aneurysm, 20 had an internal carotid artery (ICA) aneurysm (25%), 19 had a middle cerebral artery (MCA) aneurysm (24%) and 6 had a posterior circulation aneurysm (8%). There was no disagreement between the readers regarding the locations

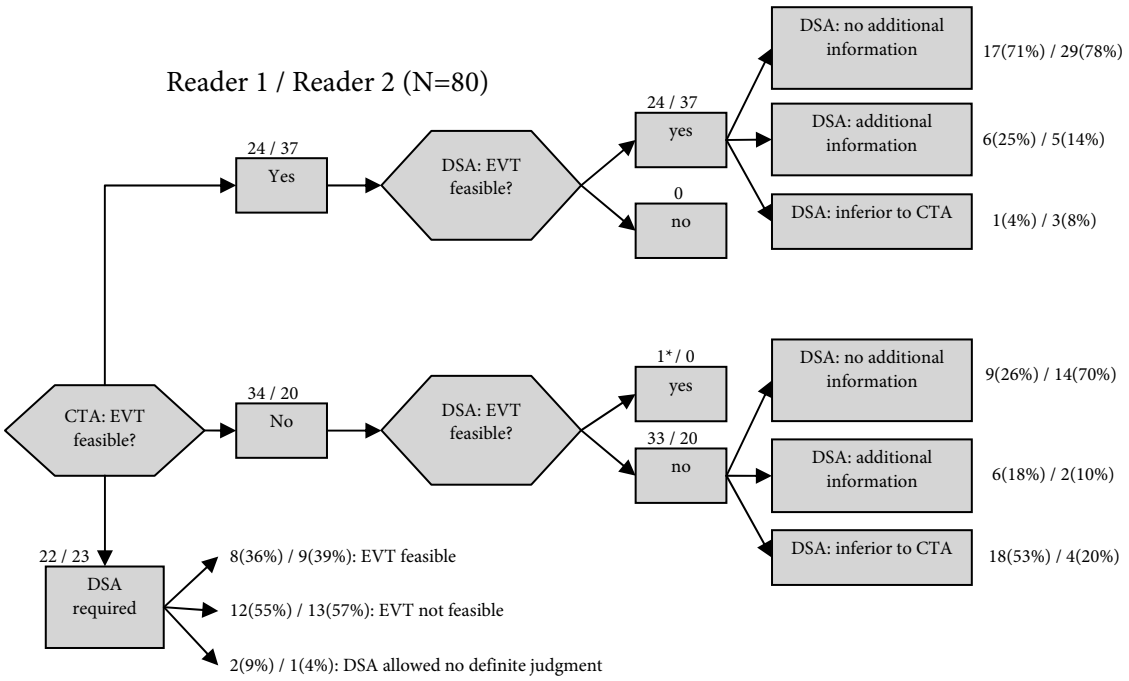
of the target aneurysms both with CTA alone and after viewing DSA, except for minor differences in the suggested locations, for instance the superior cerebellar artery by one and the basilar tip by the other reader in a broad based aneurysm.

Size (from fundus to base) distribution of the target aneurysms was as follows: 8 (10%) aneurysms were ≤3mm, 16 (20%) were >3 and ≤5mm, 46 (58%) were >5 and ≤10mm and 10 (13%) were >10mm.

Feasibility judgments on endovascular treatment and interobserver agreement

Reader 1 and 2 were able to make a definite judgment on feasibility of EVT with CTA alone in 58 (73%) and 57 (71%) of the patients, respectively (*Figure 1* and *Table 1*). DSA results never changed definite judgments by CTA alone, except in one patient by reader 1 who underwent DSA later than CTA when vasospasm had subsided. In this patient CTA showed extensive vasospasm and reader 1 judged EVT not yet feasible but noted that after the vasospasm would have subsided the target aneurysm (ICA bifurcation) would be suitable for EVT. Indeed, the DSA that was performed later did not show any vasospasm and the aneurysm was judged suitable for EVT.

Figure 1. Flowchart with flow of judgments by both readers regarding feasibility of endovascular treatment of target aneurysm with CTA both before and after viewing the DSA. Viewing DSA after CTA changed the judgment of treatment feasibility in one patient by reader 1



**Vasospasm at the time of CTA was the reason for the judgment that the feasability of endovascular treatment of the aneurysm could not be assessed. DSA was performed later, when vasospasm had subsided*

Table 1. Interobserver agreement on feasibility of endovascular treatment of ruptured aneurysms with CTA alone

CTA		Reader 2 EVT feasible?			
		yes	no	DSA needed	Total
Reader 1 EVT feasible?	yes	21	1	2	24
	no	7	15	12	34
	DSA needed	9	4	9	22
	Total	37	20	23	80

Cohen's kappa: 0,35

Table 2. Interobserver agreement on feasibility of endovascular treatment of ruptured aneurysms with CTA and DSA thereafter

CTA and DSA		Reader 2 EVT feasible?			
		yes	no	No judgment	Total
Reader 1 EVT feasible?	yes	28	5	0	33
	no	18	26	1	45
	No judgment	0	2	0	2
	Total	46	33	1	80

Cohen's kappa: 0,39

Interobserver agreement on judgments on feasibility of EVT (feasible, not feasible or need for DSA) based on CTA was just fair (Cohen's kappa 0.35, *Table 1* and see *Appendix 3* for example of disagreement). Interobserver agreement on judgments based on both CTA and DSA was similar (Cohen's kappa 0.39, *Table 2*).

We also calculated interobserver agreement with CTA before and after DSA on feasibility judgments (yes versus no) in the patients in whom both readers made a definite judgment. For the judgments with CTA alone (n=44), kappa was 0.64 and with both CTA and DSA kappa was 0.42 (n=77). Next, we calculated interobserver agreement for definite judgments on feasibility with CTA alone versus the need for DSA (n=80). Kappa was particularly low (0.16).

Additional information provided by DSA with regard to treatment decision after a definite judgment with CTA

DSA yielded additional information with regard to the treatment decision of the target aneurysm in 10% (6 patients, reader 1) and 9% (5 patients, reader 2) of the 58 and 57 patients respectively in whom CTA allowed for a definite judgment as judged by the readers (*Figure 1*). In the remaining cases where an additional value of DSA was noted by reader 1 (n=5) and reader 2 (n=2) this did not concern the target aneurysm or the treatment decision but pertained to additional aneurysms and this information is not further specified in this section.

In 2 of 24 patients in whom EVT was judged as definitely feasible with CTA by reader 1, DSA provided additional information (*Figure 1*). In one of the patients the target aneurysm appeared even better accessible for EVT with DSA than with CTA and in the other patient the target aneurysm was judged suitable for EVT with balloon remodeling with CTA whereas with DSA it was judged suitable for EVT without balloon remodeling.

In 4 of the 34 patients in whom EVT was judged as definitely not feasible with CTA by reader 1, DSA provided additional information. Anatomic visualization of the aneurysm, the aneurysmal neck and surrounding vessels was judged as superior to CTA (n=2). Kinking of the ICA was seen on DSA in one patient and filling of the target (ACA) aneurysm was from the left side (DSA) instead of the right side (with CTA), but vasospasm was more extensive on CTA resulting in a wrong assessment.

In 3 of 37 patients in whom EVT was judged as definitely feasible with CTA by reader 2, DSA provided additional information (*Figure 1*). In these patients the anatomical detail of the aneurysm neck or the neck-to-dome ratio seen on DSA was judged as complementary to the information by CTA,

Among the 20 patients in whom EVT was judged as definitely not feasible with CTA by reader 2, in one patient the ICA was additionally seen to be occluded on DSA compared with CTA and in one the anatomical detail of the complex target aneurysm was better seen on DSA.

Inferiority of DSA after a definite judgment with CTA

In 33% (19 patients, reader 1) and 12% (7 patients, reader 2) DSA was considered inferior to CTA after a definite judgment with CTA (*Figure 1* and *Appendix 4a* and *4b*).

DSA was judged as inferior to CTA after definite judgment of feasibility of EVT with CTA in 1 of 24 patients by reader 1 (*Figure 1*), because of less detail of local anatomy around the target aneurysm. After definite judgment of non-feasibility of EVT with CTA by reader 1, 18 DSA's were judged as inferior to CTA, mainly because of less anatomical detail seen on DSA.

DSA was judged as inferior to CTA after definite judgment of feasibility of EVT with CTA in 3 of 37 patients by reader 2 (*Figure 1*). After definite judgment of non-feasibility of EVT with CTA by reader 2, 4 DSA's were judged as inferior to CTA.

Reasons for requiring DSA when CTA was regarded as insufficient for a definite judgment

Reader 1 required DSA for a treatment decision in 22 patients (28%, *Figure 1*). Reasons for requiring DSA were unclear relation of sprouting arteries from or around the target aneurysm on CTA (n=12), vessels sprouting clearly from the aneurysmal dome (n=7), vasospasm and insufficient contrast filling of the target area (n=1), insufficient CTA quality (n=1). In one patient a distal medial wall aneurysm of the left ICA was doubted to be the target aneurysm because the blood distribution on the unenhanced diagnostic CT strongly suggested a left MCA aneurysm according to the reader. However, on DSA the same aneurysm was seen, and the reader concluded that this must have been the ruptured aneurysm because there was no MCA aneurysm. Because of a broad neck that was better depicted on DSA in this patient the aneurysm was judged not feasible for EVT.
After DSA, reader 1 judged EVT feasible in 8 patients, not feasible in 12 and no treatment decision could be made after DSA in 2 patients (*Figure 1*).

Reader 2 required DSA for a treatment decision in 23 patients (29%, *Figure 1*). In 12 patients that were mostly different patients than those by reader 1 (see: *table 2*) the reason for requiring DSA was that the relation of sprouting arteries from or around the target aneurysm was unclear on the CTA. In 2 patients vessels sprouting clearly from the aneurysmal dome as seen on CTA was the reason for requiring DSA. In 9 patients another reason was given: the aneurysm was too small on CTA (1), the aneurysm neck could not be evaluated well (2), local anatomy was unclear due to vasospasm (2) or the neck seemed too wide.
After DSA, reader 2 judged EVT feasible in 9 patients, not feasible in 13 and no treatment decision could be made after DSA in 1 patient (*Figure 1*).

Relation between size and location of the target aneurysm and feasibility judgments

The size of the target aneurysm (stratified by the four size categories described earlier) did not significantly affect the proportion of cases in which a definite treatment decision could be made with CTA both before and after seeing the DSA (*Table 3a* and *3b*). The smallest aneurysm that allowed for a treatment decision by both readers with CTA alone measured 1.3 mm on CTA. There was one smaller aneurysm measuring 1.2 mm for which both readers required DSA for a definite treatment decision. In both cases the readers disagreed on feasibility of EVT of the aneurysm.

The location of the target aneurysm (stratified by the four vascular territories described earlier) did not significantly affect the proportion of cases in which a definite treatment decision could be made with CTA both before and after seeing the DSA (*Table 4a* and *4b*).

Vasospasm and definite judgment on treatment feasibility

Vasospasm was present in 17 patients. The presence or absence of vasospasm had no influence on the proportion of patients in whom a definite judgment could be made with CTA alone or after viewing the DSA (*Table 5a* and *5b*).

Table 3a. Relation between size of ruptured aneurysms and judgments on feasibility of endovascular treatment with CTA

CTA			Aneurysm size category (lenghth)				
			<3mm	3-5mm	5-10mm	>10mm	Total
Judgment possible based on CTA alone?	Yes						
		Reader 1	5	10	37	6	58
		Reader 2	4	10	34	9	57
	No						
		Reader 1	3	6	9	4	22
		Reader 2	4	6	12	1	23
		Total	8	16	46	10	80

Pearson's X^2 [df=3], p=0.33 (reader 1) and p=0.24 (reader 2)

Table 3b. Relation between size of ruptured aneurysms and judgments on feasibility of endovascular treatment with CTA and DSA

CTA + DSA			Aneurysm size category (lenghth)				
			<3mm	3-5mm	5-10mm	>10mm	Total
Judgment possible based on both CTA and DSA?	Yes						
		Reader 1	8	15	45	10	78
		Reader 2	8	15	46	10	79
	No						
		Reader 1	0	1	1	0	2
		Reader 2	0	1	0	0	1
		Total	8	16	46	10	80

Pearson's X^2 [df=3], p=0.70 (reader 1) and p=0.26 (reader 2)

Table 4a. Relation between location of ruptured aneurysm and judgment on feasibility of endovascular treatment with CTA

CTA			Aneurysm vascular territory				
			ACA*	ICA	MCA	PC	Total
Judgment possible based on CTA alone?	Yes						
		Reader 1	22	18	14	4	58
		Reader 2	22	18	13	4	57
	No						
		Reader 1	13	2	5	2	22
		Reader 2	13	2	6	2	23
		Total	35	20	19	6	80

Pearson's X^2 [df=3], p=0.19 (reader 1) and p=0.19 (reader 2)

**ACA=anterior cerebral artery, ICA=internal carotid artery, MCA=middle cerebral artery, PC=posterior circulation*

Table 4b. Relation between location of ruptured aneurysm and judgment on feasibility of endovascular treatment with CTA and DSA

CTA + DSA			Aneurysm vascular territory				
			ACA*	ICA	MCA	PC	Total
Judgment possible based on both CTA and DSA?	Yes						
		Reader 1	34	20	18	6	78
		Reader 2	34	20	19	6	79
	No						
		Reader 1	1	0	1	0	2
		Reader 2	1	0	0	0	1
		Total	35	20	19	6	80

Pearson's X^2 [df=3], p=0.73 (reader 1) and p=0.73 (reader 2)

Table 5a. Relation between the presence of vasospasm and judgment on feasibility of endovascular treatment with CTA

CTA			Vasospasm		
			No	Yes	Total
Judgment possible based on CTA alone?	Yes	Reader 1	44	14	58
		Reader 2	46	11	24
	No				
		Reader 1	19	3	22
		Reader 2	17	6	84
		Total	63	17	80

Pearson's X^2 [df=1], p=0.31 (reader 1) and p=0.50 (reader 2)

Table 5b. Relation between the presence of vasospasm and judgment on feasibility of endovascular treatment with CTA and DSA

CTA + DSA			Vasospasm		
			No	Yes	Total
Judgment possible based on both CTA and DSA?	Yes	Reader 1	61	17	78
		Reader 2	62	17	79
	No				
		Reader 1	2	0	2
		Reader 2	1	0	1
		Total	63	17	80

Pearson's X^2 [df=1], p=0.46 (reader 1) and p=0.60 (reader 2)

Discussion

This study shows that assessment of the feasibility of endovascular treatment of ruptured intracranial aneurysms can be performed reliably with 16-detector row CT angiography without pre-treatment conventional angiography in the majority of patients (over 70% in our study), even in those with very small aneurysms. The size of the target aneurysm, its location and the presence of vasospasm as seen on CTA had no significant influence on the probability of a definite treatment decision with CTA alone versus the combination of CTA and DSA. On the other hand, we found considerable interobserver variability in

feasibility judgments of endovascular treatment irrespective of the diagnostic strategy. Further, the additional value of DSA after CTA was limited mainly to confirmation of the findings on CTA without affecting the treatment decisions based on CTA alone (except in one case in which CTA and DSA were not comparable due to vasospasm on CTA, but not on DSA), but some additional information was obtained with DSA that may be regarded as useful. It is of interest that although DSA provided additional information in some patients compared with CTA after a definite judgment with CTA in some cases, DSA was judged as inferior to CTA in other patients.

Our study has some limitations. First, our results may not be applicable to hospitals where 3D-DSA is used in the evaluation of intracranial aneurysms. 3D-DSA has been shown to be able to provide superior anatomical detail of ruptured aneurysms and surrounding arteries compared with 2D-DSA.[15,16] In addition, it has been suggested that, because of superior anatomic depiction, more complex endovascular procedures using balloon remodeling or stent assistance can be anticipated better with 3D-DSA than with 2D-DSA.[17] However, at present this concerns a small minority of cases and intra-procedural 3D-DSA will be able to identify these cases. On the other hand, comparison of 3D-CTA with 3D-DSA may have yielded a lower amount of DSA's that were considered inferior to 3D-CTA, but we have no reason to believe that this would have affected the high amount of patients in whom DSA did not change the treatment judgment based on CTA alone. Second, we did not include patients in whom no aneurysm was found or in whom the readers did not agree on the presence of a target aneurysm. Therefore, our results only apply to patients with a readily identified target aneurysm with a 16-detector row CT scanner but not to those with an aneurysm with a length of approximately a millimeter or less or when there is doubt on the presence of an aneurysm.

Although this is the first study with the primary aim to assess the value of CTA in the pre-treatment planning of endovascular treatment, one other recent study has reported on evaluation and treatment planning of intracranial aneurysms with 16-detector instead of 4-detector row CT angiography.[6] In the other study, 57 subjects were studied who underwent both CTA and DSA. A vascular neurosurgeon considered CTA alone sufficient for the assessment of suitability for surgical treatment in all but 5 cases in which he required DSA for further anatomical detail. However, the value of CTA for the assessment of suitability for endovascular treatment was not studied. We chose not to evaluate the DSA results separately, because in clinical practice judgments would also include the results of both examinations when performed. With this strategy we aimed at determining if, and to what extent, there was an additional value of DSA opposed to CTA alone.
Two recent studies reported on the value of 4-detector row CTA in therapeutic management, both surgically and endovascularly, of intracranial aneurysms.[9,10] In these studies DSA was performed in the acute phase after the bleed only when the CTA was judged to provide insufficient anatomical information to decide on

the appropriate management. Further, endovascular treatment was performed in the minority of patients because the results of the ISAT trial had not been published and surgical treatment still was the preferred treatment for anterior circulation aneurysms. In the first study, initial suitability of the ruptured aneurysm with CTA for endovascular treatment was withdrawn after viewing the DSA in 5 of 26 cases.[9] The less positive results of this study may be either due to inferior resolution of the 4-detector row CTA compared with 16-detector scanners or the fact that the investigators were not yet very familiar with the use of CTA in clinical practice, in contrast with our two experienced readers.

In the second study, 30 of 88 patients with aneurysmal SAH successfully underwent endovascular treatment without pre-treatment DSA, but the authors did not mention whether the intra-procedural DSA revealed unexpected findings that complicated the procedure.[10] In 15 of the 16 patients for whom the neurosurgeon requested DSA, the ruptured aneurysm was clipped. The results of this study seem to be in line with our findings, but potential additional information by DSA was not investigated.

Other previous clinical studies on the value of CTA in treatment planning used either 4-detector row or single detector CT scanners and mainly addressed diagnostic accuracy in detecting intracranial aneurysms or reported on implementation of CTA in planning of surgical treatment.[1,3-5,11,12] Comparison of our findings with these studies is difficult, because 16-detector row CT scanners have better spatial and temporal resolution[1,13] and our study aimed primarily at assessing the value of CTA in planning of endovascular treatment. Further, the requirements posed on any angiographic investigation may differ for the pre-treatment evaluation of endovascular or surgical therapy, for instance with respect to the depiction of flow dynamics.[14]

At present intra-arterial DSA is still generally accepted as the "gold standard" for the diagnostic work-up of suspected intracranial aneurysms. Our results and those of others[1,6] suggest that 2D-DSA is not suitable as reference test when compared with 16-detector row CTA. Therefore we recommend to use all available information (i.e. unenhanced CT, CTA, DSA, surgical or endovascular treatment, follow-up and post-mortem information) for the construction of the reference test.

For clinical purposes, we recommend that a patient with a readily identified ruptured aneurysm that is suitable for endovascular occlusion as assessed by 16-detector row CTA is scheduled for endovascular treatment immediately without pre-treatment DSA. This strategy will reduce demands on conventional angiographic resources significantly and improve management flow of patients with ruptured intracranial aneurysms because CTA will prove sufficient in the majority of cases. Interobserver variability in the assessment of feasibility of endovascular treatment of ruptured aneurysms is considerable. This is not easily solved because this is inherent to medical practice by many different physicians. On the other hand, this

finding should encourage interventional neuroradiologists to develop consensus guidelines on endovascular treatment of ruptured aneurysms to try and increase the proportion of aneurysmal SAH patients that can be treated endovascularly.

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4

Unruptured intracranial aneurysms

4.1

Rate of subarachnoid hemorrhage in patients with an unruptured intracranial aneurysm. A systematic review.

Abstract

Background and Purpose

Widely diverging estimates of annual risk of subarachnoid hemorrhage (SAH) in patients with an unruptured intracranial aneurysm (UIA) have been reported. We systematically assessed rupture rates reported in observational studies, taking into account methodological quality of the studies.

Methods

Studies were selected through a MEDLINE search, and by hand searching of relevant journals. Rupture rates were calculated per study stratified by size and type (incidental, additional and symptomatic UIA) by means of the patient-years at risk method.

Studies were ordered according to methodological score based on previously proposed criteria. Studies with a methodological score below a threshold level were excluded. In a sensitivity analysis, we examined the effect of changing the threshold level on rupture rate.

Results

Of 14 studies, 11 were excluded because of low methodological scores or heterogeneity. The overall annual rupture rate was 1.1% (95% CI 0.9-1.4%). The rupture rate for incidental and additional UIAs was 1.3 and 1.0% respectively (95% CI 0.9-1.7% and 0.7-1.4%). Large UIAs (≥ 10mm) had an annual rupture rate of 2.7% (95% CI 1.5-4.2%), whereas small UIAs (<7mm) had a rate of 0.7% (95% CI 0.4-0.9%). Additional UIAs were smaller than incidental UIAs, which may explain the observed difference in rupture rate.

Conclusions

Differences in methodological quality of observational studies seem to account for widely diverging estimates of annual rupture rates of UIAs. Nevertheless, our study indicates that the overall rupture rate of unruptured aneurysms is substantial and leads to high lifetime risks of subarachnoid hemorrhage.

Introduction

Widely diverging annual rupture rates of UIAs have been reported, varying between 0.27 and 7%.[1,2] Although the absolute difference between these estimates may seem relatively small, the estimates may yield an estimated life time rupture risk of as low as 9% or as high as 92% in a hypothetical healthy 45 year-old man with a life expectancy of 35 years, assuming that the annual rupture rate is constant. [3]

To date, observational studies that have assessed annual rupture rate of UIAs have not been systematically reviewed, taking into account differences in methodological quality between studies.[4] Yet, methodological quality differs considerably between studies. For example, in some studies patients were not included consecutively,[5-12] the method of follow-up was not clearly described,[6,8,10-14] or the proportion of patients who were lost to follow up was large,[12,13] or not mentioned. [5,6,8-11,14-16] Another reason for a thorough re-evaluation of published annual rupture rates is the recent publication of prospective data on rupture rates of UIAs in a large number of patients by the second International Study of Unruptured Intracranial Aneurysms (ISUIA).[15] Finally, it may be important to assess differences in rupture rate of different types of UIAs, such as incidental, additional and symptomatic UIAs, because of the large differences in rupture rate between these categories of patients in the ISUIA and in other studies.[5,15,17]

We conducted a systematic review with the aim to estimate the annual rupture rate of unruptured intracranial aneurysms, accounting for differences in methodological quality between studies and stratified by size and type (with or without previous SAH, and with or without symptoms due to mass effect) of the unruptured aneurysms.

Materials and Methods

To assess the methodological quality of observational studies on annual rupture rate of UIAs, we used previously described criteria for methodological quality of studies on prognosis of disease[18,19] and modified these criteria to fit these studies (*Appendix 5*). These criteria can help to identify inconsistencies regarding clinical course and prognosis among published series that mainly result from different selection and follow-up of patients.

Search strategy

Studies were searched using Medline accessed through Pubmed, with the following key words: "subarachnoid h(a)emorrhage", "unruptured intracranial aneurysm", "unruptured cerebral aneurysm", "(annual) rupture rate", "rupture risk". The reference lists of these articles were hand-searched for additional original articles on rupture rate until no new studies were found.

Eligibility Criteria

The primary aim of the eligible studies had to be estimation of rupture rate of unruptured intracranial aneurysms. Data collected in these studies should allow for estimation of the annual rupture rate by means of the patient-years at risk method (explained below).

Assessment of Methodological Quality

We distinguished 9 criteria that addressed methodological quality (*Appendix 5* and *6*). These criteria for methodological quality specifically addressed: 1) whether there was a prospective consecutive inception of patients, 2) method and robustness of follow-up, 3) objective assessment of outcome, i.e. subarachnoid hemorrhage during follow-up and 4) assessment of potential confounders (i.e. studies had to have studied at least the following prognostic factors for rupture for interdependence in 2x2 tables, and when indicated in a multivariable regression model: size, type [additional versus non-additional] and location). In addition, 14 subject matter criteria addressed the appropriateness and detail of the clinical data. Each fulfilled criterion was assigned a score of 1 point, and scores were added to yield a methodological quality score (0-9 points), and a total quality score (0-23 points). We assumed that studies with a higher score would yield a rupture rate estimate that was less susceptible to systematic error. Two investigators (MvdJ and DWJD) scored each study separately and after a consensus meeting. A Bland-Altman analysis[20] (data not shown) indicated that one investigator systematically assigned higher overall scores than the other. It was then decided to use the methodological score to assess the quality of the studies. We categorized studies according to high (≥ 6 points) or low (≤ 5 points) methodological quality score.

Extraction of Data

To calculate annual rupture rates, we used the patient-years at risk method, which implies that the rupture rate is calculated by dividing the number of cases with subarachnoid hemorrhage during follow-up (*I*) by the total patient-years at risk (*PYAR*). When the variables *I* and *PYAR* were not mentioned or could not be calculated directly from the data, they were calculated from survival curves when available by means of the following formula: $S_t = e^{-\lambda t}$, where S_t is the proportion at risk without event at time *t* and λ is the hazard rate (=annual rupture rate), assuming a constant annual risk.

Next, rupture rates for the subgroups of different sizes and types of unruptured aneurysms were calculated if possible. We distinguished three types of unruptured aneurysms: 1) incidental aneurysms that are discovered in patients that are investigated for another disease, 2) additional aneurysms that are found in patients with another, ruptured, aneurysm and 3) symptomatic aneurysms that have caused symptoms due to mass effect.

When mean follow-up per subject was not broken down by size and type, we applied mean follow-up per subject also for the size and type subgroups to calculate *PYAR*.

We did not include other prognostic factors for rupture apart from aneurysm size and type in this systematic review, such as hypertension, age or smoking, because in most studies, the variables *I* and *PYAR* could not be extracted separately for the different prognostic factors.

Application of Quality Score

Study results were combined to calculate rupture rates by adding up *PYAR* and events (*I*) starting with the study with the highest quality score and adding the study with the second highest quality score and so on. We calculated the annual rupture rate expressed as a percentage and did not use odds ratios or logarithmic scales. We further stratified by size and type (incidental, additional or symptomatic).

Sensitivity Analysis

A sensitivity analysis assesses how sensitive the primary outcome parameter (in this case: rupture rate estimates of unruptured aneurysms) is to plausible changes in estimates and assumptions (here: the studies included to calculate the estimates). Sensitivity analysis in this study was performed by studying the effect of inclusion of studies with lower quality scores or induction of heterogeneity. Also, the effect of inclusion of all studies, regardless of their quality, on the rupture rate estimates was assessed.

Statistical analysis

Standard formulas were used to calculate 95% confidence intervals (CI) of rupture rate estimates:[21] $CI = (I \pm 1{,}96\sqrt{I}) / PYAR$ when $I>30$, or: $CI = (\sqrt{I} \pm 1)^2 / PYAR$ when I<30. Comparison of incidence rate data was performed with STATA 8.

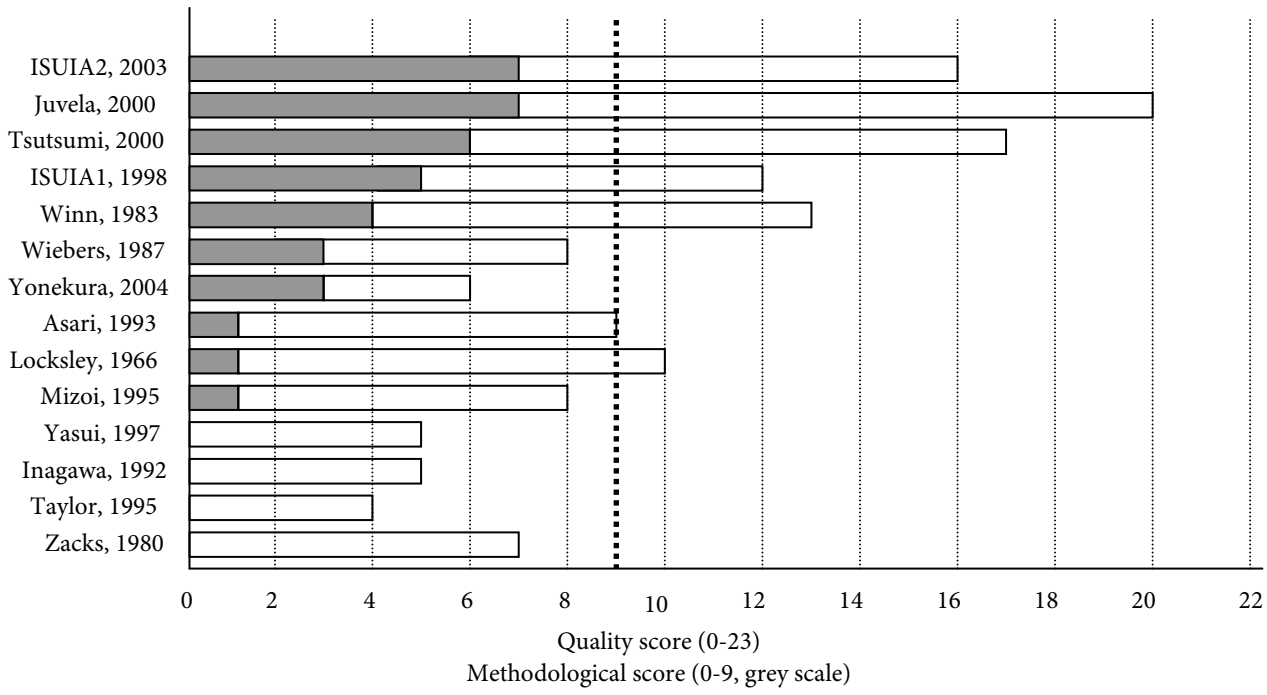
We additionally checked heterogeneity of the estimates of each study by means of standard methods. We assessed heterogeneity in a number of reported rates, using the Poisson heterogeneity of dispersion test.[22] Small values of the χ^2 statistic support the concept of homogeneity, and large values (indicating $p<0.05$) suggest heterogeneity.

Results

We identified 16 observational studies on rupture rate published between 1966 and 2004 that fulfilled the inclusion criteria.[5-16,23,24,25,26] Two studies were excluded because they concerned duplicate publications of extended case series.[25,26]

The characteristics of the 14 studies are shown in *Appendix 6*. Only three studies were considered prospective.[14,15,23] Two of these were subject to surgical selection bias,[14,15] which means that a part of the subjects in these studies underwent treatment of the unruptured aneurysm during follow-up. One of the studies was a population based study,[11] the remaining studies were hospital based case series, although only a minority of studies explicitly stated whether the recruitment of patient was through primary, secondary or tertiary referral. Only half of the studies had some form of structured follow-up, and in only six studies the percentage of subjects lost to follow-up was mentioned. We generally assumed that in the other studies follow-up was complete although this was explicitly mentioned in only one study.[23] Only two studies mentioned that subjects with cavernous sinus aneurysms were excluded. Half of the studies mentioned that subjects were censored from follow-up after successful occlusion of the unruptured aneurysm, whereas in the remaining studies this could only be assumed. In a minority of studies, it was stated that the diagnosis of subarachnoid hemorrhage from the unruptured aneurysm during follow-up was confirmed by CT, spectrophotometric analysis of the spinal fluid, or autopsy. Most studies did not make a distinction between a certain or probable diagnosis of subarachnoid hemorrhage. In none of the included studies outcome assessment was blinded to clinical and prognostic information at baseline.

Figure 1. Fourteen observational studies on rupture rate of unruptured intracranial aneurysms: total quality scores and methodological quality scores (abbreviated as methodscore, grey bars) per study



Five studies did not clearly distinguish between the three types of unruptured aneurysms (incidental, additional and symptomatic), or combined two types into one category for calculation of rupture rates (for

instance, in some studies only the distinction between UIAs in patients with and without subarachnoid hemorrhage from a separate aneurysm was made for the assessment of rupture rates, ignoring the distinction between incidental and symptomatic aneurysms[5,15,16]). In the other studies only one or two types of aneurysms were included. Three studies distinguished between all three types of unruptured aneurysms. All except two studies used three or more size categories.
In *Figure 1* the total and methodological quality scores per study are shown. We regarded the fulfillment of many additional criteria as indicative of careful study conduct, an indirect measure of study quality. Studies were ordered by methodological quality score and next by alphabetical order of the first author's name when methodological quality scores were equal.

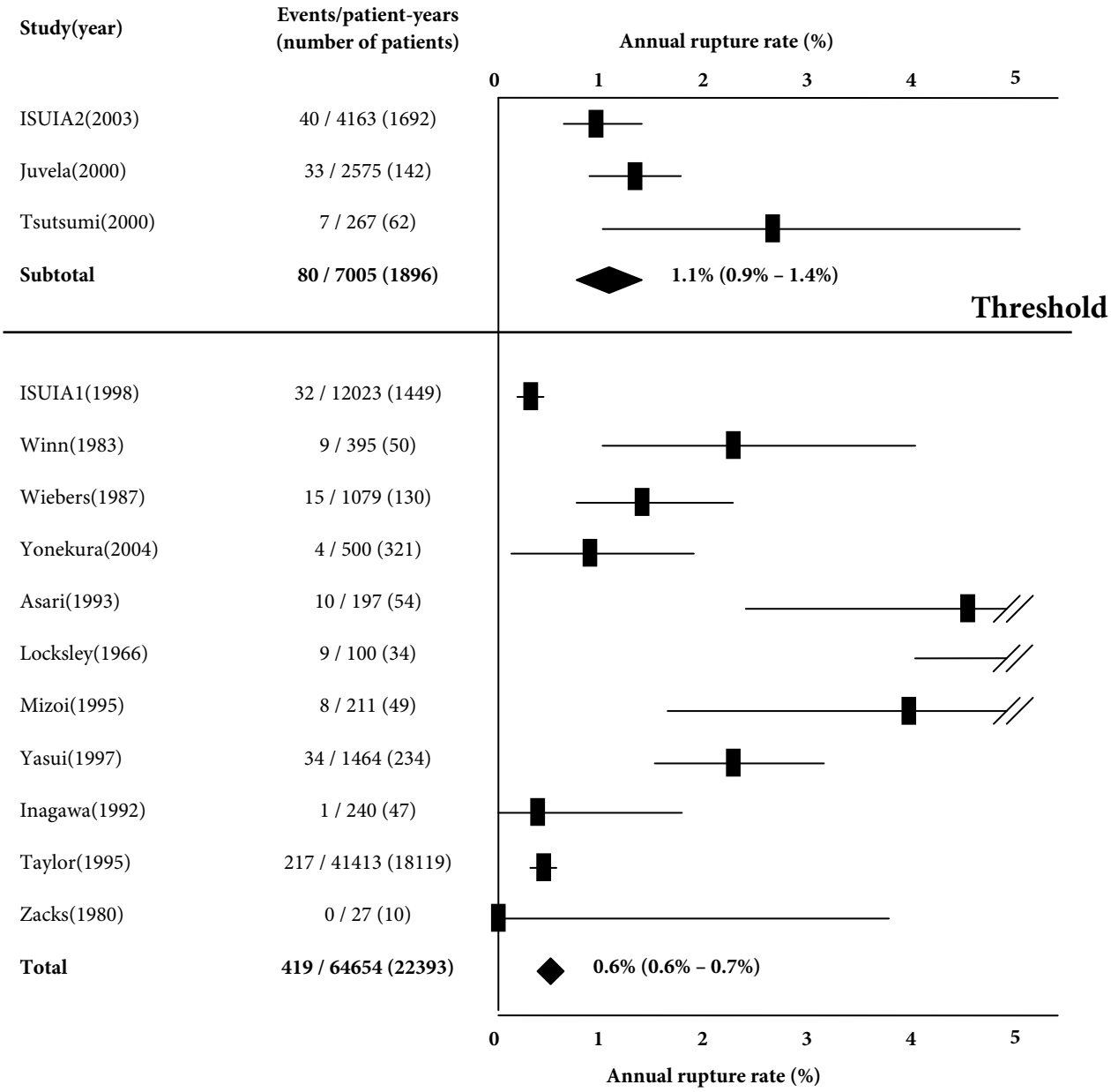
Three studies were consistently given a high methodological quality score by both investigators separately and after consensus,[15,23,24] two studies scored only one, [5] or two points[7] below the threshold, whereas the remaining studies received a low methodological quality score. We assumed that studies with high methodological quality scores would be less prone to bias than those with low methodological quality scores and considered methodological quality score more important than total quality score.

Overall Annual Rupture Rate

Overall annual rupture rate estimates and 95% confidence intervals of all individual studies are shown in *Figure 2*, ordered by methodological quality score, identified by first author and year of publication and, next, by alphabetical order in case of equal scores. For each study the number of ruptures, patient years at risk and number of included patients are given. Combined analysis of all 14 studies yields an annual rupture rate of 0.6% (95% CI 0.6 to 0.7). However, this includes many studies with low total and methodological quality scores with significant heterogeneity of rupture rate estimates. The overall annual rupture rate based on 80 ruptures during 7005 patient years at risk from the three studies with high methodological scores was 1.1% (95% CI 0.9 to 1.4). In contrast, overall annual rupture rate based only on the observational studies with low methodological quality or induction of heterogeneity in *Figure 2* (studies below the threshold line) was 0.6% (95% CI 0.5 to 0.7, not shown in *Figure 2*).

In a sensitivity analysis, significant heterogeneity was induced ($P<0.0001$ for the null hypothesis that estimates were homogeneous) after adding the next ranked study's data[5] to our estimate, even though this study had a methodological quality score of 5 points (*Appendix 6*). The overall annual rupture rate after adding the data from this study to the studies above the threshold was 0.6% (95% CI 0.5 to 0.6%). Therefore, we included only the first three studies in the final analysis (*Figure 2*).

Figure 2. Cumulative meta-analysis of cohort studies of patients with unruptured intracranial aneurysms: estimates of rupture rates per study with 95% confidence intervals, and combined estimates. Studies are ordered according to decreasing methodological quality score. The horizontal line indicates the threshold level of 5/6 points. Subtotals for studies above the threshold are indicated



Annual Rupture Rate stratified by Aneurysm Size or Type

To calculate annual rupture rates stratified by size or type of aneurysm, only data from the first three studies were used (*Table 1*).

Annual rupture rates of incidental and additional aneurysms were 1.3% (95% CI 0.9 to 1.7) and 1.0% (95% CI 0.7 to 1.4), respectively. The difference between these two estimates was not statistically significant (P=0.34, *Table 1*). However, the mean size of incidental aneurysms (9 mm) exceeded that of additional aneurysms (6

mm), and this may account for the difference in rupture rate. On the other hand, these mean sizes are only rough estimates, because crude data on the precise number of aneurysms stratified by exact size could not be completely extracted from the studies. Data on symptomatic aneurysms were too scarce to calculate a precise rupture rate estimate: only in the study by Juvela, 2 ruptures were described during 77 PYAR, yielding a rupture rate estimate of 2.6% (95% CI 0.2 to 7.6). In both USUIA studies and the study by Yonekura, no distinction was made between incidental or symptomatic aneurysms in patients without previous SAH for the analysis of rupture rate, but the authors mentioned that a small minority of the UIAs was symptomatic (up to 10%). Therefore, we calculated the rupture rate of incidental aneurysms based on the numbers provided for UIAs in patients with no previous SAH, assuming that the small number of symptomatic UIAs would not lead to a significant change of the rupture rate of incidental aneurysms. However, patient years at risk were not given for symptomatic aneurysms separately in these studies.

Table 1. Annual rupture rates for the subgroups of different sizes and types of unruptured aneurysms, based on extractable data of three studies[15,23,24] selected by high methodological quality and homogeneous rupture rate estimates

Type of UIA	Events/PYAR	Annual rupture rate (95% CI)
Incidental	38 / 2961	1.3% (0.9-1.7)*
Additional	40 / 3875	1.0% (0.7-1.4)*
Symptomatic	-	-
Size of UIA (mm)		
<7	32 / 4828	0.7% (0.4-0.9) †
7-12	19 / 1194	1.6% (0.9-2.4) †,‡
≥10	16 / 587	2.7% (1.5-4.2) ‡

** The comparison between overall rates of rupture in incidental and additional aneurysms is not significant, incidence rate-ratio (IRR) = 1.2 (95% CI 0.8 to 2.0, p=0.34, exact)*
† IRR (small versus medium size) = 0.4 (95% CI 0.2 to 0.8, p=0.004, exact)
‡ IRR (medium versus large size) = 0.6 (95% CI 0.3 to 1.2, p=0.12, exact)
IRR (small versus medium and large) = 0.3 (95% CI 0.2 to 0.6, p<0.0001, exact)

Larger size of unruptured aneurysms was associated with higher rupture rates (*Table 1*). Small (diameter of less than 7 mm), intermediate (7 to 12 mm) and large aneurysms (equal or larger than 10 mm) had annual rupture rates of 0.7% (95% CI 0.4 to 0.9), 1.6% (95% CI 0.9 to 2.4) and 2.7% (95% CI 1.5 to 4.2) respectively. Differences in rupture rates were statistically significant only between the small (<7 mm) size and medium (7-12 mm) size categories, P<0.01 and between the small size versus the other size categories, P<0.001 (*Table*

1). There was some overlap between the size categories, reflecting the cut values for size categories in the studies used for the analysis. Incidental aneurysms were associated with slightly higher rupture rates than additional aneurysms, but the difference was not statistically significant (P=0.34).
Because size and type of the unruptured aneurysms may not be independent prognostic factors for rupture, we assessed their interdependence in a 2x2 table (*Table 2*). The Tsutsumi study[24] did not provide the data on size and type that could be used for this assessment. Only in the small size category (<7 mm), but not in the intermediate and large size categories, was aneurysm type (additional aneurysms) associated with an increased rupture rate compared to incidental aneurysms.

Discussion

This systematic review shows that the wide variation in published rupture rates of unruptured intracranial aneurysms may be largely explained by insufficient methodological quality of the majority of studies. Low methodological quality has probably introduced bias resulting in relatively low or high rupture rate estimates depending on the methodological imperfections.

Table 2. Relationship between size and type of unruptured aneurysm and annual rupture rate. Small indicates less than 7 mm, intermediate 7-9 mm (Juvela) or 7-12 mm (ISUIA II), large indicates more than 10 mm (Juvela) or more than 12 mm (ISUIA II)

Annual rupture rate#	Size categories			
Type	Small	Intermediate	Large	Total
Incidental + symptomatic aneurysms *	0.2% (2 / 1366)	1.4% (10 / 704)	3.4% (18 / 524)	1.2% (30 / 2594)
Additional aneurysms $	0.9% (30 / 3463)	1.6% (8 / 491)	2.6% (5 / 189)	1.0% (43 / 4143)
Total	0.7% (32 / 4829)	1.5% (18 / 1195)	3.2% (23 / 713)	1.1% (73 / 6737)

 # Numbers represent events / PYAR (Patient-years-at-risk, percentages are annual rates.
** Data from ISUIA II only. The data from the Tsutsumi study did not allow for stratification by size and type.*
$ Data from ISUIA II and Juvela et al. More than 90% of patients from the Juvela study had additional aneurysms.

The comparison between overall rates of rupture in incidental and additional aneurysms is not significant, incidence rate-ratio (IRR) = 1.1, 95% CI 0.7 to 1.8, p=0.65, exact.

The comparisons between rates in small versus intermediate and between rates in intermediate versus large aneurysms are statistically significant (IRR = 0.4, 95% CI 0.2 to 0.8, p=0.008, and IRR = 0.5, 95% CI 0.2 to 0.9, p=0.02, exact).
The comparison between rates of rupture in incidental vs additional aneurysms, in the small size category only, is significant: IRR 0.2, 95% CI 0.02 to 0.7, p=0.003.

Our final analysis, based on three studies selected on the basis of both high methodological quality and homogeneity of rupture rate estimates, yielded an annual overall rupture rate estimate of 1.1% (95% CI 0.9 to 1.4). Furthermore, we noticed that larger aneurysm size predicted higher annual rupture rate. The fact that our results do not differ to a large extent from previously observed rupture rates may not seem surprising or new information. However, a systematic review such as ours more accurately reports the precision of estimates by combining results from several studies.

Some methodological limitations need to be discussed. First, because we used the patient-years-at-risk method for the rupture rate estimates, we extracted the two variables (aneurysm ruptures during follow-up divided by patient years at risk) for this equation from the articles, but when one of the two variables was not available it was calculated from given annual rupture rates. This may have yielded inaccurate rupture rate estimates when the variables were included in the cumulative analyses because authors did not always use the patient years at risk method or even did not mention which method was used. Second, mean follow-up per subject was not always broken down by size and aneurysm type. We then had to assume that mean follow-up per subject was similar in these subgroups. Third, the methodological quality score may yield different results when it is constructed or assessed by different investigators, although the quality assessment by consensus has been used previously in similar settings[27,28] and this probably prevents systematic error. Fourth, the patient-years-at-risk method, as well as the exponential model we used to estimate rates from curves and tables, assumes a constant annual rupture rate. This has been proven a simple and robust assumption in many analyses and it is supported by the cohort study by Juvela et al, here assigned the highest overall and methodological quality score, that reported a nearly constant annual rupture rate over time.[23] On the other hand, it has been hypothesized that a critical size for rupture exists, below which rupture risk is very low, and that aneurysms may rupture soon after they are formed.[5,15,29-32] However, this theory is contradicted by the fact that many aneurysms that rupture have been found to be quite small, assuming that size after rupture does not change significantly.[33-35] Moreover, we found relatively high overall rupture rate estimates based on the three studies we used for the final analysis and in these studies aneurysm diameter was below five to seven millimeters in the majority of subjects. The assumption of a constant annual risk of rupture forms the basis of our calculations. It implies that as much statistical weight is given to units of observation time and the number of included patients for the calculation of the denominator (i.e. patient-years-at-risk). A

potential drawback of this method is that it includes small cohorts with small clinical diversity, which may not be as representative as larger cohorts that were recruited from many centers, as in the ISUIA studies.
We first assessed overall rupture rates and thereafter we calculated rupture rates for additional and incidental aneurysms across size categories, based on more detailed data that could be extracted from ISUIA II and Juvela's study,[15,25] In these two studies, the comparison between overall rates of rupture in the incidental and additional aneurysm groups is not significant. The same comparison in the small sized group is significant, but in our opinion, this should be interpreted with caution, because the overall association is not significant, and the number of events in this subgroup is quite small.
The strengths of this study are the stratification by methodological quality to calculate rupture rates, and the systematic and transparent assessment of the included studies. Stratification of observational studies on rupture rate of unruptured aneurysms by methodological quality has not been performed previously. The very low annual rupture rate of 0.05% of aneurysms with a diameter of less than 10 millimeters in patients without previous SAH, reported in the retrospective arm of the first International Study of Unruptured Intracranial Aneurysms,[5] illustrates the potentially misleading impact of a large observational study. Several reviews and the AHA Stroke Council[36-40] have made recommendations for the management of patients with unruptured intracranial aneurysms that were in part based on these new data in spite of major methodological shortcomings. These have been addressed in a flurry of editorials that criticized the first ISUIA report, mainly because of its retrospective design that was likely to have introduced bias. In our study, the first ISUIA was assigned a high methodological quality score, but adding its overall rupture rate to the other studies with high methodological quality scores induced a major change in our estimated rupture rate and significant heterogeneity. The validity of the method we used to select only three studies based on both their quality and homogeneous rupture rate estimates is confirmed by the cut point for inclusion in the final analysis, which almost coincided for the induction of heterogeneity and the assignment of low methodological quality. Our hypothesis was that high methodological quality corresponded to less biased results which would apply better to the patients whom we encounter in clinical practice. Therefore, we think that valid data on rupture rate are to be considered when advising a patient with a fortuitously discovered intracranial aneurysm. These data should ideally be based on cohorts, in which selection of patients that have been treated for their aneurysm is avoided. This was the case only in the study by Juvela et al.
Our results indicate that more data are needed on patients with small incidental asymptomatic aneurysms. In a previous systematic review on rupture risk of unruptured intracranial aneurysms, a 1.9% overall annual rupture rate was found, which is somewhat higher than in our study.[17] Aneurysms of 10 millimeters or less had an annual rupture rate of 0.7%, which is slightly lower than in our study. A more striking difference is that additional aneurysms were found to have a higher rupture rate (1.4%, 95% CI 0.9 to 2.0) than asymptomatic (equal to incidental aneurysms in this review) aneurysms (0.8%, 95% CI 0.4 to 1.5) whereas we

found the reverse. However, in the previous systematic review this difference was not statistically significant, none of the three studies we used for the final analysis had yet been published and no adjustment had been made for differences in mean size between additional and incidental aneurysms. On the other hand, in our study a small number of patients with symptomatic aneurysms were incorporated in the incidental aneurysms group because separate data on ruptures and patient years at risk in this group could not be extracted from the second ISUIA study. Further, methodological quality[41] was not systematically taken into account in the previous review.

We conclude that differences in methodological quality of observational studies seem to account for widely diverging estimates of annual rupture rate of patients with UIA. Nevertheless, our results indicate that the overall rupture risk of unruptured aneurysms is substantial and results in high lifetime risks of subarachnoid hemorrhage.

If the results of observational studies on rupture rate of unruptured intracranial aneurysms are to be applied to clinical practice, the design, analysis and reporting of these studies should be of good quality. For future studies it is important to include separate data on ruptures and patient-years-at-risk for different types of aneurysms, size categories and other prognostic factors with adjustment for confounding variables. The methodological quality score set out in this article for study design of rupture rate studies provides a reasonable basis to assess individual studies on their quality rather than the number of included subjects, but it also exemplifies that systematic assessment of these studies is quite difficult.

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5

General discussion

The aim of the studies described in this thesis was to further elucidate clinical aspects of the diagnosis and treatment of aneurysmal subarachnoid hemorrhage (SAH) and to re-assess the rupture risk of unruptured intracranial aneurysms (UIA's). All studies were performed in a strictly clinical setting. The advantage of such an approach is that it is often possible to provide answers to questions that have clinical relevance and that the results may be used to modify current clinical practice. In this chapter, I will first summarize the main findings and then discuss the clinical implications. Finally, I will discuss some general methodological issues related to the studies described in this thesis and suggest directions for further research.

MAIN FINDINGS

Localizing value of cisternal blood on CT for the site of rupture

In patients with aneurysmal SAH and multiple aneurysms, identification of the ruptured lesion is important to guide treatment decisions. We investigated whether the localization of the ruptured aneurysm could be predicted by the blood distribution on CT (chapter 2.1). We found that interobserver agreement for the site of rupture was only 52%, with a moderate kappa value. Agreement was better in case of ruptured anterior cerebral artery (ACA) aneurysms than for other locations. When both investigators agreed on the predicted location, the prediction was correct in a high proportion of patients for supratentorial aneurysms (range: 74%-97% for ACA and MCA aneurysms) but not for posterior circulation aneurysms (40%). In 14%, the blood distribution did not allow prediction of the site of rupture. Posterior circulation aneurysms were mistaken for supratentorial aneurysms in 2-3% by both investigators and the reverse was the case in 2-4%. A ruptured posterior circulation aneurysm was wrongly predicted in almost half of the cases of nonaneurysmal SAH. Parenchymal cerebral hematoma (present in 15%) always revealed the correct site of rupture, whereas ventricular blood did not have a localizing value. Finally, we found that sensitivity, specificity and positive predictive value was high by both investigators only in case of ruptured ACA aneurysms.

Interobserver variability of cisternal blood on CT

The amount of blood on CT after aneurysmal SAH had earlier been found to be an independent predictor for the occurrence of delayed cerebral ischemia.[3] Interobserver variability in the assessment of the amount of blood on CT may affect its predictive value depending on the extent of variability. In chapter 2.2, we found that the difference between sum scores (ranging from 0 to 26 for 13 cisterns) on the diagnostic CT assigned by two investigators varied from -9 to 16 points and limits of agreement (mean ±2SD) were −4.6 to 13.3. This range of different sum scores is too wide for clinical purposes. Because of these differences, we found that a high sum score (>13) independently predicted the occurrence of cerebral ischemia for one investigator but not the other.

Diagnostic accuracy of 16-detector row CT angiography for the detection of intracranial aneurysms

We found that 16-detector row CT angiography as judged by two experienced interventional neuroradiologists detected almost all ruptured aneurysms, except one very small aneurysm (measuring 2mm) that was missed by both readers, when compared with a reference standard consisting of all available clinical and radiological information (i.e sensitivity of 99% for the ruptured aneurysms). However, additional aneurysms were detected with higher accuracy with both CTA and DSA than with CTA alone. Specificity was generally high (92% and 96% for the two readers), therefore CTA may rarely lead to subjecting patients to treatment when they do not have an aneurysm (in fact one patient underwent surgery, but no aneurysm was found during surgery). Interobserver agreement on the presence of a ruptured aneurysm with CTA was excellent. From our results it can not be concluded that DSA is superior to 16-detector CTA, but rather that DSA may have an additional value compared with CTA alone with respect to detection of additional aneurysms.

Impact of early aneurysm surgery on outcome

Most neurosurgeons perform early surgery only in patients in good clinical condition, because they feel that these patients benefit most from early intervention. However, precise clinical criteria that identify patients that may benefit from early surgery have not been properly investigated, mainly because randomized comparison has not been performed in contemporary patients. In our historical cohort study, the shift from delayed aneurysm surgery in all eligible patients to early surgery within the first 72 hours after the ictus in good grade patients did not affect overall outcome. Cerebral ischemia occurred significantly more often in the early surgery cohort. Furthermore, we found a protective effect of early surgery against rebleeds, but only after adjustment for the highly significant increase in the rate of external CSF drainage in the early surgery cohort, which might have precipitated rebleeding. In patients with favorable prognostic factors on admission (GCS>12 and/or low amount of cisternal blood on CT), we observed a strong trend for improved outcome after adjustment for confounding factors in those with either low amount of blood on CT or both low amount of blood and GCS>12 on admission. This is the first and probably the last study on the effect of early surgery on outcome in patients managed with what has been called “modern treatment” (including nimodipine and standard hypervolemic treatment and triple-H therapy for cerebral ischemia), including a control group, in which the appropriateness of performing early surgery in patients with favorable clinical characteristics on admission as adhered to by most neurosurgeons is confirmed. The advent of endovascular treatment makes future surgical studies on the selection of patients who may benefit from early surgery much less if at all feasible.

Value of 16-detector row CT angiography in planning endovascular occlusion of ruptured aneurysms

The recent introduction of 16-detector row CT scanners has improved spatial and temporal resolution in the diagnostic evaluation of intracranial aneurysms, equivalent to that of digital subtraction angiography (DSA).[32] We studied whether feasibility of endovascular treatment (EVT) could be assessed reliably by means of 16-detector row CTA, without pre-treatment DSA in patients in whom at least one aneurysm was plainly identified with CTA (chapter 3.2). We found that two interventional neuroradiologists were confident in making a definite feasibility judgment regarding EVT with CTA alone in more than 70% of the patients, including several with very small aneurysms (< 3 mm). The DSA had no additional value for the treatment decision based on CTA alone, but the presence of extensive vasospasm on CTA indicated the need for a repeat investigation after vasospasm had subsided. Interobserver disagreement with respect to the feasibility judgments (feasible or not feasible) or the requirement of additional DSA to judge feasibility of EVT was considerable. The additional value of DSA compared with CTA was a greater extent of anatomical detail in some patients and depiction of additional unruptured aneurysms in others but on the other hand an equal proportion of DSA's was judged as inferior to CTA.

Rupture rate of unruptured intracranial aneurysms

We systematically assessed annual rupture rate of unruptured intracranial aneurysms (UIA's) taking into account the methodological quality of observational studies on this subject (chapter 4.1). We limited our final analysis to the three studies with the highest methodological quality as assessed by means of a scoring system based on general criteria for methodological quality of observational studies aimed at determining the prognosis of disease.[27,28] The overall annual rupture rate was 1.1% (95% CI 0.9 to 1.4), which is significantly higher than the estimate based exclusively on the studies of lower quality (rupture rate 0.6%, 95% CI 0.5 to 0.7) and also higher than recently suggested by other investigators,[26,33] but lower than in another recent systematic review including only Japanese studies.[25] Second, we observed a greater extent of variability of estimated rupture rates among studies of low methodological quality compared with those with high methodological quality. Third, we could not confirm a difference in the overall rupture rates of incidental (found when the patient is evaluated for the presence of another disease) versus additional UIA's (in patients with SAH from another aneurysm), as has been found previously,[34] but found that size was associated with increased risk of rupture in line with previous reports. The rupture rate of symptomatic UIA's could not be reliably assessed in the included studies with high methodological quality.

CLINICAL IMPLICATIONS

CT and CT angiography in the diagnosis of aneurysmal SAH

Cisternal blood distribution on CT frequently was not helpful in the prediction of the location of rupture, except when a concurrent parenchymal cerebral hematoma was present (chapter 2.1). False prediction of a location near the true site of rupture, for instance the internal carotid artery instead of the middle cerebral artery on the same side, will not affect the therapeutic approach because more than one aneurysm at these sites may be treated during the same procedure. However, false prediction of supratentorially located aneurysms in the posterior circulation and vice versa and presumed localization of the ruptured lesion on the wrong side in case of multiple aneurysms at these locations in the same patient may result in potentially hazardous treatment of an aneurysm that has not bled. We have shown that these false localizations based on blood distribution on CT do occur, although this amounts to only a few percent of cases. Therefore, one should not rely on the cisternal blood distribution on CT alone to select the target aneurysm for treatment, but also identify other criteria that help identifying the ruptured lesion, such as size, multilobularity and wall irregularities. When in doubt, or in case of conflicting findings of blood distribution and morphological features, treatment of more than one target aneurysm in the acute phase after the bleed should be considered. Further, a repeat angiographic investigation should be considered in case of a single aneurysm that does not correspond with the location of a parenchymal cerebral hematoma or when the blood distribution strongly suggests a ruptured anterior cerebral artery aneurysm in case of a single aneurysm located at another site that would require a different therapeutic approach. It has been reported that the ruptured aneurysm may be missed on the initial angiographic investigation with clipping of another unruptured aneurysm.[35]

Considerable interobserver variability in the assessment of the amount of blood on CT limits the prognostic value of this parameter for cerebral ischemia (chapter 2.2). Therefore, we suggest that future studies that include the amount of blood on CT as an independent predictor or selection criterion for treatment should include evaluation of the CT's by at least two clinicians who have experience with the scoring method and a reasonable interobserver variability.

Detection of ruptured aneurysms ≥ 3 mm can be performed reliably with 16-detector row CT angiography. The diagnostic accuracy for the detection of additional aneurysms should be further studied. In our study, the readers did not rigorously score these aneurysms since this was not the primary aim of our study. Furthermore, DSA is probably still necessary with regard to flow dynamics surrounding anterior cerebral artery aneurysms, when the filling side of the ruptured aneurysms is not evident on CTA. This information is important for the surgical or endovascular approach.

Treatment

Our results provide no arguments for or against early surgery in patients in a poor clinical condition in whom the ruptured aneurysm can not be treated endovascularly (chapter 3.1). However, our findings confirmed the notion held by many neurosurgeons that early surgery benefits patients in good clinical condition. At present, this only applies to patients in whom endovascular treatment is judged not feasible. Therefore, we suggest that these patients be treated with early surgery. When patients who on the basis of their clinical condition are judged suitable candidates for early surgery have a high amount of blood on CT, our results suggest that chances for an unfavorable outcome may be increased and therefore extra care should be taken to identify and treat cerebral ischemia. Furthermore, our findings suggest that aggressive external CSF drainage may precipitate rebleeding and therefore this treatment should be applied with prudence, i.e.only in patients who experience a clinical deterioration or are in a poor clinical condition that can be attributed with a high degree of certainty to hydrocephalus. Spontaneous improvement of consciousness may be awaited in patients with suboptimal GCS due to mild hydrocephalus and in these patients CSF drainage can be postponed.[36] When applied, CSF drainage should be targeted at improving clinical condition and not primarily at a set CSF production. Lack of clinical improvement should cast doubt on hydrocephalus as the cause of a poor clinical condition and raise the suspicion of concurrent cerebral ischemia, especially after early surgery.

Based on the results described in chapter 3.2 we suggest the following diagnostic and therapeutic strategy in patients with suspected SAH: a diagnostic (unenhanced) CT should be performed as soon as possible, followed by immediate evaluation of the presence and location of a ruptured aneurysm by 16-detector row CT angiography when SAH is confirmed. Thereafter, an interventional neuroradiologist should assess feasibility of endovascular treatment (EVT) with CTA. When EVT is judged as feasible, endovascular treatment should be performed without delay. When judged not feasible for EVT, a neurosurgeon should be consulted and additional pre-operative DSA performed depending on the preference of the neurosurgeon. DSA should also be performed as soon as possible when required by the interventional neuroradiologist. Finally, we found substantial interobserver variability for the feasibility judgments. This underscores that the feasibility of EVT should ideally be assessed by two independent interventional neuroradiologists who subsequently aim at consensus.

Unruptured intracranial aneurysms

A patient with an unruptured intracranial aneurysm (UIA) poses several dilemma's to the neurologist or neurosurgeon. First and foremost, the treating physician should decide whether treatment of the aneurysm is indicated. This may be rather straight forward in a young patient in whom the benefit of treatment easily

outweighs the risks of treatment assuming that the lifetime risk of rupture is cumulative per year. On the other hand, the decision whether to treat or not may be more difficult if the patient is between 60 and 70 years of age, is cardiovascularly compromised and prefers to leave the treatment decision to the doctor. Variables that should then be considered are: the annual rupture rate, morbidity and mortality of rupture, fear and burden of living with an UIA (considered as a brain "time-bomb" by some patients), whether endovascular treatment or surgery is preferred and morbidity and mortality of either endovascular or surgical treatment. Formal decision analysis may be useful in such circumstances because it makes clinical reasoning explicit and may assist in avoiding decisions partly based on intuition and previous experiences. Based on our results (chapter 4.1), we suggest that an overall rupture rate of 1.1% annually be used for prognostication and decision making, but that size should be taken into account. The obvious next step is to update existing clinical decision analyses with our estimates.

METHODOLOGICAL CONSIDERATIONS[1,2]

Interobserver agreement

The clinical relevance of assessing interobserver agreement lies in the fact that lack of agreement may lead to results that may vary too widely between investigators for clinical purposes. Often Cohen's kappa is used to assess interobserver agreement in excess of the agreement that can be assigned to chance alone. Chance agreement does not relate to the reproducibility of the method of measurement nor does it give information on its clinical relevance. Kappa is assessed by first presenting the results in a two-way contingency table of frequencies with the rows and columns expressing the categories of judgments by two (or more) observers. A kappa value of 1 indicates perfect agreement between observers and a kappa value of 0 represents the extent of agreement that is expected when the judgments would be at random. A higher kappa corresponds with better reproducibility of the method of measurement. Often, familiarizing observers with the diagnostic test in advance by consensus will significantly increase kappa values, but this may lead to overestimation of agreement compared with clinical practice (chapter 2.1 and 2.2). To a certain extent interobserver variability is inherent to clinical practice by many different clinicians. In particular, treatment decisions are subject to interobserver variability because they often depend on personal experience to a great extent. The finding of significant interobserver variability with regard to treatment decisions, as we found in chapter 3.2, should be regarded as an argument in favor of critically assessing the reasons for disagreement.

Prognostic variables in aneurysmal SAH and their value in statistical models

Independent prognostic variables for outcome after aneurysmal SAH are Glasgow Coma Scale score on admission, age, loss of consciousness at ictus, amount of subarachnoid blood and presence of intraventricular

blood on initial CT and, probably, ruptured posterior circulation aneurysm.[3-6] Independent prognostic variables for the occurrence of cerebral ischemia are the amount of blood on CT, age, treatment with tranexamic acid (which is now no longer used by most clinicians), presence of intraventricular blood, loss of consciousness at ictus and, possibly, history of hypertension (this has been reported in one study[9]).[3,4,7,8] Recently reported prognostic factors for outcome or cerebral ischemia after SAH that will require confirmation are fever, leucocyte count, thrombocytopenia, global cerebral edema, prior statin use, glucose levels, the Simplified Acute Physiological Score (SAPS II) and hypomagnesemia.[10-17] Adjustment for differences in prognostic variables should be performed in statistical analyses that aim at comparing outcomes in different populations when the index and control group differ with respect to these variables, as can be expected in most non-randomized studies.

When time elapsed before reaching an outcome event is clinically important a survival analysis is appropriate with a Cox proportional hazard model to adjust for differences in baseline prognostic variables between populations. In our study on the prognostic value of the amount of blood on CT (chapter 2.2) for the occurrence of cerebral ischemia, we found an increased hazard ratio for high amount of blood for one of the observers. In a survival analysis the time to the occurrence of cerebral ischemia is taken into account when estimating the relative risk (hazard ratio).[46] This is important because not only the incidence of cerebral ischemia at the end of the follow-up period but also earlier occurrence of cerebral ischemia that may be due to high amount of cisternal blood is clinically relevant. When the outcome is binary and fixed in time (such as favorable outcome at three months in chapter 3.1) and the occurrence of the outcome is relevant, but not the time-to-event, logistic regression analysis is generally used to adjust for baseline prognostic imbalances. Finally, one should note that a limitation of the logistic regression analysis in chapter 3.1 is the relatively small number of patients and events, especially in the subgroup analyses, which resulted in wide confidence intervals of the outcome estimates. The results of subgroup analyses should generally not be taken as proof but rather as a hypothesis generating exercise.[45] However, because our findings do not seem to contradict previous insights they may be regarded as confirmative. On the other hand, it may be hypothesized that our results suggest that changes in diagnosis and treatment over time have not changed the impact of early surgery on outcome.

External validity and selection bias

Internal validity refers to the level of bias inherent to the design and conduct of studies. To be clinically useful, the study results should also be relevant and applicable to a definable group of patients encountered in clinical practice in a particular clinical setting; this is generally referred to as external validity.[18] External validity is hampered by selection bias which refers to selection of patients for inclusion into a study that are not representative of the patients to whom the results will be applied.

In our historical cohort study on the impact of early surgery on outcome after aneurysmal SAH (chapter 3.1), a factor possibly limiting external validity of our results may be that standard treatment and treatment of complications, such as cerebral ischemia and hydrocephalus, may be different in other hospitals. Another factor that warrants attention is historical transportability[19]: are all circumstances in the historical cohorts in our study still the same as those in a contemporary series of SAH patients? Circumstances that have altered over time are the improved diagnostic flow of ruptured intracranial aneurysms by the advent of CT angiography and the tendency to treat cerebral ischemia less aggressively in our hospital. These factors may have resulted in earlier planning of surgical treatment due to the immediate diagnosis of ruptured aneurysms by performing CTA in some cases and hence affected management after cerebral ischemia. For the conduct and analysis of this study we have tried to follow the paradigm of the Revised Recommendations of the CONSORT Statement on the reporting of randomized trials by considering our study a controlled trial. In line with the CONSORT statement recommendations,[21] we first defined eligibility criteria for patients from our historical cohorts to be included in the analysis and adhered to the intention-to-treat principle. Eligible for inclusion were patients in both cohorts who were potential candidates for the intervention at study, namely a treatment strategy including early surgery. Therefore, we excluded for instance patients with posterior circulation aneurysms, because at the time of our study they were generally planned for delayed surgery . Including these patients in the analysis would have potentially resulted in associations that also pertained to patients who, in real life, would never be treated with early surgery. Further, after assembling a patient flow chart by the eligibility criteria conform the CONSORT statement, we aimed at performing a prespecified analysis, to avoid data dredging. Data dredging refers to the practice of seeking statistically significant associations of a large number of variables with a large number of possible outcomes by exploratory analyses.[20] These associations may or may not have a a causal relationship with the outcome at study. In general, exploratory analyses may be best suited to generate hypotheses, and prespecified analyses to test them. Further, to assess the performance of the logistic regression analysis – or prediction model - in chapter 3.1 for the chance of favorable outcome, it should ideally be confirmed in a validation set, i.e. a preferably prospective cohort with the same clinical characteristics and distribution of prognostic variables as the derivation set (our study).[44] It is known that prediction models in a derivation set may differ in spite of good internal validity (which we did not formally test in our study) from its performance in a validation set. On the other hand, our results have face validity because they are in line with those found previously by others.

Our systematic review on rupture rate of UIA's (chapter 4.1) was aimed at minimizing selection bias by stratifying the studies according to the probability of selection bias. This was important to answer our main question: "Is the patient discussed in observational studies on rupture rate of UIA's the patient we would encounter in practice?". Unfortunately, most observational studies (except one that was assigned the lowest

probability of selection bias, i.e. the highest methodological quality) included patients selected by the fact that the neurosurgeon had decided that treatment of the UIA was not preferred and therefore the answer to the question we posed to ourselves would be "No". Because the precise reason for this decision was never made explicit and in many studies the number of patients that were excluded for this reason was not given, an unknown bias has probably been introduced resulting in either too high or too low rupture rate estimates. This was confirmed by the forest plot in chapter 4.1 that showed much more variation in the rupture rate estimates in studies prone to selection bias, than in those less prone to selection bias. Therefore, most of the results of the individual studies that included patients who had not been selected for surgery may theoretically apply better to patients who would have first been denied surgery by a(nother) neurosurgeon in the hospital where the study was performed. However, this situation is not feasible in clinical practice because of the large variation in estimates in these biased studies resulting in lack of external validity.

Systematic reviews and methodological quality

A systematic review is a systematic and objective overview of all the available reliable evidence.[22] It uses only studies with pre-specified inclusion criteria containing data appropriate to the study objective. Most systematic reviews also evaluate studies for their methodological quality and susceptibility to bias. Inclusion of an assessment of and stratification by methodological quality is valuable for a systematic review to gain insight in trends of variability of estimates that may be caused by poor methodological quality. Our systematic review (chapter 4.1) may be considered a quantitative systematic review, or meta-analysis, because it provides quantitative estimates.[23] The most important aim of systematic reviews such as ours is to resolve controversies about reported estimates when the included studies disagree. Difficulties in assembling a systematic review, which we also encountered, include accurate data extraction, variation in methodological quality and differences in outcome measures. Inaccuracies of extracted data may have resulted from the fact that we did not assess the original data from the included studies. We acknowledge that the possibility of inaccuracies of data extraction may be an important source of bias in our study. Therefore, our findings with regard to the rupture rate estimates can not be regarded as proof but rather as approximations of the estimates, that have been obtained from studies with far less than perfect methodology. Therefore, the external validity of our findings can still be questioned but at least a serious attempt was made to generate estimates from relatively less biased studies. Another important shortcoming is the fact that several potentially important prognostic factors for future rupture could not be studied because our method and the publications of the included studies did not allow for an analysis including all of these factors. In contrast, in some studies that were included in our analysis such an analysis was performed, which we regarded as a criterion for methodological quality.

One of the methodological issues of systematic reviews and meta-analyses is "English language bias".[24] Investigators working in non-English speaking countries are likely to publish some of their work in local journals. It has been found that some of these studies, including RCT's, are excluded from systematic reviews in English while the chance for these non-English RCT's of reporting non-significant results was higher than for English RCT's. Probably, inclusion of these studies would have modified the results of these systematic reviews. On the other hand, it may be problematic to include studies including subjects from different populations in systematic reviews because ethnicity itself may be a prognostic factor for the outcome at study. This is illustrated by a systematic review of studies from Japanese institutions only that was published just after completion of our systematic review and in which an overall annual rupture rate of 2.7% (95% CI 2.2 to 3.3%) was found which was significantly higher than in our systematic review.[25] However, the total number of patient years at risk (PYAR) of the studies that were not also included in our review was 1424, which was much lower than in our study (total 64654 PYAR and 7005 PYAR in the three studies with high methodological quality included in the final analysis). Furthermore, methodological quality was not taken into account in the Japanese review and not all studies were primarily aimed at assessing rupture rate. Finally, two important non-Japanese studies yielded similar results in our review (rupture rate between 0.9 and 1.4% in the ISUIA 2 study and the study by Juvela) and therefore we think that ethnicity or English publication bias was not a significant factor.

A final comment concerns methodological quality of studies in systematic reviews or meta-analyses. There is no widely accepted standard for assessing specifically methodological quality of prognostic studies[27], although the STROBE statement aims at strengthening the reporting of observational studies by rather global criteria.[55] Further, the widely used Levels of Evidence classifications was developed for the evaluation of therapeutic studies and does not seem very useful for observational studies aimed at determining prognosis.[56] However, in the case of observational studies that aim to assess the prognosis of the risk of rupture of unruptured intracranial aneurysms, we found the criteria proposed by Sackett et al.[28] the most useful and these criteria overlapped substantially with those described by others.[27] In short, these include: 1) inception cohort: patients should have been identified at an early and uniform point in the course of their "disease", which also includes adequate diagnosis according to current standards, 2) was the follow-up of patients systematic and complete?, 3) was outcome assessed according to current diagnostic standards, 4) was the referral pattern clear? The last criterion is important because population based studies tend to yield lower estimates of unfavorable outcomes or prevalence of disease compared with hospital based studies. Two other methodological quality criteria that have been suggested are blinded outcome assessment and adjustment for extraneous prognostic factors. However, in the observational studies on rupture rate of UIA's outcome assessment (i.e. occurrence of SAH) was never blinded and adjustment for confounding factors was

performed in several studies, but the data for patients with or without these prognostic factors could not be extracted from the articles for use in our systematic review, with the exception of size of the aneurysms.

SUGGESTIONS FOR FUTURE RESEARCH

Diagnosis

When the ruptured lesion can not be identified beyond any doubt in case of multiple aneurysms by angiographic morphological features and the blood distribution on CT additional features that may identify the ruptured lesion are valuable. 4D-CTA (3D-CTA plus phase data) has recently been shown to have potential value in the identification of ruptured aneurysms by revealing a pulsating aneurysmal bleb, but further research is necessary.[29] Furthermore, the rare cases in which one is unable to identify the ruptured aneurysm could be entered in a multicenter prospective registration to assess reasons for diagnostic uncertainty and clinical outcome. In the mean time, however, immediate treatment of all aneurysms that are present as soon as possible is probably still the safest way to secure the ruptured aneurysm, and the patient. The very recent introduction of 64-detector row CT scanners may provide even better spatial resolution than the 16-detector row scanners in the detection and visualization of intracranial aneurysms, although their benefit is especially expected for moving organs such as the heart due to improved temporal resolution.[51] The impact of these CT scanners for the diagnosis of intracranial aneurysms should be subject to further study.

Treatment

There is no disagreement on the fact that a ruptured aneurysm should be occluded before it reruptures, i.e. as soon as possible after rupture. It has been suggested that both surgical and endovascular treatment may also benefit patients in poor clinical grades.[37,38] However, the inherently poor prognosis may render any intervention futile in most of these patients and treatment resources are relatively sparse resulting in an understandable propensity of treating physicians to select patients for treatment by the criterion that the patient "still has a lot to lose", i.e. is in a good clinical condition. However, a small but indispensable benefit of early occlusion can not be excluded in comatose patients and therefore a randomized controlled trial may be the only way to provide a definite answer.

Although short term outcome after ruptured aneurysms has improved with the advent of endovascular treatment, patients with cerebral aneurysms have increased levels of anxiety and depression and poor general mental health, even after definite surgical occlusion.[30,31] The improved outcome after endovascular occlusion may be in part offset by an increased anxiety of patients and fear of a rebleed resulting in reduced perception of quality of life. This may be maintained in particular by the necessity of repeated investigations after endovascular treatment to exclude recanalization of the aneurysm several years after SAH. When long term

rebleeding rates in the ISAT trial will be known and are found to be higher than after surgical treatment, the level of anxiety and fear for rebleeding may gain importance to weigh endovascular versus surgical treatment and informed consent may be required in advance in the future. Therefore, further study is needed on anxiety and fear of rebleeding in patients after surgical and endovascular treatment.

Multi-detector row CT angiography has been shown to have equivalent diagnostic value to conventional angiography for treatment decisions regarding coiling[32], and also for clipping of ruptured aneurysms.[47-50] We did not investigate the value of CTA for surgical treatment decisions. Prospective protocols of 4-detector row CTA as only pre-treatment investigation for surgical occlusion have been reported repeatedly to be safe and effective when DSA was performed only on the neurosurgeon's request.[47-50] The extra information obtained by DSA compared with CTA mainly concerned details on flow dynamics, but more often no additional information was obtained with DSA. The advent of even higher resolution CT scanners and these previous studies seem to justify implementation of this strategy with CTA alone and DSA only on request. However, further research will be needed on the value of 16-detector row CTA on flow dynamics.

Medical prevention and treatment of cerebral ischemia after SAH should be further investigated to improve outcome. Several new developments in this field were mentioned in the Introduction of this thesis. Phase III trials are being conducted for some of these agents and should be planned for others. Lumbar CSF drainage[39] and intra-operative procedures such as cisternal irrigation with urokinase[40] after surgical occlusion of the aneurysm have been associated with prevention of cerebral ischemia and these interventions also require further investigation.

The second publication of the ISAT trial[41] with the complete follow-up data after one year confirmed the short term benefit of endovascular treatment over surgical clipping in patients for whom either treatment was deemed suitable. Of interest, however, is the fact that 69% of eligible patients were excluded because the aneurysm was judged unsuitable for either procedure.[42] Probably, most of these patients have been regarded more suitable candidates for surgical clipping, because this was still the first treatment choice for most aneurysms, especially those located in the anterior circulation. Regarding endovascular treatment as first treatment choice a priori may therefore not apply to all patients encountered in clinical practice in contrast to the widely held perception that the patients included in the ISAT were representative of all other patients with anterior circulation aneurysms. After all, there was a reason for not regarding the ruptured aneurysms that were excluded from the ISAT suitable for either treatment, but unfortunately these reasons were not registered. Other concerns with the ISAT results are the fact that there was a significant baseline imbalance of pre-treatment rebleeds in favor of the endovascular group which has biased the results in favor of coiling and the finding that two patients experienced a rebleed after complete angiographic occlusion after coiling. However, the current important role of endovascular treatment can not be disregarded. Therefore, the only

reasonable thing to do is to strive for concentrating (surgical) management of ruptured aneurysms in specialized centers to maintain exposure of neurosurgeons to a significant case load of these patients. The alternative may be a significant overall loss of neurosurgical expertise and neurosurgical resources for these patients with the small but not unimaginable risk of being overtaken by a higher than expected long term rebleeding rate after endovascular treatment in the years to come. Finally, patients' preference should not be disregarded now or in the future of aneurysm management because it is well known that many patients will favor a safer treatment on the short term over one that is more permanent on the long term.[43]

Unruptured intracranial aneurysms

The consequences of our findings on the rupture rate of unruptured intracranial aneurysms should be further explored in a clinical decision analysis model. To this end it may be required to perform further meta-analyses on other relevant variables to be included in such a model, taking into account methodological quality and selection bias of included studies to weigh the relative importance of the estimates. Further research is also necessary on the prognostic factors for rupture of UIA's, such as patient and aneurysmal characteristics. Therefore, future studies should disclose the number of cases and patient-years at risk stratified by relevant prognostic factors. 4D-CTA may further identify flow related characteristics of aneurysms (i.e. presence of pulsating bleb) that may predict future rupture.[52] Radiological follow-up of small unruptured aneurysms and the relation between growth and the risk of rupture also requires further study.[53] Finally, the identification of genetic risk factors may help in stratifying patients that should or should not be treated for unruptured aneurysms.[54]

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6

Summary

6.1 Summary

Hemorrhage into the thin space filled with fluid that surrounds the brain (the subarachnoid space) by a ruptured intracranial aneurysm – a saccular out-pouching at the junction of the arteries at the base of the brain – is a devastating event. Patients with a subarachnoid hemorrhage are on average younger and healthier than those with ischemic stroke. Mortality is at least between 30 and 50% and the correct diagnosis is initially overlooked in about a third of the patients which leads to increased risk of permanent sequelae. Diagnosis and treatment should be pursued immediately, to prevent the most important complications: cerebral ischemia, rebleeding and hydrocephalus. Each of these complications should be either prevented or treated without delay to prevent long term disability or death. Ideally, the hemorrhage itself may be prevented in patients who harbor a fortuitously discovered intracranial aneurysm. However, whether treatment in these patients is beneficial depends on many factors that should be carefully weighted in the decision to treat or not, most notably the risk of hemorrhage and the risk of treatment.
The aim of this thesis was to investigate several aspects of diagnosis and treatment of aneurysmal SAH and to re-assess the risk of bleeding of unruptured intracranial aneurysms, after some recent important studies on this subject had been published.

In ***chapter 2.1*** a study on the localizing value of blood distribution on CT is described. We sought to investigate whether blood distribution on initial CT predicted the site of the ruptured aneurysm. Identification of the ruptured aneurysm is important in patients with multiple aneurysms because the ruptured lesion should be occluded as soon as possible to prevent a rebleed and angiography –an investigation to depict the cerebral arteries – does not always identify this lesion. We found that the subarachnoid blood distribution did not enable a neuroradiologist and a neurosurgeon to accurately predict the site of the aneurysm, except in ruptured anterior cerebral artery aneurysms and in case of a cerebral hematoma surrounding the ruptured aneurysm.

In ***chapter 2.2*** we report interobserver variability of assessment of the amount of blood on CT by a previously validated method after aneurysmal SAH. The amount of blood has been found to be a predictor for the occurrence of delayed cerebral ischemia. We hypothesized that the predictive value of the amount of blood on CT may be subject to interobserver variability. In this study, the predictive value of the amount of blood on CT varied between two independent observers because the amount of blood on CT was rated differently by the observers. This was probably caused by the fact that the observers were not trained in advance in the method of assessment of the amount of blood.

Chapter 2.3 describes the results of a study on the diagnostic accuracy of 16-detector row CT angiography for the detection of intracranial aneurysms. Sensitivity for the detection of ruptured intracranial aneurysms was very high (99%) by two independent neuroradiologists in 108 patients with SAH. The additional value of digital subtraction angiography (DSA), which is still regarded by many as the reference standard, for ruptured aneurysms was nihil. However, we found an additional value of DSA for the detection of other – unruptured - aneurysms. Rarely, CT angiography falsely suggested the presence of an aneurysm. The sensitivity of 16-detector row CT angiography we reported is the highest to date.

Chapter 3.1 describes the results of a study comparing the outcomes in two historical cohorts consisting of aneurysmal SAH patients from a prospective registry. In the first period (1989-1992), aneurysm surgery to occlude the ruptured aneurysm was always postponed and scheduled on day 12 after the bleed in patients fit for surgery. In the second period (1996-1998), early surgery (within 72 hours after the bleed) was performed in patients in good clinical condition, whereas standard treatment was otherwise similar. Therefore, we had the opportunity to study the effect of this policy change on outcome. Our results show that the outcome in the second period was not better than in the first period. Further, the policy change did not prevent rebleeding, contrary to our expectation. On the other hand, our results suggested that increased rate of cerebrospinal fluid drainage for hydrocephalus in the second period may have precipitated more rebleeds. Further, we found that a subgroup of patients with favorable prognostic factors on admission – good clinical condition (Glasgow Coma Scale > 13) and low amount of subarachnoid blood on CT – seemed to benefit from the early surgery strategy.

In ***chapter 3.2*** we studied whether 16-detector row CT angiography provided enough information to decide if endovascular treatment was feasible in patients with aneurysmal SAH, without a DSA. Further, we investigated whether DSA could provide additional information compared with CT angiography with regard to the treatment decision. Two interventional neuroradiologists made a treatment decision based on the CT angiography alone in more than 70% of the patients. In the other patients, DSA was required because the CT angiography results did not allow for a treatment decision. DSA had no additional value after a treatment decision with CT angiography alone, but provided more anatomical detail in some patients. On the other hand, CT angiography was regarded as superior to DSA in several other patients. Finally, interobserver agreement with regard to the treatment decisions was disappointingly low.

Chapter 4.1 describes a systematic quantitative review, or meta-analysis, on rupture rate of unruptured intracranial aneurysms. We stratified 14 observational studies, primarily aimed at determining rupture rate, by methodological quality. Studies with higher methodological quality were considered to provide less biased

results that apply to patients who are encountered in clinical practice (external validity). We analyzed the data from three studies with both high methodological quality and homogeneous rupture rate estimates. Overall annual rupture rate was around 1% and larger size predicted higher bleeding risk. We could not confirm the previous finding by other investigators, that additional aneurysms (in patients with SAH from another aneurysm) had higher bleeding rates than incidental aneurysms (in patients without a previous SAH).

In ***chapter 5,*** the results and conclusions are summarized and interpreted and the scientific and clinical consequences of our results are discussed. Further, I explore some methodological issues and give suggestions for further research.

6.2 Samenvatting

Een bloeding in de met hersenvocht gevulde ruimte rondom de hersenen (de subarachnoïdale ruimte) door een gebarsten intracranieel aneurysma – een uitstulping ter hoogte van vertakkingen van de arteriën aan de basis van het brein – is een ernstige aandoening. Patiënten met een subarachnoïdale bloeding (SAB) zijn meestal jonger en gezonder dan de gemiddelde patiënt met een herseninfarct. De kans op overlijden bedraagt tussen de 30 en 50% en de correcte diagnose wordt aanvankelijk niet gesteld in grofweg eenderde van de patiënten, wat resulteert in een verhoogd risico op blijvende gevolgen van deze aandoening. Het stellen van de diagnose en het instellen van therapie dient daarom zonder uitstel plaats te vinden om de belangrijkste complicaties tegen te gaan: cerebrale ischemie, recidiefbloeding en hydrocefalus. Het is van belang te trachten deze complicaties te voorkomen dan wel tijdig te behandelen. Idealiter zou een SAB voorkomen kunnen worden bij patiënten bij wie bij toeval een cerebraal aneurysma wordt ontdekt. Echter, of deze patiënten profiteren van behandeling van het toevallig gevonden aneurysma hangt af van vele factoren die dienen te worden afgewogen, zoals het ruptuurrisico en de risico's verbonden aan behandeling.

In ***hoofdstuk 2.1*** wordt een studie naar de localiserende waarde van de bloedverdeling op de CT beschreven. Het doel was te onderzoeken of de bloedverdeling op de CT bij opname een voorspellende waarde had voor de localisatie van het gebarsten aneurysma. Identificatie van het gebarsten aneurysma is vooral van belang bij patiënten met multiple aneurysmata omdat het gebarsten aneurysma zo snel mogelijk uit de circulatie moet worden genomen om een hernieuwde bloeding te voorkomen. Angiografie van de cerebrale vaten – een onderzoek van de bloedvaten – geeft vaak geen uitsluitsel over welk van de aneurysmata is gebarsten. Wij vonden dat de verdeling van het subarachnoïdale bloed op de CT een neuroradioloog en een neurochirurg niet in staat stelde de localisatie van het gebarsten aneurysma nauwkeurig te voorspellen, behoudens in het geval van een gebarsten arteria cerebri anterior aneurysma (bloedvat aan de voorzijde van de hersenen) en indien een hematoom aanwezig was rond het gebarsten aneurysma.

In ***hoofdstuk 2.2*** wordt de interobserver variabiliteit bij het vaststellen van de hoeveelheid bloed op CT na SAB gerapporteerd, middels een eerder gevalideerde meetmethode. Onze hypothese was dat de voorspellende waarde van de hoeveelheid bloed op CT voor het optreden van cerebrale ischemie zou afhangen van interobserver variabiliteit. We vonden dat de voorspellende waarde van de bloedhoeveelheid op CT voor het optreden van cerebrale ischemie belangrijk varieerde per persoon. Dit werd waarschijnlijk veroorzaakt door het feit dat beide beoordelaars niet vooraf uitgebreid vertrouwd waren gemaakt met de gebruikte meetmethode.

Hoofdstuk 2.3 beschrijft de resultaten van een studie naar de diagnostische waarde van 16-detectoren CT angiografie (CTA) bij het detecteren van intracraniële aneurysmata. De sensitiviteit zoals deze werd vastgesteld op basis van beoordeling van de CTA's van 108 patiënten met een SAB door twee neuroradiologen was erg hoog (99%). De toegevoegde waarde van digitale subtractie angiografie (DSA), nog steeds beschouwd door velen als de goud standaard, voor de detectie van gebarsten aneurysmata was vrijwel nihil. We vonden echter wel dat de DSA, die werd beoordeeld na de CTA, wel leidde tot detectie van meer additionele – dus ongebarsten – aneurysmata. De CTA bleek in een enkel geval ten onrechte de aanwezigheid van een aneurysma te suggereren. De sensitiviteit van 16-detectoren CTA die we vonden is de hoogste die tot op heden werd gerapporteerd.

Hoofdstuk 3.1 beschrijft de resultaten van een studie betreffende de prognose in twee historische cohorten van aneurysmatische SAB patiënten geselecteerd uit een prospectieve database. In de eerste periode (1989-1992) werd chirurgische aneurysma occlusie (middels een clip) altijd uitgesteld tot dag 12 na de bloeding. In de tweede periode (1996-1998) werd vroege chirurgie (binnen 72 uur) geïntroduceerd in ons ziekenhuis bij patiënten in goede klinische conditie, terwijl het overige behandelbeleid gelijk bleef. Daarom hadden we de mogelijkheid om het effect van deze verandering in het beleid op de prognose te onderzoeken. Onze resultaten toonden geen verschil in de uiteindelijke prognose tussen beide cohorten. In tegenstelling tot wat we verwachtten, bleek ook het aantal recidiefbloedingen niet te zijn afgenomen na introductie van vroege chirurgie. Tegelijkertijd lijken onze resultaten te pleiten voor een verhoogde recidiefbloedingskans samenhangend met het agressiever draineren van hersenvocht in geval van een waterhoofd (hydrocefalus). Verder vonden we dat een subgroep van patiënten met gunstige prognostische kenmerken bij opname, namelijk goede klinische toestand (Glasgow Coma Score > 13) en weinig bloed op de CT, wel leek te profiteren van het vroege chirurgie beleid in het tweede cohort.

In ***hoofdstuk 3.2*** onderzochten we of 16-detectoren CTA voldoende informatie verschafte om een beslissing te nemen over het al dan niet behandelen van gebarsten aneurysmata middels endovasculaire behandeling (coilen), zonder een DSA. Verder onderzochten we of DSA een toegevoegde waarde zou hebben ten opzichte van CTA alléén, met betrekking tot de behandelbeslissing. Twee interventie neuroradiologen konden op basis van alleen de CTA een behandeluitspraak doen in meer dan 70% van de patiënten. In de overige patiënten werd DSA nodig geacht voor een behandeluitspraak omdat de CTA onvoldoende informatie bood. DSA had geen aanvullende waarde voor het nemen van een beslissing ten aanzien van endovasculaire behandeling, maar verschafte wel meer anatomisch detail in sommige patiënten. Anderzijds werd CTA superieur geacht aan DSA voor de afbeelding van aneurysmata in een aantal andere patiënten. Tenslotte

vonden we dat de interobserver variabiliteit voor de behandelbeslissing (wel/niet endovasculaire behandeling) teleurstellend laag was.

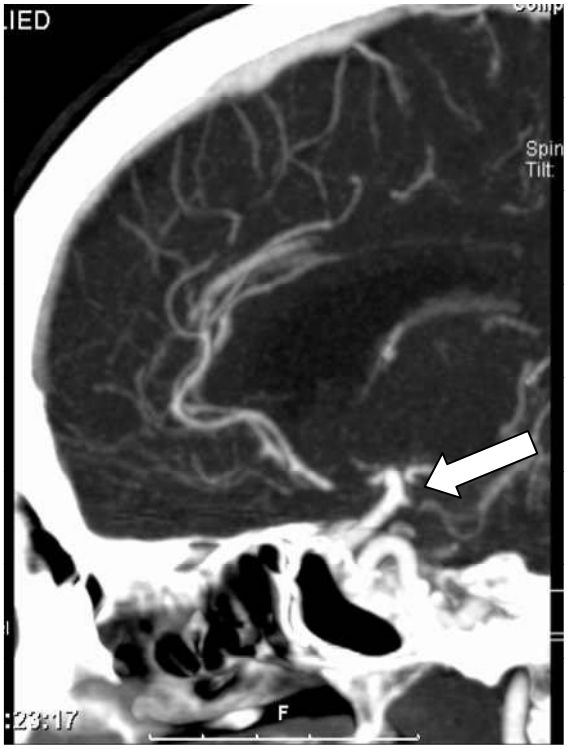
Hoofdstuk 4.1 beschrijft een systematische kwantitatieve review, of meta-analyse, over het ruptuurrisico van ongebarsten intracraniële aneurysmata. Hiertoe hebben we 14 observationele studies die ruptuurrisico als hoofdonderwerp hadden gerangschikt naar methodologische kwaliteit. Studies van een betere methodologische kwaliteit werden geacht minder bias te bevatten en beter van toepassing te zijn op de gemiddelde patiënt die men zou kunnen tegenkomen in de dagelijkse praktijk (externe validiteit). We hebben de gegevens uit drie studies die zowel een hoge methodologische kwaliteit als homogene ruptuurrisico-schattingen hadden gebruikt voor de uiteindelijk analyse. Het jaarlijkse ruptuurrisico geschat op basis van deze studies bedroeg ongeveer 1% en een grotere diameter van het aneurysma was geassocieerd met een hoger ruptuurrisico. Op basis van onze resultaten konden we het door anderen gevonden hogere ruptuurrisico van additionele ongebarsten aneurysmata (in patiënten met een SAB uit een ander aneurysma) ten opzichte van incidentele ongebarsten aneurysmata (bij patiënten zonder voorgaande SAB) niet bevestigen.

In ***hoofdstuk 5*** worden de resultaten en conclusies samengevat en geïnterpreteerd en worden de wetenschappelijke en klinische consequenties van onze bevindingen besproken. Verder wordt in dit hoofdstuk wat verder ingegaan op enige methodologische onderwerpen en worden suggesties voor verder onderzoek gedaan.

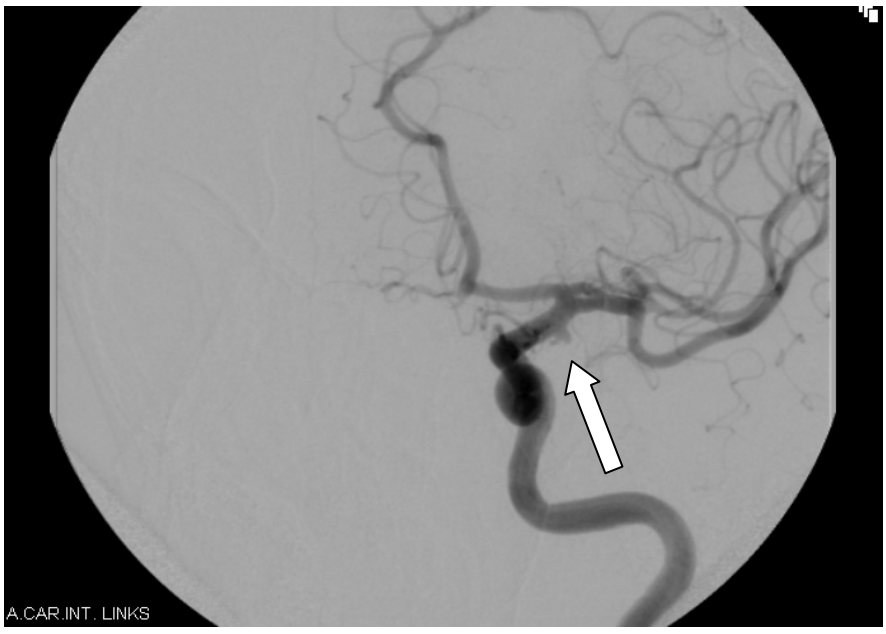
Appendix

Appendix 1 (chapter 2.3)

Appendix 1a



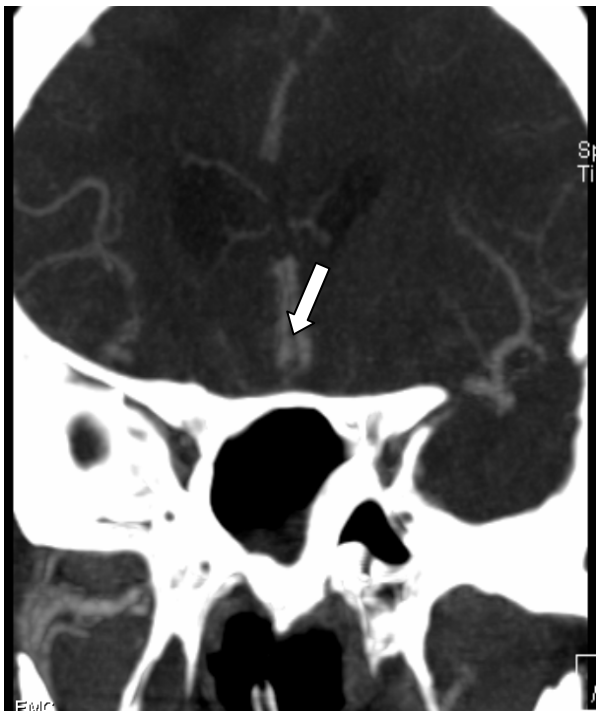
Appendix 1b



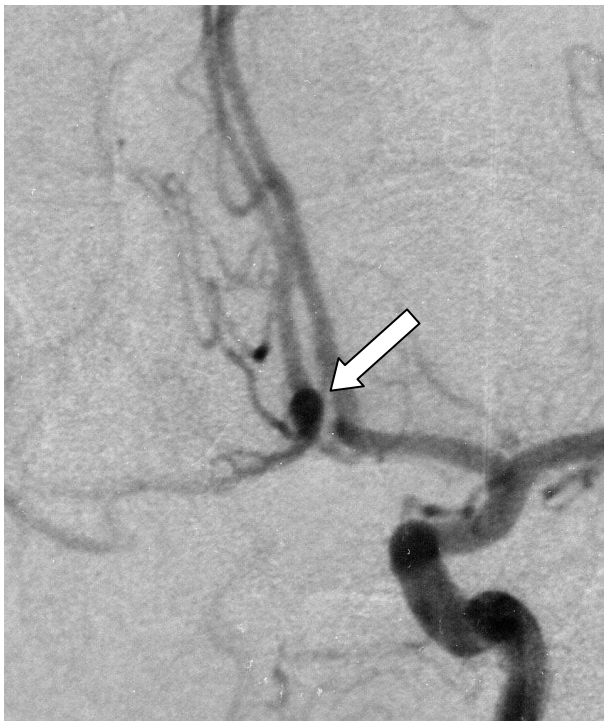
A left sided 2 mm anterior choroidal artery aneurysm (arrow) was not recognized on CTA by both readers (figure 1a), and one reader did not recognize the aneurysm after also having seen DSA (figure 1b).

Appendix 2 (chapter 2.3, table 5)

Appendix 2a



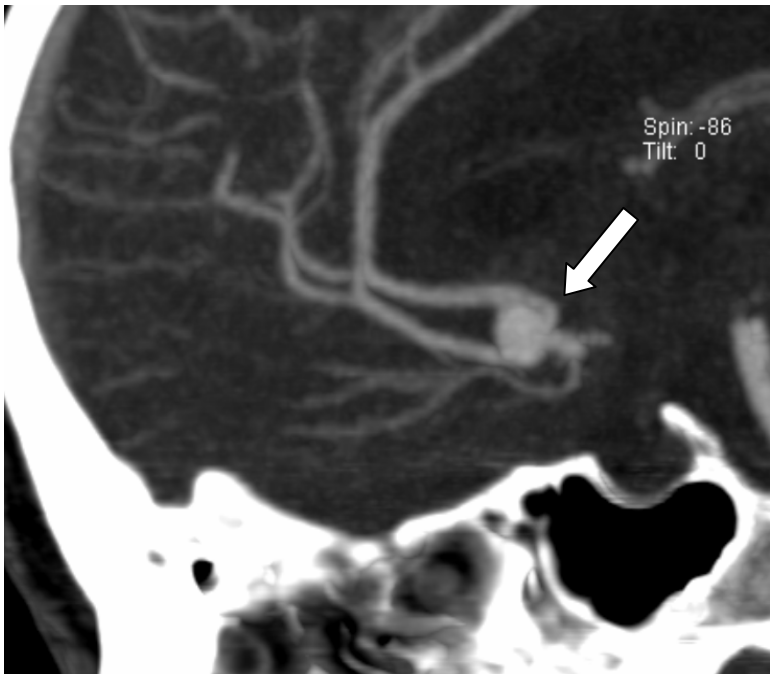
Appendix 2b



Example of false positive judgment of the presence of an aneurysm: one of the readers noted the presence of an anterior communicating artery aneurysm (arrow) both with CTA and DSA. In fact, the patient had surgery to occlude the aneurysm, but no aneurysm was found intraoperatively.

Appendix 3 (chapter 3.2)

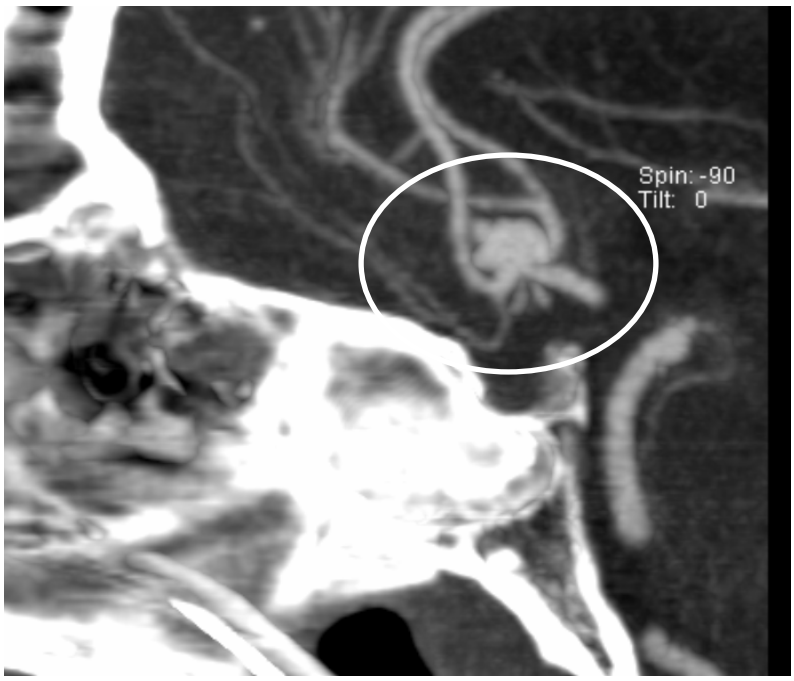
Appendix 3



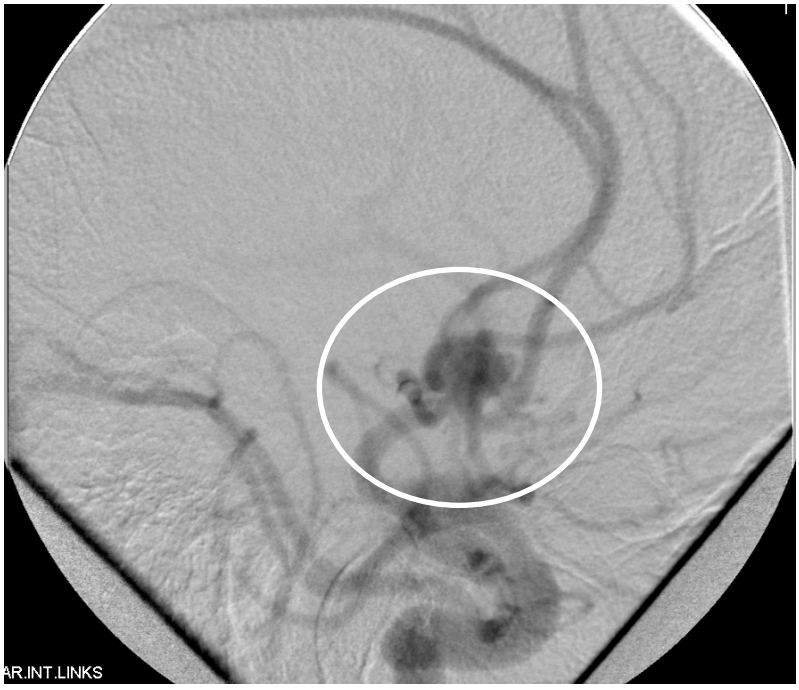
In this patient, one of the readers judged endovascular treatment as feasible, but the other reader judged it not feasible because of an artery sprouting from the base of the aneurysm (arrow).

Appendix 4 (chapter 3.2)

Appendix 4a



Appendix 4b



In this patient, both readers judged depiction of anatomical detail of local anatomy around the aneurysm to be visualized more clearly with CTA than with DSA and therefore judged DSA as inferior to CTA.

Appendix 5 (chapter 4.1)

Modified Sackett criteria for quality of prospective studies applied to studies on rupture rate of unruptured intracranial aneurysms (applied in *appendix 6*)

Numbers refer to criteria in *Appendix 6*.

Methodological quality criteria

5. Prospective	Was there a prospective, consecutive registration of patients that were included in the study?
17. Complete	Is the follow-up complete, and is this mentioned?
18. Structured	Structured follow-up; is the follow-up systematic, i.e. are there specific intervals over which the patients are followed?
19. Lost	Is it mentioned which percentage of patients is lost to follow-up?
20. Entry	Are the entry characteristics of the group that is lost to follow-up and those not lost to follow-up described and compared?
21. Surg Cens.	Is surgery considered to be a censoring event during follow-up and is follow-up counted until treatment of aneurysm, and not beyond?
22. Diagnosis	Was the diagnosis of SAH confirmed by CT, spectrophotometric analysis of the spinal fluid or autopsy?
23. Certain	Was the distinction between a certain diagnosis of SAH and an uncertain one recognized?
16. Confounding	Were potential confounders taken into account in the assessment of rupture rate estimates (these had to include at least size, group [additional versus non-additional UIA's] and location)? Analysis should consist of stratification and contingency table analysis, followed by multiple regression analysis when indicated.

Additional quality criteria

1.Type	Type of unruptured aneurysm; have the authors made a distinction between additional, symptomatic and incidental unruptured aneurysms (categories)?
2. Ruptures	Can rupture rates per category be calculated or are have they been provided by the author?
3. No surgery	Were all patients with unruptured aneurysms not treated with surgery?
4. Criteria	Were explicit indications given for surgery or no surgery?

6. Proportion	Was the proportion of patients with unruptured aneurysms that did not undergo surgery mentioned?
7. Treatment	In case the category of additional aneurysms is mentioned, was the mode of treatment of the ruptured aneurysm mentioned?
8. Cavernous	Is there explicit information concerning exclusion of intracavernous aneurysms from analysis of rupture rate?

Risk Modification

9. Entry1	Are the entry characteristics age and sex of the study population described?
10. Entry2	Is the proportion of patients who smoke and the proportion with hypertension described?
11. Entry3	Is the population under study NOT restricted to elderly patients (i.e. >60 yrs)?
12. Size1	Does the study describe the size distribution of the aneurysms?
13. Size2	Does the study distinguish at least three size categories?
14. Size Ruptures	Do the data presented in the study allow for calculation of rupture rates per size category?
15. Recruitment	Recruitment of patients; referral pattern (it has to be clearly mentioned whether patients are recruited from the population or from hospitals)?

Appendix 6 (chapter 4.1)

Adherence to quality criteria per study, using modified Sackett criteria for assessment of quality of prognostic studies (methodological quality criteria in *italics*)

Study by first author (reference)	Locksley (13)	Zacks (6)	Winn (7)	Wiebers (14)	Inaga-Wa (8)	Asari (9)	Mizoi (10)	Taylor (11)	Yasui (12)	ISUIA1 (5)	Juvela (23)	Tsutsumi (24)	Yonekura (16)	ISUIA2 (15)
Inception into study														
1. Type	1*	1	1	1	1	1	1	0	0	0	1	1	0	0
2. Ruptures	1	1	1	0	0	0	0	1	1	0	1	1	0	0
3. No surgery	0	0	0	0	0	0	0	0	0	0	1	0	0	0
4. Criteria	0	0	0	0	0	0	1	0	0	0	1	1	0	0
5. Prospective	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*1*
6. Proportion	1	0	1	0	1	1	1	1	1	0	1	1	0	1
7. Treatment	0	0	1	0	0	0	0	0	0	1	1	0	0	1
8. Cavernous	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Risk Modificattion														
9. Entry1	1	1	1	1	0	1	1	1	1	1	1	1	0	1
10. Entry2	0	0	0	0	0	0	0	0	0	1	1	0	0	1
11. Entry3	1	1	1	1	1	1	1	0	1	1	1	1	1	1
12. Size1	1	1	1	1	1	1	1	0	0	1	1	1	1	1
13. Size2	1	1	1	1	1	1	1	0	0	1	1	1	1	1
14. Size rupt.	1	1	0	0	0	1	0	0	0	1	1	1	0	1
15. Recruitment	0	0	1	0	0	0	0	1	0	0	1	0	0	0
16. Confoun-ding	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*0*	*0*	*1*
Follow-up														
17. Complete	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*
18. Structured	*0*	*0*	*1*	*0*	*0*	*1*	*0*	*0*	*0*	*1*	*1*	*1*	*1*	*1*
19. Lost	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*1*	*1*	*0*	*1*
20. Entry	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*1*	*0*
21. Surg Cens.	*0*	*0*	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*1*	*1*	*1*
Outcome														
22. Diagnosis	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*1*	*0*	*1*
23. Certain	*0*	*0*	*1*	*0*	*0*	*0*	*1*	*0*	*0*	*1*	*0*	*1*	*0*	*1*
Total score	10	7	13	8	5	9	8	4	5	12	20	17	6	16

*score based on consensus meeting between two raters (MJ and DWJD)

Dankwoord

Het traject dat vooraf ging aan de afronding van dit proefschrift bestrijkt meer dan tien jaar. Nu het eindelijk klaar is, realiseer ik me des te meer dat elke (kleine) stap voorwaarts telt als het gaat om de behandeling van patiënten met een aneurysmatische subarachnoïdale bloeding (SAB). Ik hoop dat ik hier een bescheiden bijdrage aan heb kunnen leveren. Dit proefschrift was uiteraard niet tot stand gekomen zonder de hulp en aanhoudende steun van (zeer) velen, die ik in dit dankwoord graag persoonlijk wil noemen en danken. Daarbij wil ik graag benadrukken dat het mij veel genoegen heeft geschonken in de loop der jaren met zo velen samen te hebben gewerkt, in een multidisciplinaire setting rondom de SAB patiënt, zoals die bij uitstek in een academisch ziekenhuis aanwezig is. Naast prettig was dit ook zeer leerzaam.

Allereerst wil ik Corina bedanken. Aanvankelijk had ik in dit dankwoord geschreven dat je niet veel gemerkt hebt van mijn promotieperikelen. Later heb ik deze alinea moeten bijstellen, want het kostte toch wel veel tijd de laatste maanden en regelmatige verstoring van jouw REM-slaap als ik weer eens (erg) laat naar bed ging. Ik ben erg dankbaar voor je geduld en onvoorwaardelijke steun en liefde. Ik hoop vanaf nu op iets meer rust in mijn hoofd en jouw nachtrust, maar schat in dat dat goed komt. Je hebt door je steun zeer zeker in belangrijke mate bijgedragen aan de voorspoedige afronding van dit boekje!

Graag wil ik ook mijn eerste promotor, prof.dr. P.J. Koudstaal, neuroloog, danken. Beste Peter, je hebt mij geïntroduceerd in de Rotterdamse neurologie en het wetenschappelijk onderzoek. Het was aan je enthousiasmerende manier van college geven te danken dat ik in het begin van mijn derde studiejaar geneeskunde in 1995 interesse voor de neurologie kreeg, en op je af ben gestapt met de vraag of ik onderzoek op de afdeling neurologie kon doen. Het uiteindelijke resultaat, iets meer dan tien jaar later, is dit proefschrift en een afgeronde opleiding tot neuroloog. Men zou ook kunnen stellen dat ik in mijn derde studiejaar bij je gestart ben als "AGIKO avant la lettre", gezien dit tijdsbeloop. Ik ben je zeer erkentelijk voor je begeleiding en aanhoudende vertrouwen (ondanks het feit dat ik niet zo snel vorderde als de meeste andere onderzoekers gedurende lange tijd), en de opleiding tot neuroloog en onderzoeker in bredere zin.

Mijn tweede promotor, prof.dr. C.J.J. Avezaat, neurochirurg, wil ik graag danken. Beste Cees, je aanhoudende interesse in het SAB onderzoek en altijd kritische, zinvolle en duidelijke commentaar op de artikelen heb ik zeer op prijs gesteld. Tevens ben ik je veel dank verschuldigd voor de voor mij soms enerverende, maar daardoor juist waardevolle leermomenten in de door jou geleide neurochirurgische kliniek, niet in de laatste plaats door je indrukwekkende verantwoordelijkheidsgevoel voor elke patiënt die opgenomen was op 7 Zuid en 6 Zuid IC. Van urineweginfectie tot inklemmingsbeeld. Daarnaast heb ik veel geleerd van je manier van wikken en wegen; een kunst die mijns inziens pas tot volle wasdom kan komen indien een zeer diepgaande literatuurkennis en klinische ervaring is eigen gemaakt. Dat is voor mij een nastrevenswaardig eindpunt waarvan de afronding van dit proefschrift en de opleiding tot neuroloog nog slechts een begin zijn.

Mijn eerste co-promotor, Dr. D. Hasan, neuroloog-intensivist, wil ik danken voor zijn mentorschap en vriendschap gedurende vele jaren. Beste Djo, sinds ik in 1995 aan je werd voorgesteld om onderzoek met je te doen, is er altijd een goed contact gebleven. Ik weet nog dat de eerste vraag die je me stelde was waarom ik me interesseerde voor de neurologie. Vele jaren nadien heb ik nog steeds geen goed antwoord, alleen dat het voor mij de juiste keuze is geweest. Zonder jou was dit proefschrift er niet geweest. Je hebt een cruciale rol gespeeld door je aanhoudende mental support, hulp bij de statistiek en inhoudelijke ideeën.
Ik heb bewondering voor je kennis en kunde, doorzettingsvermogen en patiëntgerichtheid (ik heb jaren lang moeten horen op mijn vervolgpoli, waar ik veel van je voormalige patiënten zag: "Dr. Hasan zei altijd...."). Je vertrek uit Rotterdam betekende in mijn overtuiging een belangrijk verlies voor de neuro-IC. Je didactische

vaardigheden, die zich het beste laten omschrijven als een "tussen de regels door" didactiek, zijn bijzonder en ik heb meer van je geleerd dan ik hier in een paar regels kan samenvatten. In dit kader wil ik met name je persoonlijke benadering van multidisciplinaire samenwerking noemen, die altijd ten dienste van de individuele patiënt stond en waar ik veel van geleerd heb. Op cruciale momenten was je in staat mij bij te sturen, te enthousiasmeren, maar ook "los" te laten. Je hebt meer dan één student uiteindelijk indirect of direct aan een opleidingsplek geholpen, meestal met een reeds aan het begin vastliggend promotie onderwerp. Het enthousiasme waarmee je ons hebt begeleid was fantastisch. Ik mis de gezelligheid van ons clubje (Smits, Van Dijk, Van der Bilt) in het van verse lucht en daglicht verstoken hok op de poli nog wel eens, maar de arbeidsinspectie zou het nu niet meer goedkeuren, denk ik (maar er zit nu wel een raam in de deur trouwens). Ik hoop nog lang met je van gedachten te kunnen wisselen over SAB's en neuro-intensive care, bij voorkeur met een single malt en de gitaar erbij: de ideale omstandigheden waarbij "alles kits enzo" is. *Bedankt voor alles!*

Mijn tweede co-promotor, Dr. D.W.J. Dippel, neuroloog, wil ik bedanken voor zijn intensieve begeleiding in een later stadium, met name bij de *rupture rate* studie. Beste Diederik, ik heb veel van je geleerd, je inzicht in de diepere lagen van de in artikelen gepretendeerde werkelijkheid is bijzonder verhelderend en er valt altijd wat met je te lachen, waardoor samenwerken met jou ook nog eens "fun" is. Ik wist niet dat "wiskunde" en allerhande formules zo leuk konden zijn en handig bij het beter hanteerbaar maken van moeilijke klinische problemen. Daar ben jij echt heel handig in! Ik hoop dat ik mijn belofte, namelijk dat we het af zouden maken – daar twijfelde je bij tijd en wijle misschien wel eens aan -, naar je tevredenheid gestand heb gedaan. Tevens bedankt voor je adviezen over en/of mede auteurschap van de meeste in dit proefschrift beschreven artikelen en de nuttige adviezen op het laatste moment voor de *oral presentations* op de European Stroke Conference 2005 op een veel te kleine hotelkamer ergens in Bologna (maar wel met *super-de-luxe* electrische blinden voor de ramen!). Ik zie ernaar uit ook in de nabije toekomst met je te blijven samenwerken bij onderzoek op het gebied van de ongeruptureerde aneurysmata.

De leden van de kleine commissie wil ik graag danken voor hun bereidheid het manuscript te willen beoordelen. Prof.dr.ir. J.D.F. Habbema, klinisch besliskundige, wil ik daarnaast danken voor zijn adviezen betreffende de *rupture rate* studie. Prof.dr. G.J.E. Rinkel, neuroloog, is voor mij een inspirerend voorbeeld als het gaat om klinisch wetenschappelijk SAB onderzoek. Beste Gabriël, je gedrevenheid ten aanzien van het SAB onderzoek spreekt me enorm aan en daarom is onze wens jou in de commissie te hebben voor mij zeer vanzelfsprekend. Vele van de onder jouw leiding tot stand gekomen onderzoeken betreffende de SAB's hebben gediend als essentiele referenties bij de in dit proefschrift beschreven onderzoeken. Prof.dr. G.P. Krestin, hoogleraar in de radiologie, wil ik tevens hartelijk danken voor zijn bereidheid zitting te nemen in de commissie.

Prof.dr. J. Bakker, intensivist, en Prof.dr. W.J.J. van Rooij, interventie neuroradioloog, wil ik hartelijk danken voor hun bereidheid zitting te nemen in de grote commissie.

Dr. A. van der Lugt, neuroradioloog, wil ik danken voor de prettige samenwerking, en zijn essentiële en coördinerende rol bij de CT-angiografie onderzoeken. Aad, met name heb ik het steeds zeer gewaardeerd dat ik altijd bij je kon binnenlopen voor tussentijds overleg, ondanks je zeer drukke overige werkzaamheden. Dan kon ik weer even door. Je hebt op de juiste momenten knopen doorgehakt en me uitstekend begeleid.

Drs. H. Bijvoet, neurochirurg, wil ik danken voor het gezamenlijk bekijken van de vele "plaatjes" voor de verschillende studies. Zonder je belangrijke input, zowel op de OK als achter de lichtkast, hadden de eerste drie van de in dit proefschrift beschreven studies niet bestaan. Het feit dat de lichtkast bijna een antieke verschijning wordt geeft aan hoe snel de ontwikkelingen gaan.

Drs. H. Pieterman, radioloog, wil ik danken voor het beoordelen van de vele CT scans ten behoeve van de eerste twee artikelen van dit proefschrift.

Drs. H. Flach en drs. H.L.J. Tanghe, interventie neuroradiologen, wil ik danken voor het beoordelen van de vele CTA's op het PACS en de DSA's voor de CTA studies. Beste Zwenneke en Hervé, mede dankzij jullie is de zorg voor SAB patiënten in het Erasmus MC op een hoog niveau gebleven. Ik heb jullie doorzettingsvermogen bij het beoordelen van de CTA's en DSA's zeer gewaardeerd, alsmede de zeer prettige samenwerking. Tevens dank dat ik vaak over jullie schouder heb mogen meekijken bij de beoordelingen. Dankzij Hervé weet ik nu eindelijk hoe ik "Glenn Morangie" (inderdaad: de whisky) moet uitspreken (klemtoon op 'mor'!). Zwenneke, ik heb je eindsprint van de beoordelingen na een periode van afwezigheid zeer gewaardeerd.

Dr. S.L.M. Bakker, neuroloog, wil ik bedanken voor zijn, weliswaar korte, begeleiding. Stef, ik heb het bijzonder gewaardeerd dat je het 3D-CTA onderzoek aan me toevertrouwde. Het heeft er mede toe bijgedragen dat ik straks achter de catheder mag staan!

Prof.dr. M.G.M. Hunink, radioloog-epidemioloog, wil ik graag danken voor haar zeer zinvolle adviezen met betrekking tot de CTA studies.

Wibeke van Leeuwen en Caroline van Bavel van het Trialbureau Radiologie ben ik zeer erkentelijk voor de hulp bij de CTA studies. Dankzij jullie is de logistiek rondom het verzamelen van de data en informed consents steeds in goede banen geleid; alleen had ik het denk ik niet of in elk geval niet tijdig voor elkaar gekregen! Met name het monnikenwerk van het blinderen/afplakken van de (naar schatting tussen de 600 en 700!) angiografie-foto's hebben jullie me bespaard, waarvoor veel dank. En dat ondanks het feit dat ik eigenlijk een vreemde eend in "jullie" radiologische bijt ben.

Van de laboranten van de afdeling radiologie wil ik met name Marcel en Ronald bedanken voor respectievelijk hulp wanneer de computer (Leonardo) mijn zin niet deed en voor het regelen van de lichtkast (die bijna niet meer te vinden zijn in het ziekenhuis) voor het beoordelen van de DSA's. Tevens wil ik de medewerkers van het röntgen-archief in de "kelder" danken voor het telkenmale opzoeken en klaarleggen van de vele foto's voor de diverse studies.

Dr. E.J. van Dijk, neuroloog in opleiding, wil ik danken voor de discussies over de statistiek en hulp bij het hanteren van SPSS. Je informele adviezen hebben voor mij op bepaalde momenten een grote betekenis gehad om statistische inpasses en writer's blocks te kunnen doorbreken. Ik hoop dat we in de toekomst op een of andere wijze kunnen blijven samenwerken.

Matthijs de Sain-Groen wil ik zeer bedanken voor zijn belangenloze hulp en voortvarendheid bij het lay-outen van het proefschrift. Je hebt het supersnel en –goed gedaan! Ik had me geen betere layout manager kunnen wensen.

Prof.dr. P.A.E. Sillevis Smitt en de stafleden neurologie van het Erasmus MC wil ik danken voor de zeer prettige samenwerking de laatste maanden na de afronding van mijn opleiding. Beste Peter, ik heb het bijzonder gewaardeerd dat je me tijdelijk wilde aanstellen als staflid met de taak de zorg voor neurologische patiënten op de IC's en SEH te begeleiden, waar mijn interesse ook ligt. Het mogen aanblijven als staflid in de afrondingsperiode van het proefschrift heeft aan de afronding ervan zeker positief bijgedragen. Dorine Siepman en Joost Jongen wil ik danken voor de gezelligheid dit laatste half jaar op het op twee neurologen ingeschaalde, maar vaak met drie neurologen gevulde, kamertje in het "stafgebouw".

Enigszins buiten het kader van dit proefschrift wil ik graag nog enkele andere mensen bedanken, omdat de afronding van dit proefschrift samenvalt met het (voorlopige) einde van mijn carrière in de neurologie in het Erasmus MC.
Betty van der Woude en de andere dames van de poli neurologie wil ik bedanken voor hun mental support en gezelligheid gedurende vele jaren, in voor- en tegenspoed, zou ik bijna willen zeggen.
Drs. W.J. Thijsse, neuroloog-intensivist, wil ik danken voor haar betrokkenheid bij de SAB en andere patiënten op de voormalige 6-Zuid IC. Willy, ik heb veel respect voor de enthousiaste en efficiënte manier waarop je de zorg op 6-Zuid altijd hebt gecoördineerd, en dank voor alles wat ik van je mocht leren en je toegankelijke schouder (om uit te huilen), zeker in het begin tijdens mijn eerste schreden als assistent op de IC. Je bent denk ik de enige die altijd letterlijk kon zien hoe ik "in mijn vel" zat.....
De verpleegkundigen van de "vroegere" Neuro-Intensive Care 6-Zuid wil ik danken. Zonder jullie geen hoogstaande neuro-IC zorg of onderzoek bij SAB patiënten. Bedankt voor alle leermomenten en jullie geduld met tegelijk kritische èn (vaak) onervaren assistenten door de jaren heen. Ik hoop dat jullie allen je weg zult vinden in de nieuwe IC-organisatie en hoop dat velen van jullie ook in de toekomst "neuro-minded" zullen blijven.
Tenslotte wil ik de neurologen, secretariaat en verpleging van de afdeling neurologie van het Albert Schweizer Ziekenhuis Dordrecht danken voor het fantastische jaar "perifere" neurologie. Ik heb aan de tijd bij jullie meer overgehouden dan kennis, ervaring en goede herinneringen alléén!

Mijn ouders, broer, schoonzus en overige (schoon)familie en vrienden wil ik vanaf deze plek groeten: weer een stapje verder! Art, de tribune is echt véél comfortabeler dan achter de catheder...!! En Cobus, ik beloof champignonnen van Lutes te blijven kopen, oh nee, die andere bedoel ik! Ivo, nu ben jij aan de beurt om te promoveren, maar ik ben ervan overtuigd dat dat goed gaat komen, mits je niet gaat stuntvliegen. Je bent al aardig op weg het woord "multidisciplinair" een nieuwe betekenis te geven, het koninklijke lintje ontbreekt alleen nog.... Helwin, mijn verre vriend, na eerst een tijd goede buur te zijn geweest: "Jetzt bist du am Setz" (om te promoveren bedoel ik; is dat goed Duits?)

Benno, eigenlijk twee handen op een buik vanaf vrijwel het eerste uur dat we elkaar kennen van de middelbare school, meer dan 15 jaar terug. De deadline van de legendarische *weddingschap* (je weet wel...) nadert langzaam maar zeker, maar eigenlijk gun ik jou de winst als geen ander. En Thjon, inderdaad, zoals je in het dankwoord van jouw proefschrift schreef: "aanvankelijk tegenpolen, later collega en vriend". Ik hoop je koelbloedigheid te kunnen evenaren op het moment suprème. Dank dat jullie mij willen flankeren achter de catheder op deze bijzondere dag.

Curriculum Vitae

Mathieu van der Jagt was born on September 25th, 1974 in Oud-Beijerland, the Netherlands. He attended grammar school (gymnasium) at the Regionale Scholengemeenschap in Oud-Beijerland and graduated in 1993 (cum laude).

He studied Medicine from the same year on at the Erasmus University Rotterdam. He worked as a student assistant at the department of Anatomy for three months where he participated in research on c-Jun immunoreactivity in spinal cord and brainstem neurons in transgenic SOD-1 knock out mice, an animal model for motor neuron disease. Thereafter, he worked with Dr. Hasan starting in 1995 in clinical research on aneurysmal subarachnoid hemorrhage, the results of which form the basis of this thesis. Graduation from medical school followed September 1999 after an internship neuro-oncology at the Daniel den Hoed Cancer Center in Rotterdam, after which he started as a resident at the department of Neurology of the Erasmus Medical Center in Rotterdam (Head: Prof.dr. P.A.E. Sillevis Smitt, formerly: Prof.dr. F.G.A. van der Meché). From March 1st, 2000 until December 1st 2005 he was trained in clinical neurology. During 2002, he worked as a resident at the department of Neurology of the Albert Schweizer Hospital Dordrecht (Head: Dr. R.P. Kleyweg). Internships 'Neurocritical Care' were done from November 1999 to March 2000, December 2001 and from Februari 2003 to August 2003 on the neurological/neurosurgical ICU of the Erasmus MC.

In 2002-2003 he cooperated with Dr. G.A.M. Pop, cardiologist, in experimental research on a new method of indirect measurement of whole blood viscosity.

From December 1st, 2005 he has been working as a neurologist at the department of neurology of the Erasmus Medical Center. Starting June 1st 2006 he will attend a clinical fellowship in Intensive Care Medicine at the Intensive Care Unit of the Onze Lieve Vrouwe Gasthuis in Amsterdam to become a neurologist-intensivist.

He lives in Delft with Corina Buis.

The author was a member of the board of the Society of Neurologists-in-training (VAAN) in the Netherlands, and was treasurer of this board until 2005. He was also a member of the Biemond Committee of the Dutch Society of Neurology that is involved in continuing education in clinical neurology in the Netherlands.

Further, the author is secretary of the board of "Stichting Theaterfestival Delft". This is an organization that is responsible for the theatre festival, held yearly in and around Delft's historic city center.

List of publications

Manuscripts based on the studies described in this thesis

Van der Jagt M, Hasan D, Bijvoet HWC, Pieterman H, Dippel DWJ, Vermeij FH, Avezaat CJJ. Validity of prediction of the site of ruptured intracranial aneurysms with CT. *Neurology* 1999; 52: 34-39.

Van der Jagt M, Hasan D, Bijvoet HWC, Pieterman H, Koudstaal PJ, Avezaat CJJ. Interobserver variability of cisternal blood on CT after aneurysmal SAH. *Neurology* 2000; 54: 2156-2158.

Van der Jagt M, Hasan D, Dippel DWJ, Van Dijk EJ, Avezaat CJJ, Koudstaal PJ. Impact of early surgery on the outcome of patients after aneurysmal subarachnoid hemorrhage. *Submitted.*

Van der Jagt M, Flach HZ, Tanghe HLJ, Bakker SLM, Hunink MGM, Koudstaal PJ, Van der Lugt A. Assessment of feasibility of endovascular treatment of ruptured intracranial aneurysms with 16-detector row computed tomographic angiography. *Submitted.*

Van der Jagt M, Habbema JDF, Koudstaal PJ, Dippel DWJ. Rate of subarachnoid hemorrhage in patients with an unruptured intracranial aneurysm. A systematic review. *Submitted.*

Van der Lugt A, Van der Jagt M, Flach HZ, Tanghe HLJ, Bakker SLM, Hunink MGM, Koudstaal PJ. Diagnostic accuracy of 16-detector row CT angiography for the detection of intracranial aneurysms. *To be submitted.*

Other publications

Van Dijk EJ, Hupperts RMM, Van der Jagt M, Bijvoet HWC, Hasan D. Diagnosis of perimesencephalic nonaneurysmal subarachnoid hemorrhage with computed tomography. *J Stroke Cerebrovasc Dis* 2001; 10: 247-251

Pop GAM, Hop WJ, Moraru L, Quak J, Van der Jagt M, Dekkers D, Chang Z, Gijsen FJ, Duncker DJ, Slager CJ. Blood electrical impedance closely matches whole blood viscosity as parameter of hemorheology and inflammation. *Appl Rheol* 2003; 13: 305-312