Considerations for the acute management of aneurysmal subarachnoid hemorrhage

Jasper van Lieshout
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Considerations for the acute management of aneurysmal subarachnoid hemorrhage

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Dedicated to all those who suffer an aneurysmal subarachnoid hemorrhage
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General introduction
“When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days.”

Hippocrates 460-370-BC, *Aphorisms on Apoplexy*¹
Historical perspective

The clinical presentation of aneurysmal subarachnoid hemorrhage (aSAH) followed by subsequent delayed neurological deterioration is likely to have already been described by Hippocrates almost 2,500 years ago. Millennia later, today’s sufferers of aSAH still have a high risk of morbidity and mortality during the course of the disease, even after surviving the initial bleed.

In 1962, Tappura demonstrated that conservative treatment of aSAH is ineffective. In his study of patients who survived the initial hemorrhage, 55% suffered from aneurysmal rebleeding and 75% died as a result of the disease. By the late 1960s, the results from the first Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage were published in a monograph, revealing a clear benefit of aneurysm ligation over conservative management. Although direct clipping was generally considered the best treatment for most aneurysms by the late 1970s, the question of when to perform surgery was not definitively answered. Vast improvements have been made in the operative results of aneurysm clipping, but initially this was not reflected in a proportional improvement of overall disease management as too many patients experienced rebleeding and delayed cerebral ischemia (DCI) during the waiting period. Aneurysm surgery was considered more effective after a period of medical stabilization, which seemed to reduce the risk of the postoperative ischemic complications, often encountered after early surgery. In 1965, Kagstrom et al. demonstrated DCI usually occurs at least three days after the initial subarachnoid hemorrhage, and is not restricted to patients who undergo surgical clipping. Simultaneously, the mortality rate associated with aneurysm clipping decreased to a point that further microsurgical improvements could be directed towards reducing morbidity. Lougheed, Yaşargil, and others developed microsurgical techniques for aneurysm closure, while technical advances included improved aneurysm clips created by Norlén and Olivecrona. The value of medical management in prevention of cerebral ischemia had shown to have limited value; only oral Nimodipine treatments were found to be beneficial. Momentum therefore shifted towards early aneurysm closure to improve patient outcome. A series of early and ultra-early surgeries performed in good-grade patients improved mortality and morbidity rates; moreover, the International Cooperative Study on the Timing of Aneurysm Surgery demonstrated excellent results when performing early surgeries in good-grade patients with aSAH. A decade later, the benefits of early clipping have been extended to patients with lower clinical grades, and today most centers adhere to an ultra-early (within 24 hours) treatment protocol for aneurysm closure.
Acute management of subarachnoid hemorrhage

As the temporal focus of disease management shifted toward the first 24 hours following ictus, it has become clear that early medical management and decision-making is likely to influence the later course of the disease as is reflected in our pathophysiological concepts of aSAH. Commonly, two phases are distinguished in the course of aSAH: the initial pathophysiological changes within the first three days were termed “early brain injury” (EBI), whereas DCI describes the complex of issues that occur later in the course of the disease. Previously, DCI was considered the most important determinant of patient outcome following aSAH and most animal studies therefore focused on the prevention of this secondary complication; however, the failure to translate the results of animal studies into humans has forced us to reevaluate our understanding of the complex pathophysiological processes following aSAH. Indeed, a substantial amount of evidence indicates that EBI begins at the aneurysm rupture and evolves over time, and is therefore an important prognostic factor for the occurrence of DCI and poor patient outcomes. Rather than being an epiphenomenon of an associated process, a causal connection between EBI and DCI would mean that future therapies should more specifically address EBI.

The acute phase of aSAH is a complex multifaceted disorder and patients are at risk for a host of secondary insults. Besides the direct risks presented by EBI and DCI, two other major early complications of aSAH significantly worsen a patient’s prognosis; aneurysmal rebleeding and other medical complications, including cardiac and pulmonary complications. Poor-grade aSAH is an independent predictor for myocardial necrosis, suggesting that cardiac injury after subarachnoid hemorrhage is neutrally mediated. Cardiac complications following aSAH are associated with poor outcomes and the resulting hypoxia and hypotension are important factors for DCI. Treatment aimed at minimizing early adverse cardiovascular events therefore deserves further study. Cardiopulmonary consequences which might occur in response to EBI can also delay the diagnostic process and complicate the acute treatment of aSAH.

The risk of aneurysmal rebleeding is highest immediately after the hemorrhage and declines over time. In the hours following ictus, an estimated 5.8–15% of patients experience a sudden clinical deterioration due to aneurysmal rebleeding. Patients who survive the first day have a rebleeding risk of 1.2% during the next 48 hours, with a cumulative risk of 40% without intervention. The prognosis after rebleeding is significantly worse: 80% of these patients die or remain disabled. Rebleeding is definitively prevented by an aneurysm obliteration, either using a surgical or endovascular approach. Prior to aneurysm repair, factors associated with rebleeding should be avoided and used in the clinical risk assessment of individual
patients. Despite all efforts, the pretreatment aneurysmal rebleeding remains an unresolved concern as the risk of its occurrence must to be balanced against concurrent challenges, such as the treatment of acute hydrocephalus and the timing of aneurysmal obliteration.

**Thesis outline**

This thesis evaluates several aspects and impacts of medical decisions made in the early phase of disease for patients suffering from aSAH. First, we review the pathophysiological processes following aSAH.

Disease-specific incidence rates are often used to evaluate national healthcare programs or policy decisions. Studies from countries with exceptional incidence rates are sometimes disregarded because of concerns regarding their external validity. In the third chapter we discuss controversies in the epidemiology of SAH and their possible impact on clinical decision-making.

Ultra-early treatment is currently advised for aSAH but this is sometimes delayed by suboptimal logistics or delayed diagnoses. In the fourth chapter we investigate the effect of delayed admission to specialized care on the mortality rate of patients with poor-grade aSAH.

As previously stated, patient outcome after aSAH is strongly related to the prevention of aneurysmal rebleeding, which is therefore of paramount importance in the treatment of this disease. In chapter five, we sought to determine whether aneurysm size is a predictor for aneurysmal rebleeding and should therefore be used in clinical risk assessments.

Early hydrocephalus is a known complication of aSAH. The initiation of cerebrospinal fluid drainage (CSF) is assumed to be a risk factor for aneurysmal rebleeding but a causal relation has not yet been proven. The amount of CSF drainage has previously not been correlated to aneurysmal rebleeding however, as is discussed in chapter six.

Emergency aneurysm closure may theoretically reduce the aneurysmal rebleeding rate and improve patient outcomes. Previous studies have not been able to provide definitive proof that ultra-early or emergency-based treatment protocols result in a clinical benefit and early aneurysm closure may actually expose the patient to additional risks. The possible negative effects of emergency endovascular aneurysm obliteration on complications and patient outcome are evaluated in chapter seven.

In chapter eight, the various aspects of this thesis are discussed, and I present an outlook for the future management of patients with aSAH.
References


An introduction to the pathophysiology of aneurysmal subarachnoid hemorrhage


* Contributed equally

Abstract

Pathophysiological processes following aneurysmal subarachnoid hemorrhage (aSAH) present survivors of the initial bleeding with a high risk of morbidity and mortality during the course of the disease. As angiographic vasospasm is strongly associated with delayed cerebral ischemia (DCI) and clinical outcome, clinical trials in the last few decades focused on prevention of these angiographic spasms. Despite all efforts, no new pharmacological agents have shown to improve patient outcome. As such it has become clear that our understanding of the pathophysiology of aSAH is incomplete and we need to reevaluate our concepts on the complex pathophysiological process following aSAH. Angiographic vasospasm is probably important. However, a unifying theory for the pathophysiological changes following aSAH has yet not been described. Some of these changes may be causally connected or present themselves as an epiphenomenon of an associated process. A causal connection between DCI and early brain injury (EBI) would mean that future therapies should address EBI more specifically. If the mechanisms following aSAH display no causal pathophysiological connection but are rather evoked by the subarachnoid blood and its degradation production, multiple treatment strategies addressing the different pathophysiological mechanisms are required. The discrepancy between experimental and clinical SAH could be one reason for unsuccessful translational results.
Background

The incidence of non-traumatic subarachnoid hemorrhage (SAH) based on nationwide epidemiological data has shown to be more or less homogeneous and displays minor differences based on different age distributions, study periods and autopsy rates. Cerebral aneurysm rupture is the cause of spontaneous SAH in up to 85–98.9% of the patients. With a mean age of 55 at rupture, the average age is significantly lower compared to other types of stroke. Not just the initial hemorrhage, but also pathophysiological processes following aneurysmal subarachnoid hemorrhage (aSAH) present survivors with significant mortality and morbidity which have major personal and socio-economic impact. As angiographic vasospasm is strongly associated with delayed cerebral ischemia (DCI) and clinical outcome, clinical trials in the last few decades focused on prevention of these angiographic spasms. However despite all efforts, no pharmacological agents have shown to improve patient outcome. In this respect, we aim to reevaluate some of the recent concepts on the pathophysiological mechanisms following aSAH.

The pathophysiology of subarachnoid hemorrhage – an introduction

As aneurysm rupture and early pathophysiological responses usually do not occur under medical monitoring, most data regarding the very early phase of aSAH results from experimental SAH, observations made during aneurysmal re-rupture in hospitalized aSAH patients or post-mortem data. Commonly, two phases are distinguished during the course of aSAH: initial pathophysiological changes within the first three days were given the term “early brain injury” (EBI), whereas “delayed cerebral ischemia” (DCI) describes a complex of reactions that occur later during the course of disease. DCI usually appears 3–4 days after ictus, the highest incidence and severity is reached after 6–8 days and usually resolves after 12–14 days. Few case reports document late onset DCI beyond 14 days. The concept of EBI has been coined more recently and evolved after the full mechanisms of action behind angiographic vasospasms resulted in a cornucopia of theories and refers to the events that occur in the brain before the development of DCI. The etiology of EBI lies at the pathophysiological mechanisms that have been initiated by the initial bleeding that predisposes the brain to secondary injury. It has also been suggested that the etiology of DCI and EBI are linked. However, causality between the two processes has not yet been established. In contrast, DCI has first been reported over 150 years ago and in the '70 the association between delayed neurological deficits and angiographic vasospasm led to a rational assump-
tion of causation. As angiographic vasospasm is strongly associated with DCI and clinical outcome, clinical trials in the last few decades focused on prevention of vasospasm with the aim to improve clinical outcome. However, DCI is likely to consist of a complex pathophysiologic complex involving microvascular dysfunction, thrombosis of cerebral – especially cortical vessels, cortical spreading depolarizations and depressions and ischemia or inflammatory reactions.

The following sections will broadly cover the complex pathophysiological mechanisms following aSAH.

**Early brain injury**

The extravasation of blood in the subarachnoid space leads to intense headache and an increase in intracranial pressure (ICP). ICP can rise up to similar values as the diastolic blood pressure or more. ICP usually decreases within 10 to 15 minutes but may also be sustained. High levels of ICP and arrest of cerebral circulation might be aggravated by mechanical factors such as cerebral edema and acute hydrocephalus as they can increase ICP and promote cerebral hypoperfusion.

An increase in ICP results in a significant reduction of regional cerebral blood flow (rCBF) and cerebral perfusion pressure (CPP). These pathophysiological responses are well documented under experimental and clinical conditions. Clinical studies assessing early cerebral perfusion within 72 hours after ictus described a correlation between the initial impairment of perfusion parameters, occurrence of DCI and outcome.

Cerebral autoregulation (comprising both pressure autoregulation and chemoregulation) seems to be frequently impaired after aSAH and is expected to be a major factor contributing to initial rCBF impairment. It may therefore be a prognostic factor for the occurrence of DCI and poor outcome. Cerebral perfusion impairment is likely to result in functional disturbances of the brain: in experimental SAH, raised ICP and cerebral hypoperfusion is accompanied by a profound suppression of total EEG power. Temporary ischemia may underlie the observed impairment of cortical function and total ECoG impairment may be the result of global transient ischemia. The observation that electrocorticographic activity recovers in parallel to normalization of cerebral perfusion suggests a possible causality. Alternatively, the neurovascular coupling of cortical activity and rCBF might lead to the reduction of rCBF when cortical signaling is disrupted.
Impaired rCBF may lead to either transient global or focal ischemia, which initiates a cascade of further pathophysiological events. Initial hypoxia leads to early metabolic failure, disturbed ionic homeostasis and to cytotoxic, ionic and vasogenic cerebral edema. Moreover, ischemia initiates apoptosis of neurons, astrocytes and vascular cells by activation of caspase-dependent and -independent pathways. These pathways might be the target of new therapeutic strategies that aim at the effects of early brain injury, such as hypothermia mediating the caspase-3-, PI3K/AKT- and NF-κB-dependent pathways. Hypoxia also activates inflammatory pathways and the coagulation system.

The steep rise in ICP with subsequent possible herniation and destruction of brain tissue contributes to the pathology of aSAH. Physiological responses following aSAH result in reduced cerebral perfusion and induce several pathophysiological changes within minutes after ictus. Many patients with aSAH survive this initial phase but suffer from cerebral perfusion impairment due to DCI in a later course of disease which may result in further neurological deterioration.

**Angiographic vasospasm and delayed cerebral ischemia**

DCI can be reversible or it may progress to cerebral infarction. As many as half of the patients suffering from aSAH develop delayed neurological deficits caused by DCI. In 2010, Vergouwen et al. proposed a standard definition for DCI and cerebral infarction which separates the concept of angiographic vasospasm from DCI, which is a clinical diagnosis, and cerebral infarction, a radiological diagnosis.

After the first observation of arterial narrowing following aSAH by Ecker and Riemenschneider (1951), angiographic vasospasms were believed to induce a causal chain of cerebral hypoperfusion with infarctions, neurological deterioration and poor outcome. The development of ischemic damage often coincides with angiographic vasospasm. However, DCI can develop in absence of angiographic vasospasms and angiographic vasospasm may resolve without causing ischemic lesions. The occurrence of angiographic vasospasms is related to the amount of subarachnoid blood and indeed blood breakdown products have been shown to induce arterial spasms. In fact, about 70% of aSAH patients show angiographic vasospasms. However, not all aSAH patients that present with angiographic vasospasms develop DCI-related cerebral perfusion impairment and the percentage of patients that develop actual neurological deterioration due to DCI lies at 30%.
Angiographic vasospasm induced ischemia has been regarded as a target for therapeutic management of DCI. However, a systematic review of several studies (including the CONSCIOUS-1 trail) showed that the pharmacological reduction of angiographic vasospasm did not translate into improved clinical outcome \(^{11,12}\). The reason for the unsatisfying
translation of experimental results into clinical practice is unclear and one may only speculate about the reasons: one reason for this observation might be that drug side effects may negate the benefit of the investigated pharmaceuticals or that insensitive outcome measures result in unspecific results. However, it seems unlikely that all investigated drugs have side effects negating its benefits. Second, the connection between DCI and EBI is unknown: EBI-related pathophysiological changes might not be a prerequisite for DCI. Both EBI and DCI could present themselves as an epiphenomenon of an associated process that itself is the true cause of infarction or independently caused by an associated process. In fact, fresh subarachnoid blood causes EBI and a cocktail of blood degradation production can result in cerebral vasoconstriction and likely also in neuronal dysfunction. Conversely, as discussed in the previous section, EBI could have a causal relationship with DCI. The pathophysiological processes during EBI including transient global ischemia might initiate the later cerebral ischemia and dysfunction of neuronal signaling after the third day following aSAH ictus. Indeed, EBI incorporates several pathophysiological changes such as transient global ischemia, apoptosis, early metabolic failure and induction of inflammation, which could promote later ischemia and neuronal dysfunction. In this view, a targeted treatment of EBI-related pathophysiological changes might also address DCI and treatment of DCI alone without treatment of EBI would not improve the clinical results. Whether EBI and DCI exhibit a causal pathophysiological connection remains unclear. A final reason for the disappointing therapeutic management of DCI might be that the pathophysiological mechanisms of DCI go far beyond angiographic vasospasm of the major cerebral vessels and an ischemia in the downstream territory. Ischemia seems to be crucial factor during DCI as several experimental and clinical studies have suggested (e.g. for experimental SAH in mouse models). However, various other pathophysiological processes next to vasoconstriction of the major cerebral vessels were considered to contribute to ischemia, such as microvascular dysfunction, microthrombosis, cortical spreading depolarization and inflammation and their possible contribution to the development of DCI in aSAH patients are discussed in the following section.

**Microvascular dysfunction**

Angiographic vasospasm of the cerebral microvasculature has been observed in different experimental animal models of aSAH. These microvascular spasms have been reported to affect up to 70% of all arterioles and were thought to be caused by blood components, in particular oxygenated hemoglobin and partially by breakdown products such as Bilirubin...
oxidation products (BOXes) which have a direct vasospastic effect. Other factors such as swollen astrocytic endfeet, constricted pericytes and cerebral edema might also directly narrow small vessels and reduce rCBF.

Recently, the attention has shifted toward the role of pericytes located around cerebral arterioles, capillaries and venules. Pericytes are considered as the main factor of microcirculation regulation in aSAH pathology. Especially the postcapillary system is easily compressed and provides little access for therapeutic interventions. rCBF may even reverse after constriction of pericytes, also known as the no-reflow phenomenon. Pericyte contraction often leads to their programmed cell death, increased capillary transit time heterogeneity and microcirculation shutdown.

Occlusion and narrowing of the microvasculature induces several changes in cerebral microcirculation. Maintaining cerebral microcirculation is essential as cerebral oxygenation depends on both cerebral blood flow (CBF), and the microscopic distribution of blood, the so-called capillary transit time heterogeneity (CTH). Elevated CTH after aSAH could therefore lead to tissue hypoxia in the absence of severe CBF reduction. Paradoxically, reduction in CBF improves brain oxygenation if CTH is critically elevated. In this respect, angiographic vasospasm and inverted rCBF might reduce CTH and therefore improve net tissue oxygen extraction. Whether treatment of increased microcirculatory heterogeneity through reduction of CBF results in better long-term clinical outcome remains to be evaluated in further clinical and experimental studies.

**Microthrombosis**

Microthrombosis is initiated in the early course of the disease, around the second day after aSAH. It is the result of a multifactorial process which includes activation of the coagulation cascade with a procoagulant activity, impairment of the fibrinolytic activity, platelet aggregation in cerebral vessels, arteriole and capillary lumen narrowing by swollen astrocytic endfeet and cerebral edema or inflammatory processes. It is thought to contribute to microvascular dysfunction, increased CTH subsequently leading to ischemia and if changes are irreversible, to degenerative changes and permanent neurocognitive impairment.

In autopsy studies microthrombosis has been correlated to DCI and death due to symptomatic angiographic vasospasm. In the clinical setting, microthrombosis has also been correlated to DCI and microemboli are detected in 30% to 70% of the patients with aSAH.
Indeed the degree of vasoconstriction correlates with the micro clot burden. Also, there seems to be a correlation between the micro clot burden and the amount of SAH. However, not all patients that show histological evidence of cerebral ischemia and microthrombosis suffer from clinically apparent DCI.

It is likely that microthrombosis is a significant feature in the pathophysiology of aSAH and a possible target for new therapeutic strategies. However, vessels subjected to microthrombosis cannot be reached by interventional or surgical efforts. Therapeutic approaches therefore mainly focus on a pharmaceutical reduction of clot development. So far limited treatment modalities are available. In a meta-analysis analyzing the impact of antiplatelet therapy to inhibit micro clot formation after aSAH, a trend of improved outcome and reduced secondary brain ischemia was found. However, these results did not reach statistical significance.

**Cortical spreading depolarization, depression and ischemia**

Cortical spreading depolarization and depression (CSD) is a well-known phenomenon since the 1940’s, and its pathophysiological relevance after aSAH has been investigated in a series of experimental and clinical studies mainly by Dreier and coworkers since 1998. Spreading depolarization are propagating, polyphasic slow potential changes and are characterized by waves of neuronal depolarization. CSD are a cerebral reaction to various stimuli such as ion imbalances, trauma, ischemia, electrical stimulation or pharmaceutical agents. These brief states of hyperexcitability are followed by depression of neuronal activity leading to negative tissue potentials which last at least one minute in normal brain tissue. CSD causes depression of cortical activity and can be associated with cortical spreading or non-spreading depression. Therefore, depression is an epiphenomenon of spreading depolarization and is defined as depression of EEG activity propagating with a velocity across the brain cortex of 2 to 5 mm/min.

CSD are associated with various changes at the cellular level. This includes a disturbance in cerebral ion homeostasis: extracellular K⁺ ion levels increase, whereas Na⁺, Ca²⁺ ion levels and the pH decrease. This change in cerebral ion homeostasis results in a net shift of water from the extracellular space into neurons causing neuronal edema with a swelling and distortion of the dendritic spines. Excitatory transmitters such as glutamate and aspartate are already released during the depolarization before CSD. Elevated extracellular K⁺ and/or the elevated concentration of excitatory transmitters can promote propagation of spreading depolarization.
Cerebral resistance vessels respond with tone alterations. In normal cerebral tissue, CSDs induce a net increase in rCBF similar to physiological neuronal activity. This increase can result in spreading hyperemia and lasts for several minutes. The typical vascular response of CSD is a large hyperperfusion followed by a protracted hypoperfusion. Hyperemia may not be fully adequate to sufficiently supply distant territories. Therefore, focal ischemia may occur despite hyperemia. In injured cerebral tissue, neuro-vascular coupling may further be inverted and CSD may result in a net vasoconstriction, ischemia and “spreading ischemia”, with a significant delay of the energy-dependent recovery from spreading depolarization. In tissue already at risk for progressive damage, this will contribute to lesion progression. Local microvascular dysfunction was suggested to be one of the major factors contributing to initiation of spreading ischemia and may act together with spreading ischemia in lesion progression: spreading ischemia may promote microvascular dysfunction and decrease neurovascular reactivity as CSD increases the extracellular K+ and reduces NO.

Clinically, electrophysiological evidence exists that CSD occurs in a multitude of patients with aSAH and other types of stroke. After aSAH, CSDs were detected by implantation of subdural strip electrodes in 18 patients in a prospective multicenter study. Nearly 300 spreading depolarizations were observed in 72% of patients. Recurrent spreading depolarization occurred in parallel to delayed ischemia induced deficits with positive and negative predictive values of 86% and 100%, respectively. Furthermore, patients developing aSAH-related strokes had associated progressive prolongation of electrocorticographic depression periods to > 60 min. In a further prospective multicenter study with 13 SAH patients, a subdural electrode was implanted allowing simultaneous recording of the ECoG, laser-Doppler flowmetry / rCBF and tissue partial pressure of oxygen ptO2. Isolated CSDs are associated with a physiological response resulting in either hyperemia, tissue hyperoxia or in an absent or inverse vascular response leading to hypoxemia and hypoxia inverse response. Clusters of CSDs were detected in patients that developed structural brain damage as observed by neuroimaging. They were associated with a significant depression of high-frequency-ECoG power, an inverse hemodynamic response and a sustained reduction of ptO2. In experimental SAH, inverse hemodynamic response of CSD led to a harmful prolongation of depolarization – ultimately to terminal depolarization – and severe spreading ischemia and cortical necrosis.

In ischemic stroke, cortical activation increases oxygen demand, worsens the supply-demand mismatch, and therefore leads to episodic hypoxemia or hypotension and triggers peri-infarct
An introduction to the pathophysiology of aneurysmal SAH

Depolarization. Therapies targeting CSD, minimizing neuronal activity or inverting the hemodynamic response may therefore reduce neuronal damage.

**Inflammation**

Inflammatory reactions following aSAH have been assumed to play a crucial role in the pathophysiology of aSAH, leading to secondary complications associated with angiographic vasospasm, EBI and microthrombosis as various inflammatory cascades are being activated within the first hours after ictus. Systemic inflammatory markers such as C-reactive protein (CRP) and cytokines may increase in response to aSAH, and are correlated with poor clinical outcome. After aSAH, an inflammatory environment develops in the subarachnoid space and adjacent brain parenchyma. Therefore, several inflammatory agents and cascades were hypothesized to promote EBI as well as DCI.

Sadly, there has been very little success in clinical trials for anti-inflammatory strategies with immune-modulating drugs (e.g. steroids, cyclosporin A, Nafamostat). With the exception of methylprednisolone, none of these pharmacological agents demonstrated an improvement in outcome. The use of steroids showed improved patient outcome but displayed no effect on either angiographic vasospasm or DCI. One of the key factors that may complicate clinical trials with immune-modulating drugs is the interpersonal variability of the injury and inflammatory response.

A recently published study demonstrates the role of microglial activation after aSAH and proposes a new concept referred to as “cortical spreading inflammation”: a mechanism of delayed brain injury after aSAH that could offer novel approaches for treatment of the long-term effects of aSAH. In experimental SAH as well as in aSAH patients, SAH induced an intracerebral accumulation of immune cells. The spread of immune cells was accompanied by an increase of pro-inflammatory cytokines (IL-6; TNFα), axonal and neuronal injury with increased intracerebral accumulation of the extracellular amyloid precursor protein and an increased rate of neuronal cell death. Using a chimeric mouse model for green fluorescent protein-labeled peripheral leukocytes, the spreading immune cells were identified as resident microglia. The authors further conclude that microglia activation causes secondary brain injury after aSAH, and microglial activation may therefore correlate with patient outcome.
Voltage-gated calcium channels in delayed cerebral ischemia.

Calcium antagonists reduce the risk of DCI related complications after aSAH. Prophylactic administration of dihydropyridine L-type calcium (Ca^{2+}) channel antagonists is currently recommended in clinical practice for the prevention and treatment of DCI \textsuperscript{151}. Evidence for L-type Ca^{2+} channel antagonists in the treatment of angiographic vasospasm and DCI is well documented \textsuperscript{152}. However, other types of voltage-gated Ca^{2+} channels might also contribute to the pathophysiology of DCI and provide novel means of treatment.

In total, ten different types of voltage-gated Ca^{2+} channels have been described of which only four can be attributed to L-type Ca^{2+} channels (Table 2.1). Recent studies revealed a possible significance of other voltage-gated calcium channels (VGCCs): between the fourth and 21\textsuperscript{st} day after ictus, HVA VGCCs are significantly decreased and LVA VGCC currents increase during experimental SAH in dogs \textsuperscript{153}. In parallel, protein expression of the Ca_{1.2} and Ca_{1.3} L-type α1 subunits decreases in the dog basilar artery during DCI while expression of Ca_{3.1}, Ca_{3.3} T-type α1 subunits and Ca_{2.3}-containing R-type VGCCs are increased \textsuperscript{153}. In rabbit cerebral artery myocytes, SAH induces an increase of Ca_{2.3} transcripts and protein as well as R-type currents \textsuperscript{154}. In contrast to the study of Nikitina and coworkers (2010), induction of Ca_{2.3} transcripts and protein occurred only in small resistance cerebral vessels but not in the basilar artery \textsuperscript{154}. SAH may therefore differently impact vessels of different sizes \textsuperscript{155,156}. Ca_{2.3} (R-type) VGCCs were suggested to have their pathophysiological significance in small diameter arteries \textsuperscript{155,156}. The Ca_{2.3} VGCC antagonist SNX-482 improves DCI-related rCBF impairment after SAH in rats \textsuperscript{157}. SNX-482 reverses oxyHb induced vasoconstriction five days after exposure of cultured rabbit cerebral arteries to oxyHb more than L-type blocker Diltiazem \textsuperscript{99}. Furthermore, the beneficial effects of dihydropyridine antagonists in prevention and treatment of DCI might not solely be attributed to its effects on L-type VGCCs. As Nimodipine reaches comparatively high serum concentrations during treatment, its specificity on L-type Ca^{2+} channels reduces, leading to additionally therapeutic effects on other types of voltage-gated Ca^{2+} channels, such as R-type VGCCs \textsuperscript{158-161}.

In addition to R-type VGCCs, T-type Ca^{2+} channels may also have a functional significance: in response to experimentally induced SAH, Ca_{3.1} and Ca_{3.3} α1 subunits are upregulated \textsuperscript{153}. However, the functional role of these T-type Ca^{2+} channels remains unclear. Cisternal injection of the T-type blocker Mibefradil did not attenuate angiographic vasospasms as assessed by CT angiography in cynomolgus macaques – in contrast to the dihydropyridine Nicardipine \textsuperscript{162}. However, Mibefradil is not a very selective drug that is used in submicromolar
Table 2.1 The ion-conducting Cav of voltage-gated calcium channels (Adapted after Kamp et al., 2005)

<table>
<thead>
<tr>
<th>Channel type</th>
<th>Ca&lt;sub&gt;x&lt;/sub&gt;</th>
<th>α1 subunit</th>
<th>Chromosomal location</th>
<th>Typical blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-voltage-activated calcium channel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca&lt;sub&gt;1&lt;/sub&gt; subfamily: “L”-type calcium channels</td>
<td>Ca&lt;sub&gt;x&lt;/sub&gt; 1.1</td>
<td>α1S</td>
<td>1q31-q32</td>
<td>L-type calcium channel antagonists, such as 1,4-dihydropyridines (nimodipine; nicardipine); phenylalkylamine (verapamil) or benzothiazepine (diltiazem)</td>
</tr>
<tr>
<td></td>
<td>Ca&lt;sub&gt;x&lt;/sub&gt; 1.2</td>
<td>α1C</td>
<td>12p13.3</td>
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concentrations used to block T-type channels. As SAH leads to a cell depolarization, T-type VGCCs may further be inactivated at resting membrane potentials around −75 to −65 mV.

**Clinical significance of voltage-gated calcium channel blockade in the treatment of delayed cerebral ischemia**

The dihydropyridine L-type VGCC blockers are the only pharmaceuticals which improve clinical outcome and reduce DCI after aSAH. Nimodipine is a lipophilic dihydropyridine L-type VGCC blocker and was introduced for the treatment of cerebral disorders in Europe in 1985 and approved three years later by the US Food and Drug Administration. Nimodipine is administered either orally or intra-venously. A meta-analysis and Cochrane Review showed the beneficial effect of VGCC antagonists following aSAH. L-type Ca<sup>2+</sup> channel antagonists reduce the risk of poor outcome (relative risk: 0.81; 95% confidence interval 0.72–0.92; number need to treat: 19) by preventing secondary ischemia. Furthermore, administration of VGCC blockers causes a favorable trend towards improvement of case fatality. The pathophysiological mechanism through which dihydropyridines prevent secondary ischemia and subsequently improve outcome following aSAH has not been
clearly identified. It has been proposed Nimodipin exerts its effect through changes in rCBF, reduction of angiographic microvasospasms, cortical spreading ischemia and microthrombi formation. Additionally, a possible neuro-protective effect of dihydropyridines has been discussed. However, this concept remains controversial as its application in treatment of acute ischemic stroke has shown no beneficial effect on clinical outcome or case fatality.

Although oral or intravenously administrated dihydropyridine antagonists show a benefit following aSAH, they are not capable of completely preventing DCI. Intrathecal application of dihydropyridines was considered to be a promising alternative to improve effectivity compared to oral or intravenous application. Intrathecal administration of Nimodipine was successfully evaluated in experimental SAH in the 1980s. Later, Nicardipine, another dihydropyridine L-type VGCC antagonist, was formulated in prolonged-release implants. Intrathecal application of these Nicardipine prolonged-release implants was analyzed in a few retrospective studies and may reduce the risk of angiographic vasospasms, DCI associated neurological deficits and secondary brain ischemic lesions. Intrathecal administration of Nimodipine was formulated in prolonged-release microparticles for intrathecal application. Intrathecal application of EG-1962 Nimodipine prolonged-release microparticles reduces angiographic vasospasm in experimental SAH in a rat SAH model. More recently, Nimodipine was formulated in prolonged-release microparticles for intrathecal application. Intrathecal application of EG-1962 Nimodipine prolonged-release microparticles reduces angiographic vasospasm in experimental SAH in a rat SAH model. More importantly, the recently published NEWTON trial (Nimodipine Microparticles to Enhance Recovery While Reducing TOxicity After subarachNoid Hemorrhage) showed that intrathecal application was safe and associated with not only a reduced DCI and rescue therapy but also improved clinical outcome as measured by the extended Glasgow Outcome Score.

**Subcellular organelles**

The importance of the functional disturbance of subcellular organelles in the pathophysiology of aSAH is gaining interest and could provide novel modes of treatment for patients with aSAH. Most of the available data stems from preclinical studies but shows that the nucleus, the endoplasmatic reticulum (ER), mitochondria and the autophagy-lysosomal system display alternate functions during the course of aSAH and could be implicated in its pathophysiology. Nuclear signaling pathways such as the factor-erythroid 2-related factor 2 (Nrf2)–antioxidant response element (ARE), and NF-kB signaling are involved in various CNS disorders and play a role in the pathogenesis of EBI and angiographic vasospasm in experimental SAH. However, the functional role of these pathways remains unclear.
An introduction to the pathophysiology of aneurysmal SAH

and further in-vivo experiments are needed to elucidate the effect of possible agonist or antagonist on the course of disease. In neurons, activation of autophagy has been detected during EBI. Although autophagy is key to cell homeostasis, excessive autophagy can induce cell death and is linked to aSAH. Moreover, in response to lethal conditions ER stress can result in apoptosis and it is hypothesized this may result in apoptosis of endothelial cells and results in disruption of the blood-brain-barrier. More research is needed to establish the exact roles of these organelles in aSAH and may lead to translational results into clinical practice. The clinical impact could be significant as a multimodal approach that focuses on subcellular organelles has the potential of being highly effective since these organelles are interrelated components.

**Perspective and limitations**

A unifying theory explaining all the pathophysiological changes following aSAH has not yet been described. First, several new concepts and mechanisms were described and brought forward during the last two decades. Some are quite new and their clinical value (e.g. of microcirculatory dysfunction, CTH or cortical spreading inflammation) has to be evaluated in further studies. A clinical impact of cortical spreading depolarization, depression and ischemia or EBI is documented and the role of angiographic vasospasms was questioned as described above. Second, it remains unknown how these different pathophysiological mechanisms following aSAH are connected. As previously discussed, some of them may be causally connected or present themselves as an epiphenomenon of an associated process. Further studies are required. If all the mechanisms following aSAH have no causal pathophysiological connection and are solely evoked by the subarachnoid blood and its degradation production, multiple treatment strategies addressing the different pathophysiological mechanisms are required. If there is a causal connection between DCI and EBI, future therapies should address EBI more specifically. Next, experimental SAH and animal models are used to resemble the human condition and to study pathophysiological changes following aSAH and the effect of pharmaceuticals and interventions. However, these experimental findings might not necessarily mimic the human condition: originating from a study comparing inflammatory changes in mice and humans, a large debate questioned the scientific value of certain animal models of human diseases. Although data from inflammatory diseases do not necessarily translate to hemorrhagic stroke, pathophysiological changes after experimental SAH will not completely match human conditions. A recent meta-analysis aimed to determine case fatality in mouse DCI models, to compare mortality...
in mouse DCI models to case fatality in human aSAH patients and to identify factors influencing mouse mortality. The study described a significant lower mean overall mortality rate in mouse DCI models compared to human case fatality rates following aSAH and identified the chosen experimental SAH model (endovascular vs. injection model) as the only significant predictor for mouse mortality after 48 hours. Further analyses are required to establish whether and to which extent different DCI models affect mortality and reflect human pathophysiology.

**Conclusion**

A unifying theory for the pathophysiological changes following aSAH has yet not been described. Angiographic vasospasm is probably important. Some changes may be causally connected or present themselves as an epiphenomenon of an associated process. A causal connection between DCI and EBI would mean that future therapies should address EBI more specifically. If the mechanisms following aSAH display no causal pathophysiological connection but are rather evoked by the subarachnoid blood and its degradation production, multiple treatment strategies addressing the different pathophysiological mechanisms are required. The discrepancy between experimental and clinical aSAH could be one reason for unsuccessful translational results.
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An introduction to the pathophysiology of aneurysmal SAH
Subarachnoid hemorrhage in Germany between 2010–2013: estimated incidence rates based on a nationwide hospital discharge registry


World Neurosurg. 2017;104:516-521
Abstract

Background
Nordic countries are the primary source for nationwide data on the incidence of subarachnoid hemorrhage (SAH). Reliable estimates of national incidence rates of SAH in other countries are lacking, yet studies from Nordic countries with exceptional incidence rate are sometimes disregarded because of concerns regarding external validity. Autopsies are rarely performed for sudden deaths, therefore estimates of the SAH incidence commonly reflect the hospital discharge rates. Our aim was to estimate the nationwide incidence of non-traumatic SAH in Germany using a national hospital discharge register.

Methods
The German federal statistical office provided the number of patients discharged from all German hospitals between 2010 and 2013 with the primary diagnosis of non-traumatic SAH (ICD Code I60.0–I60.9) and corresponding age distribution. Age standardised attack rates of non-traumatic SAH were calculated using the 2011 German demographic distribution.

Results
Between 2010 and 2013, the overall age standardized incidence rate of non-traumatic SAH was 11.3 per 100,000 person-years and reached a maximum of 22.1 per 100,000 person-years in the oldest age group. The absolute number of SAH was highest in the group aged 50–55 years. The distribution of intracranial aneurysms displayed a propensity towards the posterior circulation with advancing age (p<0.001), although in absolute numbers SAH originated mostly from the anterior circulation.

Conclusions
Our estimate of the German nationwide attack rate suggests that the incidence of non-traumatic SAH is more homogeneous than previously assumed. Rejecting the external validity of studies from countries believed to display an exceptional incidence rates may therefore not be justified.
Background

The global incidence rate of subarachnoid hemorrhage (SAH) is approximately 8 per 100,000 person-years and geographical differences between countries have been reported in smaller cohorts \(^1\). Nordic countries are the primary source for nationwide epidemiologic data on the incidence of SAH and have shown to be more or less homogeneous. The incidence rates display minor differences based on age differences in the cohorts, different study periods and autopsy rates \(^2\)\(^-\)\(^7\). SAH has been reported to originate from intracranial aneurysms in as high as 98.9% of the cases and harbouring an intracranial aneurysm is not a lifetime condition but is rather considered a dynamic pathology that develops during life \(^7\)\(^,\)\(^8\). Other cohorts with a different risk factor profile are likely to display different incidence rates. However, other than Nordic studies, little detailed reports on nationwide incidence rates of SAH are available for comparison. Comparing international incidence rates allows testing hypothesis about the causality of SAH. Moreover, disease-specific incidence rates are often used to evaluate national healthcare programmes or policy decisions and sometimes studies from countries with exceptional incidence rate are disregarded because of the concerns regarding external validity \(^6\)\(^,\)\(^9\). Very few studies take into account out-of-hospitals deaths from SAH, like Nordic studies, because autopsies are rarely performed for sudden deaths. Therefore, estimates of the SAH incidence commonly reflect the hospital discharge rates \(^6\). The aim of this study was to estimate the nationwide incidence of SAH in Germany using a national hospital discharge register.

Methods

Identification of SAH patients

Data was provided by the German Federal Statistical Office (Statistisches Bundesamt, Wiesbaden). A discharge diagnosis using International Classification of Diseases (ICD) codes is legally required to be provided to the statistical office. The database contains all public inpatient care of which for each hospital discharge or in-hospital death, one primary diagnosis is recorded. These data therefore resemble the admission data. Patients who died outside of the hospital are not included. Out of hospital deaths in Germany are registered on a municipal level. Retrieving nationwide data would therefore be challenging and not warranted based on the validity of the data. The validity of a death registry is dependent on the national autopsy rate and the autopsy rate in Germany is extremely low compared to
other European countries\textsuperscript{10,11}. We identified all records in the database between the 4-year period of January first 2010 and December 31\textsuperscript{st} 2013, with a primary diagnosis of non-traumatic SAH. In absence of a standard definition we included patients classified under the rubric I60.0–I60.9 of the ICD, like previously \textsuperscript{4}. This includes patients with the main diagnosis of a non-traumatic SAH from unspecified localization (I60.6–I60.9) and patients with non-traumatic SAH assorted to specific parental artery localization (I60.0–I60.5, a. carotis interna, a. cerebri media, a. communicans anterior, a. communicans posterior, a. basilaris and a. vertebralis). The hospital discharge registry only contains anonymized patient data and according to German legislation, analysis of nationwide registries does not require institutional ethical review board approval.

**Statistical analysis**

Age was categorized according to age groups <1 year, 1–4 years and after that in 5 year intervals. The age adjusted discharge rate (ADR) can be used as a surrogate for the age-specific incidence, although adjustments have to be made for multiple admissions or lost patients.

Hospital discharge rates (HDR) are expressed as cases per 100,000 persons and ADR were calculated. Direct standardization was done using the total German population on the median time point of the study period, the 2011 population of Germany on the 31st of December (Statistisches Bundesamt, Wiesbaden). The standardized ADR was modelled by applying a Poisson regression. Since the presented data are nationwide incidence rates, we chose to not report confidence intervals. Binary logistic regression analysis was used to identify a trend between anterior of posterior localized intracranial aneurysms across the ages groups. The Type I error was set at 0.05 and the tests were 2-tailed. All statistical analysis was performed using the R statistical computing package, R version 3.2.2 as released on 2015-08-14 (https://r-project.org/).

**Results**

The source population consisted of all German citizens during 2010–2013 with 321.2 million cumulative person-years at risk compiled by age category. The mean age at time of hemorrhage was 59.0±15.4 years. The census population of Germany on the 31\textsuperscript{st} of December 2011 was 80,327,900. In total, the database search identified 35,693 patients with a diagnosis of non-traumatic SAH (I60.0–I60.9) of which 17,005 (47.6%) were coded to specific parental
artery localization (I60.0–I60.5). The absolute number of SAH was highest in the group aged 50–55 years (4,902 hospital discharges) and shows a rapid decline after the eight decade of life (Figure 3.1).

Overall mean ADR of non-traumatic SAH was 11.3 per 100,000 person-years (Figure 3.2). The ARD was 0.05 per 100,000 person-years within the first year, increased exponentially from the age group 25–30 years (2.6 per 100,000 person-years) and reaches a plateau around

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**Figure 3.1** Absolute number of non-traumatic subarachnoid hemorrhage discharges (I60.0–I60.9) in Germany, stratified by age groups.

**Figure 3.2** Age adjusted discharge rates (ADR) of non-traumatic subarachnoid hemorrhage (I60.0–I60.9) in Germany. The mean ADR (horizontal line) is 11.3 per 100,000 person years.
the sixth decade (20.4 per 100,000 person-years, mean overall ADR <60 years was 6.6 per 100,000 person-years, Figure 3.2). The ADR was highest in the age group of 85–90 years (22.1 per 100,000 person-years, Figure 3.2). The maximum ADR of SAH assorted to specific parental artery localization (I60.0–I60.5) was reached at the age group of 55–60 years, 10.6 per 100,000 person-years (mean overall ADR 4.5 per 100,000 person-years, Figure 3.3A). Mean overall ADR for I60.6–I60.9 was 6.8 per 100,000 person years (Figure 3.3B). SAH originated

![Figure 3.3A](image1)

**Figure 3.3A** Age adjusted discharge rates (ADR) in Germany of non-traumatic subarachnoid hemorrhage assorted to specific parental artery localization (I60.0–I60.5). The mean ADR (horizontal line) is 4.5 per 100,000 person years.

![Figure 3.3B](image2)

**Figure 3.3B** Age adjusted discharge rates (ADR) in Germany of non-traumatic subarachnoid hemorrhage from unspecified localization (I60.6–I60.9). The mean ADR (horizontal line) is 6.8 per 100,000 person years.
mostly from aneurysms the anterior circulation but its distribution changed with progressing age towards the posterior circulation. Binary logistic regression analysis showed a significant increase in the incidence of posterior circulation aneurysms with advancing age (Figure 3.4, p<0.001). Analysis of specific parental artery aneurysm localizations did not show significant differences between age groups.

Discussion

Using a nationwide registry we monitored the German population (80 Million) during 321.2 million person-years of follow up and identified 35,693 patients with SAH. The overall ADR between 2010 and 2013 was 11.3/100,000. The ADR of SAH increased until the sixth decade and reached a plateau thereafter. Previous cross-sectional comparisons of different populations have shown a divergent epidemiology of SAH. Based upon these smaller cohorts the age-adjusted average annual SAH attack rate in Germany has been reported to be around 5 per 100,000 and was considerably higher in Nordic populations. Nationwide incidence rates of SAH for very few other countries are known but Nordic SAH studies show little variation between them, although they vary in case ascertainment. Using an approach previously used to estimate the Swedish national attack rate, our estimate of the
German mean nationwide SAH attack rate is not only higher than previously reported from smaller cohorts but also similar to the incidence rate reported by Nordic countries. In Finland, the incidence of SAH between 1989 and 1991 was 13.7 per 100,000 person-years and decreased as the European Standard Population (ESP) standardized incidence declined from 11.7 in 1998-2000 to 8.9 per 100,000 in 2010-2012 as result of decreasing smoking rates. In Norway, the reported crude incidence rate was 10.3 per 100,000 person-years, and the ESP standardized incidence was 8.7 per 100,000 person years between 1984-2007. In Sweden the crude incidence of SAH was 12.4 per 100,000 person-years between 1987 and 2002, and in Denmark the ESP standardized incidence of SAH was 12.3 per 100,000 person-years in 2002.

Furthermore, our study shows that the prevalence of posterior circulation aneurysms increased with advancing age. Elderly with SAH have a higher risk of unfavourable outcome, which can be partially appointed to a less active management and more conservative referral patterns. Indeed, we find a higher rate of unspecified SAH diagnosis with advancing age, which probably reflects a reduced propensity to refer this group of patients. The higher rate of posterior circulation aneurysms could also be responsible for less favourable outcomes as posterior circulation aneurysms are associated with poor clinical outcome and increased risk of sudden death after SAH.

The strength of this study is the large number of people that were monitored over an extended period of time, although it is impossible to identify the true incidence numbers based on a hospital discharge registry. Patients with subarachnoid haemorrhage are likely to be admitted to the hospital due to the severity of their clinical symptoms, but most sudden deaths after SAH take place outside of hospitals. As mentioned previously, very few studies take into account out-of-hospitals deaths from SAH, as autopsies are rarely performed for sudden deaths and estimates of the SAH incidence therefore commonly reflect the hospital discharge rates.

There are several limitations of our study that need to be addressed. Firstly, to our knowledge the accuracy of the German electronic health record system has never been described. However, the accuracy of several international electronic ICD-coded hospital discharge registries for SAH report a positive predictive value ranging from 86–96% and has been demonstrated to be the most accurate among various types of stroke. There is little reason to assume that the German system would by any less accurate and results from this database have been published before. Nevertheless, it is likely that some
episodes of SAH are miscoded in clinical practice. Secondly, we included all diagnoses of non-traumatic SAH (I60.0–I60.9), not only the ones of confirmed aneurysmal origin. This approach has been described before but presents a source of possible overestimation of the incidence of aneurysmal SAH. Alternative strategies have been described too but are prone to underestimate the true incidence of aneurysmal SAH as the group of patients categorized under I60.7–I60.9 may very well include patients with SAH of aneurysmal origin. Comparison of the reported incidence rates between studies should be done with caution as these differences in study approach could damp possible differences in incidence rates.

There is no reason to assume that miscoding rates differ between age groups and therefore does not influence the internal validity of our study. Also, since we only included patient with SAH as the primary diagnosis we might have missed true episodes of SAH that may have had SAH as a secondary diagnosis. This source of underestimation seems negligible due the severity of the disease. Thirdly, our study cannot be regarded as a true incidence study since we did not include death certificates in our analysis. This is in contrast to the previously mentioned Nordic cohorts. Registration of deaths in Germany is organized on a municipal level and the autopsy rates in Germany (3%) are frighteningly low compared to other European countries. Since the validity of a death registry is highly dependent on the autopsy rate, acquisition of this data for our cohort was not warranted. This could have lead to an significant underestimation of the incidence rates as an estimated 12.4% of all SAH episodes result in sudden death before patients reach the hospital. On the other hand, including death certificates could also lead to an overestimation of the incidence rate. Nevertheless, extrapolating our reported overall discharge rate of non-traumatic SAH with an estimated 12% rate of out of hospital deaths, would yield a figure very similar to previous reported Norwegian, Swedish and Finnish cohorts that did include a death register. Differences in autopsy rates between the death registers used in these studies need to be considered when interpreting their results. Another source of overestimation might be recurrent admissions or admissions after referrals that have been miscoded as first events. In general the effect of over- and underestimation seems minimal as our findings are in concordance with previous studies. Lastly, we only adjusted for age as data on other risk factor such as smoking and high blood pressure was unavailable.

Despite the limitations we think that our study presents interesting findings. Nationwide incidence data on SAH has already shown that Finland does not have an increased incidence of SAH compared to other Nordic countries. To our knowledge this is the first nationwide epidemiologic evidence that exists about the incidence of SAH apart from the nationwide
Nordic SAH studies and suggests that the incidence rate of SAH in much more homogenous than previously reported. Minor differences between the reported incidence rates of SAH are likely to result from a different prevalence of risk factors for SAH such as smoking and blood pressure level, autopsy rates and population structure. Nevertheless, Finnish SAH studies have previously been excluded from pooled analysis and its application to reference populations has been questioned based on the high SAH incidence and concerns regarding the external validity. Apart from the risk of publication bias, this approach might also alter conclusions from pooled analysis such as the PHASES risk prediction chart for unruptured intracranial aneurysms and could consequently lead to misguided treatment decisions.

Conclusions

Nationwide attack rates of SAH from Nordic countries have shown to be more or less homogeneous but vary in case ascertainment. Our estimate of the German nationwide attack rate suggests that the incidence of non-traumatic SAH is more homogeneous than previously assumed. Rejecting the external validity of studies from countries believed to display an exceptional incidence rates may therefore not be justified.

Acknowledgments

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Increased mortality of patients with aneurysmatic subarachnoid hemorrhage caused by prolonged transport time to a high volume neurosurgical unit


* Authors contributed equally

Abstract

Background
Time has shown to be a relevant factor in the prognosis for a multitude of clinical conditions. The current analysis aimed to establish whether delayed admission to specialized care is a risk factor for increased mortality in case of poor grade aneurysmal subarachnoid hemorrhage (aSAH).

Material and methods
Consecutive patients with aSAH were enrolled retrospectively if they had a World Federation of Neurological Surgeons Grading System (WFNS) - Grade of 5. Predictor variables for in-hospital mortality reflecting demographic, spatial, temporal treatment and neurological factors were recorded from hospital records and emergency doctor’s reports. We performed statistical analysis on the relationships between the predictor variables and in-hospital mortality.

Results
The study included 61 patients with an average age of 58 years. The overall in hospital mortality rate was 28% (17/61 patients). A delayed transport to specialized neurosurgical care was associated with increased in-hospital mortality. Transportation time was mainly prolonged in cases where an alternative diagnosis was made by the emergency physician. Mortality was highest in patients with cardiovascular complications of subarachnoid hemorrhage.

Conclusion
Delayed admission to specialized care is associated with a higher mortality rate in patients with poor grade aSAH. Accompanying non-neurosurgical, mainly cardiac complications might be a significant factor leading to delayed admission. The emergency physician should be aware that cardiovascular abnormalities are a relevant complication and sometimes the first identified clinical feature of poor grade aSAH.
Introduction

There have been several studies that aimed to identify risk factors in order to reduce mortality in patients with intracranial pathology 1-4. Most of these prognostic factors for outcome are present at ictus and cannot be influenced by medical management. However, for some conditions such as ischemic stroke and myocardial infarction a substantial contribution to outcome can be made by reducing time until admission 4. For traumatic acute subdural hematoma too, it has been shown that if all patients were taken directly to hospitals equipped to diagnose and treat the hematoma within mere hours after the injury, mortality rates could be reduced 1.

In most cases of traumatic brain injury the possibility of intracranial pathology cannot be overseen and transport of a patient to a non-trauma center is seldom 1. One of the problems the emergency doctor faces in case of a non-traumatic loss of consciousness is to exclude intracranial pathology. If the patient arrives in a hospital without a neurosurgery department, cerebral computed tomography (CCT) has to be performed alongside other diagnostic procedures and in case of aneurysmal subarachnoid hemorrhage (aSAH) the patient has to be referred to a neurosurgical department. Delay of transport to a neurosurgical clinic is therefore expected to be more likely. By studying the time from emergency call of an unconscious patient with an aSAH until arrival in our neurosurgical department we seek to identify whether the delay from ictus to neurosurgical admission is a risk factor for increased mortality in aSAH.

Methods

Study population

We conducted a retrospective study of patients with aSAH admitted to our neurosurgical department between January 1\textsuperscript{st} 2012 and December 31\textsuperscript{st} 2014. The inclusion criteria for this study were as follows: subarachnoid hemorrhage demonstrated by CCT and the presence of an aneurysm confirmed by cerebral digital subtraction angiography or CT-angiography. Only patients with a World Federation of Neurological Surgeons Grading System (WFNS) - Scale for subarachnoid hemorrhage of 5 upon arrival of the emergency response team were included. The primary outcome of the study was in-hospital mortality. The study was approved by the Heinrich Heine University Institutional Ethics Committee, study number 5277.
Treatment protocol

Patients were admitted to a specialized intensive care unit (ICU) and given treatment according to a standardized management guidelines. Patients are monitored on our ICU under a minimal touch regime until aneurysm closure. Aneurysm closure was preferably performed within 24 hours. Antifibrinolytic agents are only applied when definite aneurysm closure cannot be achieved within 36 hours. Emergency surgery was performed if hematoma evacuation or decompressive hemicraniectomy was indicated. In all patients with a WFNS grade 4 or 5, invasive neuromonitoring with an intraventricular catheter is initiated. The systolic blood pressure is lowered not to exceed 140 mmHg. Prophylactic treatment with dihydropyridine L-type calcium channel antagonists is started and all patients undergo serial perfusion computed tomography (PCT) during their stay on the ICU.

Clinical and radiological data collection

For all included patients, demographic data, suspected initial diagnosis and clinical features at onset were obtained from emergency response teams protocols. Neurological status was assessed with the WFNS grade and Glasgow Coma Scale (GCS). Significant clinical interval changes and interventions during hospitalization were retrieved from patient charts and documentation from the primary hospitals and our patient records. Admission CCT scans from the referring hospital and our own clinic were also assessed.

Definition of outcome parameters

In hospital mortality or neurological devastation leading to withdrawal of care were identified after analyzing all available clinical and radiological data. In hospital mortality was defined as death within 30 days after admission. The distance from the initial location of onset to our neurosurgical department was determined as the shortest distance in kilometers (km). Distance was measured using a desktop web mapping service: http://maps.google.de. Transportation time was determined by retrieving the emergency units response time and emergency room admission time from the treatment protocols. Rush hour was defined from 6:00 to 9:00 a.m., and 4:00 to 7:00 p.m.
Delayed admission following aSAH

Statistical analysis

Categorical data are presented as counts and percentages and continuous variables as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the normality of data. The statistical analysis was performed with t-test and chi square test. Statistical significance was set at p<0.05. All statistical analysis was performed using the R statistical computing package, R version 3.2.2 as released on 2015-08-14 (https://r-project.org/).

Results

Overall mortality

In total, 356 patients had been admitted with an aSAH during the study period. Sixty-one patients (17%) fulfilled the inclusion criteria. We could complete our database for 51 patients. In the remaining ten patients we could review the parameters for which the information was available. Excluding these patients from the analysis did not alter the results. The mean age was 58.1 years (22–84 y). Twenty patients were male and 41 female (m:f, 1:2). The overall in hospital mortality rate was 28% (17/61 patients). Forty patients displayed an aneurysm located on the anterior circulation of the circle of Willis and mortality was 35% (14/40). The remaining 21 patients with an aneurysm on the posterior circle had a mortality of 14% (3/21, not significant). Figure 4.1 shows the distribution of aneurysms in the brain as well as the mortality rate for each location.

Figure 4.1 Distribution of aneurysm location in the study population.
Most aneurysms were located in the anterior communicans artery. Aneurysms located on the anterior circulation were twice as common as aneurysms on the posterior circulation. The blue columns represent the absolute numbers, whereas the red columns represent fatalities. The mortality difference between anterior and posterior circulation aneurysms failed to show statistical significance.
**Transport time and mortality**

The time required from arrival of the first medical response team until admission to our neurosurgical department is depicted in Figure 4.2A. Thirty-five patients (57%) were admitted to another hospital for further diagnostics and transported to our hospital after CCT showed subarachnoid hemorrhage, whereas 26 patients were admitted to our hospital directly (mean transportation time 262 vs. 71 minutes p<0.001). There was a significantly higher transport time in the mortality group compared to the survival group (Figure 4.2B, mean transport time 230 vs 115 minutes p<0.05). Longer hospital stay in the primary hospital was also associated with increased mortality (mean 300 vs. 150 minutes, p<0.05, Figure 4.2C). However, there was

---

**Figure 4.2 Association between mortality and onset-to-neurosurgical center time.**

A Onset-to-neurosurgical admission time was significantly longer when the transport was indirect, i.e. when a local hospital without a neurosurgical department was targeted first (p<0.001).

B In fatal cases the mean transport time to the neurosurgical center was significantly longer compared to patients who survived (230 vs. 115 minutes, p<0.05).

C When a non-neurosurgical center was targeted first and cranial imaging was delayed, mortality increased. The transportation time was significantly higher in the mortality group then in the survival group (300 vs. 150 minutes, p<0.05).

D When patients were directly transferred to our clinic there was no difference in transport time between the 2 groups.
no significant difference in transport time between the death- and survival group when patients were transported directly to our neurosurgical department (Figure 4.2D, 60 vs. 79 minutes).

**Initiation of neurosurgical treatment and mortality**

Shorter transportation time did not result in faster initiation of neurosurgical treatment for aneurysm closure. Emergency surgery did not influence the outcome in any direction. Patients without external ventricular drain showed a higher mortality. However only few patients N=5 had no ventricular drainage because the therapy had to be discontinued.

**Alternative diagnosis and mortality**

When aSAH was suspected, mean transport time until admission at the neurosurgical department was 79 minutes compared to 220 minutes when alternative pathology was suspected (Figure 4.3A, p<0.05). Suspicion of an alternative diagnosis was associated with increased mortality (Figure 4.3B). In cases where cardiac pathology was suspected (n=8) mortality reached 75% (Figure 4.3B). Four patients received a diagnostic coronary angiography and none of them survived.

![Figure 4.3 Ambulance team diagnosis and transport time.](image)

**Figure 4.3** Ambulance team diagnosis and transport time. 
A When aSAH was suspected the onset to neurosurgical admission time was significantly lower compared to cases where an alternative diagnosis was made. These patients had a greater chance of first admission to a non-neurosurgical hospital (p<0.05). 
B The suspicion of an aSAH by the emergency response team was associated with a significantly lower mortality rate compared to patients who received an alternative diagnosis (20 vs. 45%). The highest mortality was seen in patients diagnosed with a myocardial infarction (75%). The patients who received a cardiac angiography had a mortality of 100% (4/4) (p<0.05).
**Distance to neurosurgical department**

Patient mortality was not correlated with the distance from the incident to the neurosurgical department. The mean distance in patients who died was 18 km against 25 km in those who survived (not significant, Figure 4.4A). Figure 4.5 provides an overview of the area from which patients were admitted to our department, as well as the distance and transport times between the four university hospitals and three additional Level I trauma centers in the area. Transport during rush hour did not affect patient survival (Figure 4.4B).

**Discussion**

The present study demonstrates that delay of specialized care for poor grade aSAH is correlated with increased mortality. Prolonged transport is associated with suspicion of an alternative diagnosis by the emergency physician and the highest mortality rates are reached in cases where primary cardiac pathology was suspected. Decreased mortality in patients with short or direct transportation was not due to a different neurosurgical intervention strategy in our series.

However, medical complications are another main cause of death after aSAH. A reported 15–23% of in-hospital deaths have been attributed to medical complications. Early brain injury (EBI) is one of the key aspects in the pathophysiology of SAH as the extravasation of blood in the subarachnoid space initiates several pathophysiological responses that are...
Delayed admission following aSAH is expected to influence patient outcome. The concomitant increase in intracranial pressure is accompanied by a severe impairment of cerebral perfusion. This reduction of cerebral perfusion as measured by the mean transit time is correlated with both the occurrence of delayed cerebral ischemia (DCI) and clinical outcome. The impairment of cerebral blood flow can lead to either transient global or focal ischemia, which initiates a cascade of further events.
pathophysiological changes. Early initiation of neuroprotection directed at minimizing EBI related pathophysiological changes might reduce the risk of DCI and subsequently improve patient outcome \(^4, 30\). This could explain the better outcome of patients with a reduced transportation time.

aSAH has a complex pathophysiology and besides significant neurological damage it can also involve systemic organ injury. The high rate of alternative diagnosis in patients with prolonged transportation times or indirect admission may reflect additional non-neurosurgical challenges that often accompany the aSAH and delay transport. In our cohort we find the highest mortality rate in patients with suspected cardiovascular complications. aSAH frequently results in myocardial necrosis with release of cardiac enzymes which can lead to a coronary angiography before a CCT scan has been performed \(^31\). Poor grade aSAH is a strong independent predictor of myocardial necrosis after aSAH \(^31\). This finding supports the hypothesis that cardiac injury after aSAH is mainly a neurally mediated process with a disturbance of brain-heart connection. The association of troponin elevation with stunning of the myocardium, hypotension and poor outcome after aSAH has been well documented and supports multimodality monitoring data which has identified hypoxia and hypotension as important factors for secondary brain injury \(^4, 32\). Treatment aimed at minimizing myocardial toxicity in order to reduce adverse cardiovascular events, the risk of DCI and improve outcome therefore deserves further study.

The present study has several limitations that need to be addressed. Due to the retrospective design we could not demonstrate causality between delayed transport and mortality. However, the association we found between delayed admission to specialized care and increased mortality is in concordance with a previous study which has shown that case volume is related to patient outcome \(^33\). Patients with a diagnosis of aSAH on their discharge record who initially presented through the emergency department of a hospital with a high volume of aSAH cases had significantly lower mortality rates \(^33\). For patients with acute intracerebral hemorrhage, admission to a specialized neurosurgical intensive care unit has also been associated with reduced mortality \(^34\). Furthermore, we could not demonstrate a positive effect of emergency surgery on patient outcome. Multiple studies have shown that ultra-early aneurysm closure (<24 hours) or even emergency application of surgical clip placement or endovascular coiling results in a reduced incidence of recurrent bleeding and improves clinical outcomes \(^35, 36\). Within our ultra-early treatment protocol, patients qualified for emergency surgery when hematoma evacuation or decompressive hemicraniectomy was indicated. This lack of a uniform treatment protocol for aneurysm closure on an emergency
basis is a likely cause why we did not observe reduced mortality after emergency surgery. In addition it has to be recognized that our cohort comes from a densely populated area with an abundance of medical resources and it is questionable whether our results can be transferred to less populated areas.

**Conclusion**

In conclusion, the present study demonstrates that delay in specialized care is associated with increased mortality in poor grade aSAH. Strategies directed toward minimizing early brain injury with prevention and treatment of cardiovascular complications, hold promise for further reducing mortality after aSAH. The emergency physician should be aware that cardiovascular abnormalities are a relevant complication and sometimes the first identified clinical feature of poor grade aSAH. Due to the correlation with malignant aSAH, high level of clinical suspicion, prompt recognition and treatment of this complication are necessary.
References


Delayed admission following aSAH
Aneurysm diameter as a risk factor for pretreatment rebleeding: a meta-analysis


*J Neurosurg*. 2015;122(4):921-928
Abstract

Object
Aneurysmal rerupture prior to treatment is a major cause of death and morbidity in aneurysmal subarachnoid hemorrhage (aSAH). Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. It is uncertain if the size of the aneurysm is related to rebleeding. This meta-analysis was performed to evaluate whether an association could be determined between aneurysm diameter and the rebleeding rate before treatment. Potentially confounding factors such age, aneurysm location, and the presence of hypertension were also evaluated.

Methods
The authors systematically searched the PubMed, Embase, and Cochrane databases up to April 3, 2013, for studies of patients with aSAH that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to evaluate study quality.

Results
Seven studies, representing 2,121 patients, were included in the quantitative analysis. The quality of the studies was low in 2 and very low in 5. Almost all of the studies used 10 mm as the cutoff point for size among other classes, and only one used 7 mm. An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2,121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively. The meta-analysis of the 7 studies revealed that larger size aneurysms were at a higher risk for rebleeding (OR 2.56 [95% CI 1.62–4.06]; p=0.00; I²=60%). The sensitivity analysis did not alter the results. Five of the 7 studies reported data regarding age; 4 studies provided age-adjusted results and identified a persistent relationship between lesion size and the risk of rebleeding. The presence of hypertension was reported in two studies and was more prevalent in patients with rebleeding in one of these. Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate. One study identified a lower risk of rebleeding associated with posterior location aneurysms.

Conclusions
This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. The authors’ results confirmed the current guidelines and underscored the importance of acute treatment for large ruptured aneurysms.
Introduction

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is about 5–10 cases per 100,000 \(^{21, 26}\). Closure of the aneurysm after initial aSAH is the primary goal to prevent aneurysmal rebleeding, which has an associated mortality rate of up to 50% \(^{32}\). The incidence of rebleeding after an aSAH has been estimated to be 14%–17% during the first 24 hours, and studies have shown that 87%–92% of all rebleeding occurs within the first 6 hours after the initial bleed \(^{9, 32}\). Endovascular coiling or clipping to secure the aneurysm is advised as early after rupture as is feasible to reduce the rate of rebleeding \(^{8}\). Currently, ultra-early treatment, considered to be within 24 hours, is advised for patients in good clinical condition \(^{34}\). Although nonmodifiable causes, such as transfer from other hospitals and late diagnosis, might delay treatment, ultra-early treatment can also be difficult due to internal logistics issues like limited 24/7 surgical coverage and access to operating theaters and anesthetic and nursing staff \(^{34}\).

Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. In recent years, several risk factors, such as hypertension and the location and size of the aneurysm, have been shown to be associated with rebleeding \(^{9, 10, 19, 28, 37}\). Biomechanical studies have indicated that cerebral aneurysmal rupture occurs when there is a decrease in the ratio of the artery wall thickness to the radius of the aneurysm \(^{7}\). This concept might explain the possible relationship between aneurysm diameter and the risk of rebleeding. However, the association between the risk of rebleeding and aneurysm size might be confounded by age \(^{28}\). In particular, older patients may have larger aneurysms, and their general condition makes it more likely that treatment is postponed, leaving these individuals more prone to rebleeding. This meta-analysis was performed to evaluate whether an association could be established between aneurysm diameter and rebleeding rate before treatment. Potentially confounding factors like age, aneurysm location, and the presence of hypertension were also evaluated.

Methods

Search strategy and selection criteria

The meta-analysis was constructed using the MOOSE guidelines \(^{38}\). In particular, an independent, experienced librarian systematically searched the PubMed, Embase, and Cochrane
databases up to April 3, 2013, for studies of patients with aSAH that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The search strategy is set out in Table 5.1.

**Data extraction**

Two authors (J.V.L. and H.B.) independently read all titles and abstracts and selected those that appeared to be relevant for a full text review without language restrictions. Conference abstracts, reviews, meta-analyses, editorials, and animal studies were excluded. From the remaining studies, full-text articles were obtained and independently evaluated by two of the authors (J.V.L. and H.B.). Studies were deemed to be eligible if they included: 1) patients with aSAH in either a prospective or retrospective population-based design; 2) the association between aneurysm diameter and the rebleeding rate; and 3) results that included or enabled the calculation of an odds ratio. A third author (R.B.) was consulted to resolve

### Table 5.1 Search strategy and results in Pubmed, EMBASE and Cochrane databases

<table>
<thead>
<tr>
<th>Step</th>
<th>Search terms</th>
<th>No. of studies</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pubmed</td>
<td>Embase</td>
<td>Cochrane</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>subarachnoid haemorrhage.ti,ab. OR Subarachnoid Hemorrhage[Mesh:noexp] OR (subarachnoid.ti,ab. AND hemorrhage.ti,ab.) OR subarachnoid hemorrhage.ti,ab. OR subarachnoid haemorrhages.ti,ab. OR subarachnoid hemorrhages.ti,ab. OR SAH.ti,ab. OR SAHs.ti,ab. OR SAHs.ti,ab. OR subarachnoid bleeding.ti,ab. OR ((Brain Aneurysm.ti,ab. OR brain aneurysms.ti,ab. OR Cerebral Aneurysm.ti,ab. OR cerebral Aneurysms.ti,ab. OR &quot;Intracranial Aneurysm&quot;[Mesh]) AND (rupture*.ti,ab.)))†‡</td>
<td>25,423</td>
<td>35,627</td>
<td>998</td>
<td></td>
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<tr>
<td>2</td>
<td>(&quot;Recurrence&quot;[Mesh] OR Recurrence.ti,ab. OR Recurrences.ti,ab. OR Rebleed*.ti,ab.)</td>
<td>306,816</td>
<td>339,678</td>
<td>21,206</td>
<td></td>
</tr>
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<td>1,844</td>
<td>2,151</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>(&quot;Risk&quot;[Mesh] OR Risk.ti,ab. OR sized.ti,ab. OR sizes.ti,ab. OR 10 mm.ti,ab. OR 7 mm.ti,ab. OR 5 mm.ti,ab. OR 6 mm.ti,ab. OR 8 mm.ti,ab. OR 9 mm.ti,ab. OR diameter.ti,ab.)</td>
<td>1,849,179</td>
<td>2,355,608</td>
<td>111,279</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Step 3 AND Step 4</td>
<td>610</td>
<td>773</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Limits: none</td>
<td>610</td>
<td>773</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

MeSH = Medical Subject Headings; mm = millimeter; noexp = no explosion of MeSH heading; ti,ab = title/abstract.

† The asterisk in this field indicates that rupture was a major topic of these articles.
‡ Quotation marks indicate that the entire phrase was searched.
Aneurysm diameter and risk of rebleeding

any disagreements. Reference screening was conducted to identify additional studies from the full-text articles that were evaluated. Included studies were selected for a quality review. The methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the quality of evidence were applied. The ORs and 95% CIs between small and large intracranial aneurysms were extracted or calculated. Size categories were then registered. The cutoff between small and large size had to be established according to the published data. In cases of overlapping cohorts, we excluded the one with the lesser-quality data or, if equal in quality, the one with the fewest patients to prevent an artificial increase in effect size.

**Statistical analysis**

Comprehensive Meta-Analysis software (Version 2.2.046, 2007, Biostat, Inc.) was used to perform statistical analysis. The odds ratio for the risk of the rebleeding of small compared with large intracranial aneurysms was used as the effect size. Size cutoff was determined based on the presence of a (close to) common value across the studies. Both fixed- and random-effect models were used to calculate the summary ORs and 95% CIs. The significance of the overall OR was determined using a Z-test. For the sensitivity analysis, each study was removed from the total and the remaining studies were reanalyzed. The Type I error was set at 0.05 and the tests were 2-tailed. We assessed the heterogeneity between the study estimates using the I² statistic, with thresholds for a low degree of heterogeneity set at 40%. The funnel plots were inspected, and the Egger test was used to look for evidence of publication bias.

**Results**

**Included studies**

The literature search revealed a total of 1,408 records: 610 in PubMed, 773 in Embase, and 25 in the Cochrane database (Figure 5.1, Table 5.1). An additional study was found by screening the references. After the removal of duplicates, we were able to identify 867 studies. Review of the abstracts left us with 26 studies for the full-text evaluation. Ten studies were excluded because they did not evaluate aneurysm diameter as a risk factor for rehemorrhage rate. Two other articles were excluded because one was a review and the other was an editorial. One study was written in Japanese and was thus also excluded. Four studies used an overlapping cohort, and the one with most appropriate
data was selected. In total we identified 9 studies that met our inclusion criteria. Clinical and/or radiological definitions of rebleeding were given in 8 studies and these are listed in Table 5.2. Only 1 study reported the median time to rebleeding and the median time to aneurysm repair. Aneurysm size categories were given in 7 studies, while 2 others reported the mean size for the lesions in the non-rebleeding group compared with the rebleeding group (Table 5.2). Four studies reported on time to treatment or time to rebleeding (Table 5.2).

**Quality assessment**

The methodological quality of the 9 included studies was assessed. Of a total of 45 scores, there was no disagreement (Table 5.3). As a consequence of their observational design, all of the studies started with a maximal quality score of low. None of the studies were rated down based on serious inconsistency, indirectness, imprecision, or publication bias. In 5
Table 5.2 Definitions of aneurysmal rebleeding, time to treatment, and aneurysm size categories

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of centers</th>
<th>Clinical Definition of rebleeding</th>
<th>Radiological Definition of rebleeding</th>
<th>Max follow-up (time to last rebleed)</th>
<th>Aneurysm size categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kassell &amp; Torner, 1983</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0–4.9, 5–9.9, 10–14.9, 15–19.9, 20–30 mm</td>
</tr>
<tr>
<td>Paré et al., 1992</td>
<td>1</td>
<td>Rebleeding confirmed by bloody ventricular drainage, cataclysmic clinical deterioration, or intraoperatively</td>
<td>Rebleeding confirmed on CT</td>
<td>NR</td>
<td>&lt;1.0 cm, ≥1.0 cm</td>
</tr>
<tr>
<td>Beck et al., 2006</td>
<td>1</td>
<td>Any deterioration; new neurological deficit; a decrease in the level of consciousness; or severe headache. In comatose patients, any suspicious event like bradycardia &amp; sudden rise in blood pressure or appearance of new blood on ventricular drainage</td>
<td>NR</td>
<td>Mean time at risk for nonrebleeding &amp; rebleeding group: 80±157 vs 97±139 hrs (p=0.91)</td>
<td>NR: reported mean size in non-rebleeding &amp; rebleeding group: 6.9±4.7 vs 11.2±9.2 mm (p=0.002)</td>
</tr>
<tr>
<td>Machiel Plezier et al., 2006</td>
<td>1</td>
<td>Sudden decrease in consciousness or a sudden increase in headache</td>
<td>Any increase of hemorrhage on CT</td>
<td>Max 30 days</td>
<td>≤10 mm, &gt;10 mm</td>
</tr>
<tr>
<td>Inagawa, 2010</td>
<td>1</td>
<td>Definite clinical deterioration</td>
<td>Fresh blood on CT</td>
<td>Max 14 days</td>
<td>&lt;5, ≥5–10, ≥10 mm</td>
</tr>
<tr>
<td>Guo et al., 2011</td>
<td>1</td>
<td>Sudden deterioration in consciousness or sudden increase in headache</td>
<td>Any increase of hemorrhage on CT</td>
<td>Max 72 hours</td>
<td>≤5, &gt;5 to ≤10, &gt;10 to ≤15, &gt;15 to ≤20, &gt;20 mm</td>
</tr>
<tr>
<td>Shue et al., 2011</td>
<td>4</td>
<td>NR</td>
<td>Fresh hemorrhage found on repeat neuroimaging</td>
<td>NR</td>
<td>&lt;5, 5–9, ≥10 mm</td>
</tr>
<tr>
<td>Lord et al., 2012</td>
<td>1</td>
<td>Acute deterioration in neurological status in conjunction w/ CT changes</td>
<td>New hemorrhage or increase in hemorrhage burden on repeat CT</td>
<td>NR</td>
<td>NR: reported mean size in non-rebleeding &amp; rebleeding group: 7 mm (5–10) vs 8 mm (6–15) (p=0.001)</td>
</tr>
<tr>
<td>Tsui et al., 2012</td>
<td>1</td>
<td>NR</td>
<td>Active bleeding w/ contrast extravasation during CTA or hematoma vol difference (max diameter difference, &gt;3 mm) or new hematoma location between 2 consecutive CT scans</td>
<td>NR</td>
<td>&lt;7 mm, ≥7 mm</td>
</tr>
</tbody>
</table>

CTA = CT angiography; NR = not reported.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kassell &amp; Tomer, 1983</td>
<td>Observational</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Very low</td>
</tr>
<tr>
<td>Paré et al., 1992</td>
<td>Observational</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Very low</td>
</tr>
<tr>
<td>Beck et al., 2006</td>
<td>Observational</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>Machiel Plezier et al., 2006</td>
<td>Observational</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>Inagawa, 2010</td>
<td>Observational</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Very low</td>
</tr>
<tr>
<td>Guo et al., 2011</td>
<td>Observational</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Very low</td>
</tr>
<tr>
<td>Shiue et al., 2011</td>
<td>Observational</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Very low</td>
</tr>
<tr>
<td>Lord et al., 2012</td>
<td>Nested case-control study</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
</tr>
<tr>
<td>Tsui et al., 2012</td>
<td>Observational</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
</tr>
</tbody>
</table>
studies, however, the quality was rated down because of serious limitations: Adjustment of the rebleeding rate for the time after the initial hemorrhage was not performed, or consecutive series were not reported 10, 19, 23, 33, 37.

**Data analysis**

Seven of 9 studies provided core data, making calculation of the OR possible 10, 19, 23, 28, 33, 37, 41. Almost all of the studies used 10 mm as the cutoff point for aneurysm size among others classes, with only 1 study using 7 mm (Table 5.4). An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2,121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively (absolute risk difference 9.6%). The meta-analysis of the 7 studies revealed that larger size aneurysms had an overall OR for

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Aneurysm size used for analysis</th>
<th>Rebleeding rate (%)*</th>
<th>Total rebleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kassell &amp; Torner, 1983</td>
<td>&lt;10 mm ≥10 mm</td>
<td>49/469 (10.4) 21/195 (10.7)</td>
<td>70/664 (10.5)</td>
</tr>
<tr>
<td>Paré et al., 1992</td>
<td>&lt;10 mm ≥10 mm</td>
<td>2/61 (3.3) 13/67 (19.4)</td>
<td>15/128 (11.7)</td>
</tr>
<tr>
<td>Beck et al., 2006</td>
<td>NA: reported mean size in non-rebleeding &amp; rebleeding group; 6.9±4.7 vs 11.2±9.2 mm (p=0.002)</td>
<td>NR NR NA</td>
<td></td>
</tr>
<tr>
<td>Plezier et al., 2006</td>
<td>≤10 mm &gt;10 mm</td>
<td>68/281 (24.2) 22/73 (30.1)</td>
<td>90/354 (25.4)</td>
</tr>
<tr>
<td>Inagawa, 2010</td>
<td>&lt;10 mm ≥10 mm</td>
<td>48/205 (23.4) 33/80 (41.3)</td>
<td>81/285 (28.4)</td>
</tr>
<tr>
<td>Guo et al., 2011</td>
<td>≤10 mm &gt;10 mm</td>
<td>18/169 (10.7) 52/157 (33.1)</td>
<td>70/326 (21.5)</td>
</tr>
<tr>
<td>Shiue et al., 2011</td>
<td>&lt;10 mm ≥10 mm</td>
<td>13/195 (6.7) 9/59 (15.3)</td>
<td>22/254 (8.7)</td>
</tr>
<tr>
<td>Lord et al., 2012</td>
<td>NA: reported mean size in non-rebleeding &amp; rebleeding group; 7 mm (5–10) vs 8 mm (6–15) (p=0.001)</td>
<td>NR NR NA (case-control study)</td>
<td></td>
</tr>
<tr>
<td>Tsui et al., 2012</td>
<td>&lt;7 mm ≥7 mm</td>
<td>5/75 (6.7) 7/35 (20.0)</td>
<td>12/110 (10.9)</td>
</tr>
<tr>
<td>Total</td>
<td>NA NA</td>
<td>203/1455 (14.0) 157/666 (23.6)</td>
<td>360/2121 (17.0)</td>
</tr>
</tbody>
</table>

NA = not applicable; NR = not reported.
* The rebleeding rate is the percentage derived by dividing the number of patients with a rebleed by the total number of patients.
Chapter 5

A Meta-Analysis: rebleed risk in large vs small aneurysms

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kassel &amp; Torner, 1983</td>
<td>1.039</td>
<td>0.603</td>
<td>1.792</td>
<td>0.138</td>
<td>0.890</td>
</tr>
<tr>
<td></td>
<td>Pare et al., 1992</td>
<td>7.102</td>
<td>1.532</td>
<td>32.922</td>
<td>2.505</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Machiel Plezier et al., 2006</td>
<td>2.430</td>
<td>1.191</td>
<td>4.956</td>
<td>2.441</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Inagawa, 2010</td>
<td>2.297</td>
<td>1.325</td>
<td>3.981</td>
<td>2.992</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Guo et al., 2011</td>
<td>4.154</td>
<td>2.301</td>
<td>7.922</td>
<td>4.723</td>
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</tr>
<tr>
<td></td>
<td>Shue et al., 2011</td>
<td>2.520</td>
<td>1.019</td>
<td>6.234</td>
<td>2.090</td>
<td>0.045</td>
</tr>
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<td></td>
<td>Wu et al., 2012</td>
<td>4.333</td>
<td>1.243</td>
<td>15.104</td>
<td>2.302</td>
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</tr>
<tr>
<td>Fixed</td>
<td></td>
<td>2.319</td>
<td>1.772</td>
<td>3.036</td>
<td>6.123</td>
<td>0.000</td>
</tr>
<tr>
<td>Random</td>
<td></td>
<td>2.562</td>
<td>1.619</td>
<td>4.056</td>
<td>4.015</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The squares indicate the mean, the whiskers indicate the 95% CI, and the diamonds indicate the pooled estimate (the width of the diamond represents the 95% CI).

B Sensitivity-Analysis: rebleed risk in large vs small aneurysms

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Cumulative statistics</th>
<th>Cumulative odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kassel &amp; Torner, 1983</td>
<td>1.039</td>
<td>0.603 1.792 0.138 0.890</td>
</tr>
<tr>
<td></td>
<td>Pare et al., 1992</td>
<td>2.364</td>
<td>0.367 15.237 0.905 0.366</td>
</tr>
<tr>
<td></td>
<td>Machiel Plezier et al., 2006</td>
<td>2.130</td>
<td>0.849 5.342 1.612 0.107</td>
</tr>
<tr>
<td></td>
<td>Inagawa, 2010</td>
<td>1.069</td>
<td>1.130 3.790 2.354 0.019</td>
</tr>
<tr>
<td></td>
<td>Guo et al., 2011</td>
<td>2.457</td>
<td>1.380 4.376 3.054 0.002</td>
</tr>
<tr>
<td></td>
<td>Shue et al., 2011</td>
<td>2.441</td>
<td>1.493 3.992 3.558 0.000</td>
</tr>
<tr>
<td></td>
<td>Wu et al., 2012</td>
<td>2.562</td>
<td>1.619 4.056 4.015 0.000</td>
</tr>
<tr>
<td>Random</td>
<td></td>
<td>2.562</td>
<td>1.619 4.056 4.015 0.000</td>
</tr>
</tbody>
</table>

Figure 5.2  Forest plots showing results of the meta-analysis of studies reporting rebleeding risk of large versus small aneurysms (upper) and sensitivity analysis (lower).

rebleeding of 2.32 (95% CI 1.77–3.04; p=0.00) and an OR of 2.56 (95% CI 1.62–4.06; p=0.00) for a fixed- and a random-effect model, respectively (Figure 5.2 upper). The results were subject to heterogeneity, which was determined by the $I^2$ statistic to be 60%, indicating that the random-effect the results (Figure 5.2 lower). The funnel plot gave no indication of publication bias, but the findings are of limited value because of the small number of studies considered (Figure 5.3). The Egger regression test revealed an intercept of 2.3 with a 2-tailed p-value of 0.22, and it was accordingly not statistically significant. Five of the 7 studies reported data on age; 4 studies provided age-adjusted results and identified a persistent relationship between size and the risk of rebleeding $^{10, 19, 28, 37}$. The presence of hypertension was reported in 2 studies and was more prevalent in patients with rebleeding in 1 of these
Aneurysm diameter and risk of rebleeding studies. Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate. One study identified a lower risk of rebleeding associated with posterior circulation aneurysms. These findings provide insufficient evidence to relate hypertension and/or location of the aneurysm with the rebleeding rate.

Only a single study evaluated the risk of rebleeding over time dichotomized for size; the authors found a difference of rebleeding rate within 24 hours that persisted for 3 days after the initial hemorrhage. They reported a hazard ratio for large aneurysm of 2.4 (95% CI 1.2–4.5). In another study, median time to aneurysm obliteration did not differ between rebleeding and non-rebleeding groups but was not stratified according to lesion size.

The use of antifibrinolytic agents was reported only by 1 study; the investigators included patients from 1996 to 2011, and from 2003 on, they used, on a routine basis, aminocaproic acid for all patients before aneurysm clipping or coiling.

Conflicting results have been reported regarding the effect of clinical grade on the risk of rebleeding. Six studies evaluated Hunt and Hess grade as a factor in relation to rebleeding. One study matched for Hunt and Hess grade found a significant difference in aneurysm size in those with rebleeding versus those without rebleeding. Two studies reported no significant association between Hunt and Hess grade and rebleeding risk. The authors of one study concluded that the larger the aneurysm, the worse was the World Federation

Figure 5.3  Funnel plot.
The points correspond to the treatment effects from individual studies, the diagonal lines show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale.
of Neurosurgical Societies grade, but did not report it as a independent risk factor. Two studies found Hunt and Hess grade to be a statistically significant independent risk factor for rebleeding (ORs 2.5 and 4.9). Clinical grade at admission is a possible independent risk factor for rebleeding.

**Discussion**

The findings of this meta-analysis show that aneurysm size is an important determinant of aneurysmal rebleeding. Age and location are unlikely to be confounding factors. The presence of hypertension was insufficiently registered to determine the role of possible confounding effects. To reduce rebleeding rates, patients with large aneurysms should, when feasible, undergo acute treatment rather than ultra-early treatment, despite possible logistical issues. Additionally, if patients are referred from other centers, or if the diagnosis is delayed, those with large aneurysms still require urgent treatment because it has been shown that the effect size of this association might persist for up to 72 hours after the initial bleed. An increased risk is seen even within 24 or 48 hours, the time window in which most aneurysm are currently treated.

The results of this analysis for ruptured aneurysms correspond with those of the ISUIA study, in which the primary bleeding risk was greater for individuals with larger unruptured aneurysms.

The present research has several limitations. First, there is a potential for publication bias; studies showing no association between aneurysm diameter and rebleeding rate are less likely to be published. The estimated effect size in this meta-analysis could therefore be overestimated. Second, the studies considered did not include data from patients who had died before hospital admission, and this rate would be estimated to be as high as 15%. Rebleeding rates during transfer to the hospital were also included and may be as high as 24%. Moreover, the average time to hospital admission varied considerably after the initial aSAH. Only one study reported median time to aneurysm repair and aneurysm rebleeding. The research by Machiel Pleizier et al. revealed that there is no significant difference between small and large aneurysms when it comes to the risk of rebleeding 72 hours after the initial SAH. Third, only one study reported the use of aminocaproic acid. Although antifibrinolytic therapy does not improve survival or the chance of being independent in activities of daily living, it does reduce the risk of rebleeding by approximately 35%, as indicated in a recent Cochrane review. Therefore, it is an important factor in rebleeding rate; unfortunately, the published studies did
not provide data with which to evaluate the effects of both size and antifibrinolytic therapy together. Fourth, the cutoff for aneurysm size at 10 mm is artificial and chosen based on the categories set out in the published literature. Fifth, even if rebleeding is prevented in patients with large aneurysms, there is still a substantial rate of rebleeding events (14.0%) in cases involving small aneurysms. Only the acute treatment of all patients is optimal for prevention of rebleeding 38.

Hypothetically, acute treatment could be associated with additional treatment risks like increased intraoperative rupture due to the newly formed instable thrombus. However, for treatment within 24 hours, it has been shown that this timeframe was associated with improved clinical outcomes, although the benefit was more pronounced for coiling than clipping 34. Moreover, it is unlikely that the risks of acute treatment will accrue in such a way that they outweigh the very high morbidity and mortality rates associated with rebleeding.

Conclusions

This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. Our results confirmed the current guidelines and stressed the importance of acute treatment for large ruptured aneurysms.

Acknowledgment

We would like to thank A.H.J. Tillema for her support with our literature search.
References


Aneurysm diameter and risk of rebleeding
Volume of cerebrospinal fluid drainage as a predictor for pretreatment aneurysmal rebleeding


J Neurosurg. 2018;128(6):1778-1784
Abstract

Background
Initiation of external cerebrospinal fluid (CSF) drainage has been associated with a significant increase in rebleeding probability after aneurysmal subarachnoid hemorrhage (aSAH). However, the implications for acute management are uncertain. The purpose of this study was to evaluate the role of the amount of drained CSF on aneurysmal rebleeding.

Methods
Consecutive patients with aSAH were analyzed retrospectively. Radiologically confirmed cases of aneurysmal in-hospital rebleeding were identified and predictor variables for rebleeding were retrieved from hospital records. Clinical predictors were identified through multivariate analysis and logistic regression analysis was performed to ascertain the cutoff value for the rebleeding probability.

Results
The study included 194 patients. Eighteen cases (9.2%) of in-hospital rebleeding could be identified. By multivariate analysis, in-hospital rebleeding was associated with initiation of CSF drainage (p=0.001) and CSF drainage volume (63 ml [55–69] vs. 25 ml [10–35] p<0.001). Logistic regression shows that 58 ml CSF drainage within 6 hours results in a 50% rebleeding probability. The relative risk for rebleeding after drainage of more than 60 ml in 6 hours is 5.4 times greater as compared to patients with less CSF drainage (RR 5.403, 95% CI 2.481–11.767; p<0.001, NNH 1.687).

Conclusion
Volume of CSF drainage was highly correlated with the probability of in-hospital aneurysmal rebleeding. These findings suggest that the rebleeding probability can be affected in acute management should the placement of an external ventricular catheter be necessary. This necessitates meticulous control of the amount of drained CSF and the development of a definite treatment protocol for this group of patients.
Background

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) ranges from 2 to 23 cases per 100,000 and is associated with significant morbidity and mortality. Of all aSAH patients, an estimated 5.8–22% will suffer from aneurysmal rebleeding. These events usually occur within the first 24 hours of the primary bleed and have an associated mortality rate of 50–60%. As rebleeding significantly impairs prognosis, its prevention is one of the primary goals of acute management.

However, concurrent challenges such as acute hydrocephalus or the need for invasive neuromonitoring may demand the use of an external ventricular drain (EVD), which leads to changes in transmural pressure across the aneurysm wall. Changes in transmural pressure have long been regarded as a possible cause for rebleeding, and studies have shown that indeed the initiation of external cerebrospinal fluid (CSF) drainage is associated with a significant increase in rebleeding probability.

In clinical practice, it is still unclear whether this intervention complicates acute management and what consequences for patients with aSAH should be drawn. In this context, we aimed to identify risk factors for in-hospital rebleeding before aneurysm occlusion and focus on the effect of CSF drainage on the incidence of aneurysmal rebleeding.

Methods

Study population

We conducted a retrospective study of 194 consecutive patients with radiologically confirmed aSAH admitted to the Heinrich-Heine University Medical Centre between May 2012 and January 2016. The ethics committee of the Heinrich-Heine University Medical Centre approved this study (study number 5361).

Treatment protocol

A standardized treatment protocol is applied to all patients admitted to our center with a SAH as described elsewhere. All patients undergo immediate computed tomographic angiography and perfusion computed tomography (PCT) upon admission. Patients are monitored on our neuro-intensive care unit (NICU) under a minimal touch regime until
aneurysm closure. The systolic blood pressure (SBP) is lowered not to exceed 140 mmHg. Antifibrinolytic agents are only applied when definite aneurysm closure cannot be achieved within 36 hours.

**Management of EVD and CSF drainage**

In patients with a Glasgow Coma Scale below 13 invasive neuromonitoring with insertion of an intraventricular catheter is initiated. All patients adhered to a standardized drainage protocol. The intracranial pressure (ICP) threshold is set at 18 mmHg. ICP is monitored continuously and CSF is drained in case of sustained elevation of ICP above the set limit. When the ICP exceeded 18 mmHg for a period >15 minutes, the EVD was opened at a hydraulic pressure level of 18 mmHg. Drainage of CSF was halted immediately when ICP dropped to 18 mmHg and none of the patients were treated under a continuous hydraulic drainage paradigm. The drained volume of CSF is documented hourly.

**Data collection and definitions**

For all 194 included patients epidemiologic, clinical and radiological data were collected. From this study population the number of rebleeding events was identified. Aneurysmal rebleeding was defined as CT-confirmed episodes of in-hospital rebleeding in which imaging was prompted by any neurological deterioration, or otherwise clinical suspicious events in comatose patients; like bradycardia, sudden rise in blood pressure or the appearance of fresh blood through ventricular drainage. The amount and intensity of blood was compared to that on the preceding CT. Rebleeding before hospitalization was registered, events after aneurysmal obliteration were not included. For further analysis, only patients with CSF drainage initiated at least 6 hours before aneurysm closure were included to allow for uniform analysis of the retrospective data (Figure 6.1). 117 patients were excluded from secondary analysis because CSF drainage had been started after aneurysm closure (n=45), or no CSF drainage was initiated (n=72). Another 12 patients were excluded because of incomplete data or variable duration of CSF drainage. In total, 65 patients (21 Men, [32.3%], mean age 58.6 ± 12.6 years) were included for further analysis (Figure 6.1). For the included patients we registered the volume of CSF drainage at 6, 12 and 24 hours before aneurysm closure.
Cerebrospinal fluid drainage and prevention of rebleeding

**Statistical analysis**

Categorical data are presented as counts and percentages and continuous variables as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the normality of data.

We performed univariate analysis of all clinically important covariates (see Table 6.1). For categorical data (Fisher-Grade, WFNS scale) we discriminated between a poor grade and a good grade due to the strong dichotomy: WFNS ≤3, ≥4, Fisher score <4, =4. Variables were tested for an association with rebleeding with the Fisher exact test (grouped data), t-test (for continuous normally distributed variables), or the Mann-Whitney test (for continuous, non-normally distributed variables). Multivariate analysis was performed to identify factors associated with aneurysmal rebleeding. We considered a 2-tailed p-value of 0.05 statistically significant. Binary logistic regression analysis was performed to ascertain the cutoff point from the variable identified through multivariate analysis for the prediction of rebleeding. For the patients with a volume of CSF drainage above the 50%-probability line in the binary logistic regression analysis we calculated a relative risk with 95% confidence interval (CI) and

![Flowchart demonstrating the selection process for the study.](image-url)
number needed to harm (NNH); to cause one rebleeding due to high volume CSF drainage. Correlation (R) between individual variables was calculated using Pearson’s product-moment correlation. All statistical analysis was performed using the R statistical computing package, R version 3.2.2 as released on 2015-08-14 (https://r-project.org/).

Table 6.1 Univariate and multivariate factors related to a rebleeding event in 194 aneurysm patients

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Rebleeding</td>
<td>Non-rebleeding</td>
</tr>
<tr>
<td>Total</td>
<td>194 (100%)</td>
<td>26 (13.4%)</td>
<td>168 (86.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>116 (59.8%)</td>
<td>16 (61.5%)</td>
<td>100 (59.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>78 (40.2%)</td>
<td>10 (38.5%)</td>
<td>68 (40.5%)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>55.6 ± 12.4</td>
<td>60.3 ± 12.4</td>
<td>54.8 ± 12.3</td>
</tr>
<tr>
<td>WFNS-grade on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>61 (31.4%)</td>
<td>0 (0%)</td>
<td>61 (36.3%)</td>
</tr>
<tr>
<td>2</td>
<td>27 (13.9%)</td>
<td>1 (3.8%)</td>
<td>26 (15.4%)</td>
</tr>
<tr>
<td>3</td>
<td>16 (8.2%)</td>
<td>5 (19.2%)</td>
<td>11 (6.5%)</td>
</tr>
<tr>
<td>4</td>
<td>31 (16.0%)</td>
<td>3 (11.5%)</td>
<td>28 (16.7%)</td>
</tr>
<tr>
<td>5</td>
<td>59 (30.4%)</td>
<td>17 (65.4%)</td>
<td>42 (25%)</td>
</tr>
<tr>
<td>Fisher grade on admission</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>10 (5.2%)</td>
<td>0 (0%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (3.6%)</td>
<td>0 (0%)</td>
<td>7 (4.2%)</td>
</tr>
<tr>
<td>3</td>
<td>50 (25.8%)</td>
<td>1 (3.8%)</td>
<td>49 (29.2%)</td>
</tr>
<tr>
<td>4</td>
<td>127 (65.5%)</td>
<td>25 (96.2%)</td>
<td>102 (60.7%)</td>
</tr>
<tr>
<td>Aneurysm size§</td>
<td>0.059</td>
<td>0.095</td>
<td></td>
</tr>
<tr>
<td>0 – &lt;5 mm</td>
<td>69 (35.6%)</td>
<td>4 (15.4%)</td>
<td>65 (38.7%)</td>
</tr>
<tr>
<td>5 – &lt;10 mm</td>
<td>99 (51%)</td>
<td>16 (61.5%)</td>
<td>83 (49.4%)</td>
</tr>
<tr>
<td>10 – &lt;15 mm</td>
<td>20 (10.3%)</td>
<td>5 (19.2%)</td>
<td>15 (8.9%)</td>
</tr>
<tr>
<td>15 – &lt;20 mm</td>
<td>2 (1%)</td>
<td>1 (3.8%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>4 (2.1%)</td>
<td>0 (0%)</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td>0.344</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>134 (69.1%)</td>
<td>17 (65.4%)</td>
<td>117 (69.6%)</td>
</tr>
<tr>
<td>Posterior</td>
<td>60 (30.9%)</td>
<td>9 (34.6%)</td>
<td>51 (30.4%)</td>
</tr>
<tr>
<td>External CSF drainage before aneurysm closure</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77 (39.7%)</td>
<td>17 (94.4%)</td>
<td>60 (34.1%)</td>
</tr>
<tr>
<td>No</td>
<td>117 (60.3%)</td>
<td>1 (5.6%)</td>
<td>116 (65.9%)</td>
</tr>
</tbody>
</table>

* Values are presented as number (%), unless otherwise indicated.
§ Missing data: Aneurysm size N=1 (0.5%).
Results

Patient demographics and rebleeding incidence

The characteristics of the study population are listed in Table 6.1. Pretreatment rebleeding was radiologically confirmed in 26 of 194 patients (13.4%). These 26 patients had a total of 28 rebleeding events. Ten of these patients had a rebleeding event during transport from the referring hospital to our clinic (5.2%). Two patients had both an out-of-hospital and in-hospital rebleeding event, resulting in a 9.3% (n=18) in-hospital rebleeding rate. The time distribution of patients with in-hospital rebleeding is depicted in Figure 6.2.

![Figure 6.2 Time interval between admission and in-hospital aneurysmal rebleeding.](image)

Interventions

The median time to aneurysm repair in all patients was 15 hours (IQR 6–23) after admission; the median time for EVD placement was three hours (IQR 2–5). From the 77 patients that received CSF drainage before aneurysm closure, 17 patients (22.1%) suffered from aneurysmal rebleeding. Two patients had aneurysmal rebleeding shortly after initiation of CSF drainage and no documented amount of drained CSF volume could be retrieved from the charts. There was no difference in duration of CSF-drainage between the rebleeding and non-rebleeding group (17 hrs. [IQR 7.5–21.5 hours] vs. 14 hrs. [IQR 8.5–21 hours], p=0.58). In total, 65 patients (33.5%) underwent CSF drainage over a course of at least 6
hours. Characteristics of these patients are listed in Table 6.2. Rebleeding occurred in 15 of these patients (23.0%). In 25 cases (12.9%), CSF drainage continued over a course of 24 hours and four of the 15 rebleeding events occurred after this timeframe. Of these four patients, aneurysm closure was delayed because of cardiac or respiratory complications (three patients), or logistic reasons (one patient). None of the patients was treated with antifibrinolytic agents.

**Risk factors for aneurysmal rebleeding**

In multivariate regression analysis the independent predictors for aneurysmal rebleeding were WFNS grade ≥4 (p=0.010) and the initiation of CSF drainage before aneurysm closure (p=0.001) (Table 6.1). Factors related to aneurysmal rebleeding in patients with EVD before aneurysm closure are presented in Table 6.2. The rebleeding-positive group had a significantly higher volume of CSF drainage before aneurysmal rebleeding compared to the rebleeding negative group (Figure 6.3; 63 ml [55–69] vs. 25 ml [10–35], p<0.001). In logistic regression analysis, a drained volume of 58 ml within 6 hours was identified as cutoff value (CV); the lower range of the 95% CI establishes the 50% probability line at 49 ml (Figure

<table>
<thead>
<tr>
<th>Table 6.2</th>
<th>Univariate and multivariate factors related to a rebleeding event in 65 patients with EVD before aneurysm closure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rebleeding positive</td>
</tr>
<tr>
<td>n=15</td>
<td>n=50</td>
</tr>
<tr>
<td>WFNS grade ≥4</td>
<td>12 (80.0%)</td>
</tr>
<tr>
<td>Fisher grade &gt;3</td>
<td>14 (93.3%)</td>
</tr>
<tr>
<td>Aneurysm diameter &gt;10 mm</td>
<td>9 (60.0%)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
</tr>
<tr>
<td>Amount of CSF drainage in 6 hours, ml [IQR]</td>
<td>63 [55–69]</td>
</tr>
<tr>
<td>Time of EVD insertion after admission, hours [IQR]</td>
<td>2 [1–2.5]</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (33.3%)</td>
</tr>
</tbody>
</table>

* Values are presented as number (%), median values are presented with IQR.

* Missing data: CSF drainage in 6 hours in N=2 (3%).
At 12 hours after EVD insertion the effect remained statistically significant (CV 122 ml, lower 95% CI 98.5 ml; p<0.001). However, the effect was lost after 24 hours as patients were excluded from further analysis due to aneurysm closure (p=0.062). The relative risk for rebleeding after drainage of more than 60ml in 6 hours is 5.4 times greater as compared to patients with less CSF drainage (RR 5.403, 95% CI 2.481–11.767; p<0.001, NNH 1.687). Independent predictors for a high volume of CSF drainage were aneurysmal diameter (R: 0.301, 95% CI 0.058–0.511; p=0.016) and WFNS grade (R: 0.263, 95% CI 0.016–0.479; p=0.038) (Table 6.3).
We did not find a significant difference in maximal SBP during admission between the rebleeding and the non-rebleeding group (152 mmHg ± 24 vs. 150 mmHg ± 20, p=0.737), nor was there a difference with the maximum SBP within the 30 minutes before aneurysmal rebleeding (126 mmHg ± 17 vs. 150 mmHg ± 20). We also did not observe more SBP spikes between the rebleeding and the non-rebleeding group (above 140 mmHg p=1.000, or 160 mmHg p=0.740). There were no significant differences in international normalized ratio (INR 1.07±0.07 vs. 1.04±0.06, p=0.099), partial thromboplastin time (PTT 23.3±3.6 vs. 25.9±11.4, p=0.388), anti platelet therapy (p=0.153) or oral anticoagulation (p=0.381). The absolute thrombocyte count did not differ between the rebleeding (222 x1000/µl ±101) and non-rebleeding group (226 x1000/µl ±56, p=0.869). Five patients fulfilled the criterium for thrombocytopenia (thrombocyte count below 150 x1000/µl) and all belonged to the rebleeding

<table>
<thead>
<tr>
<th>Table 6.3 Independent predictive value for amount of CSF drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFNS grade</td>
</tr>
<tr>
<td>Fisher grade</td>
</tr>
<tr>
<td>Aneurysm diameter</td>
</tr>
<tr>
<td>Aneurysm location</td>
</tr>
</tbody>
</table>

Figure 6.4 Graph of the logistic regression for the identification of the rebleeding probability. The right (blue) and left (green) vertical lines represent the cutoff value and the lower range of its 95% CI, respectively.
group (p<0.001). When presence of thrombocytopenia was included in the multivariate analysis it lost significance due to the strong effect of CSF drainage (p=0.993) (Table 6.2).

**Discussion**

This study revealed some novel issues about management of aSAH before aneurysm closure. First, initiation of external ventricular CSF drainage is independently associated with pretreatment rebleeding. Second, the amount of CSF volume drained is independently correlated to the rebleeding probability.

The initiation of CSF drainage is, among other factors such as clinical condition, hypertension, aneurysm size and amount of subarachnoid blood, an independent risk factor for a rebleeding event after aSAH 3,5,7,13-16. Moreover, its deleterious effect during aneurysmal re-rupture suggested CSF drainage should be avoided during recurrent hemorrhages 17.

However, the use of an EVD remains an undisputed and pertinent tool to treat acute hydrocephalus and continuous CSF drainage has also been advocated in the acute phase after aSAH to reduce the risk of ischemic complications 18,19. Despite this controversy, thresholds for the volume of CSF drainage remain undefined even though there have been multiple reports on the adverse effects of early CSF drainage and accidental over-drainage on the incidence of aneurysmal rebleeding within the first 24 hours, underlining the need for CSF drainage guidelines with defined thresholds 3,14. This volume mediated effect constitutes one of the most important predictors for rebleeding as demonstrated in our cohort. A volume of drained CSF above 60 ml within the first 6 hours increases the rebleeding risk significantly and should be avoided. In this respect, automated intracranial pressure- and volume-controlled CSF drainage systems might reduce the risk of rebleeding in these patients. Interestingly, although insertion of an EVD contributes to the rebleeding risk, timing of EVD placement and duration of monitoring and CSF drainage does not (Table 6.2).

Both premorbid hypertension and hypertension (HT) upon admission are well known risk factors and associated with increased severity of the initial bleeding event and represents a significant risk factor for aneurysm rebleeding 16,20. Though HT upon and during admission was assessed, we did not include premorbid hypertension in our model. This might have influenced our results because of its significant effect in other reports. In our study, patients with thrombocytopenia are at increased risk of aneurysmal rebleeding. However this did not improve the validity of risk assessment compared to CSF drainage volume alone. The
application of antifibrinolytic drugs prior to EVD placement in patients requiring treatment for acute hydrocephalus should be discussed as this medication effectively reduces the incidence of rebleeding \(^{21}\). However, the benefits of antifibrinolytic agents are still inconclusive due to a significantly higher rate of delayed cerebral ischemia and the failure of these agents to improve overall survival and functional outcome \(^{21}\). Its effectiveness in this selected situation therefore remains highly speculative. Recent publications show that aneurysm closure within 24 hours after ictus results in a lower rebleeding rate and improves clinical outcome \(^{22}\). However, the median time to aneurysm closure in our population was significantly lower than 24 hours. Aneurysm closure on an emergency basis would be an alternative strategy in order to reduce rebleeding \(^{23}\).

Limitations of this preliminary study are those that are generally associated with the retrospective analysis of small patient cohorts. As a result, we were unable to include patients with short periods of CSF drainage and exact amounts of CSF volume prior to rebleeding could not be determined. We realize that the cutoff of CSF drainage over a 6-hour period is arbitrary and it was chosen to allow for uniform analysis between patients. Two rebleeding patients were excluded because of this reason and this might affect our results. Also, as WFNS grade and aneurysm size were independent predictors for a high volume of CSF drainage, it is possible that these factors were driving the rebleeding events as these parameters have been linked to aneurysmal rebleeding in previous studies \(^{3,15}\).

Moreover, our treatment protocol uses an intermitted drainage system and is likely to result in greater drops in ICP. As no continuous ICP values were available, we could not determine whether absolute drops in ICP play a role in the etiology of aneurysmal rebleeding. Finally, it is possible that our study underestimates the incidence of early rebleeding. Although the focus of this study does not lie at pre-admission rebleeding, patients in poor clinical condition might have had a rebleeding event without clear clinical signs, but it is unlikely that this would go unnoticed under invasive neuromonitoring.

Despite these limitations, we were able to demonstrate a threshold for CSF drainage as one of the paramount contributors to aneurysm rebleeding and identify a group of patients in need for a yet undefined but much-needed treatment protocol. We believe that the risk for early rebleeding can be affected by an adequate treatment strategy and thus the protocol for a prospective trial to evaluate the role of controlled automated CSF drainage, the use of antifibrinolytic medication and ultra-early aneurysm closure is currently under development. Begin of this study is planned for the near future.
Conclusion

The most significant factor for in-hospital rebleeding from an unsecured cerebral aneurysm was initiation of CSF drainage and the volume of drained CSF. This necessitates meticulous control of the amount of drained CSF in patients where drainage is needed due to acute hydrocephalus. Development of a definite treatment protocol for these patients is mandatory.
References


Per-procedural aneurysm re-rupture in relation to timing of endovascular treatment and outcome

Jasper H. van Lieshout, Dagmar Verbaan, Rogier Donders, René van den Berg, W. Peter Vandertop, Catharina J.M. Kijn, Hans J. Steiger, Joost de Vries, Ronald H.M.A. Bartels, Kerim Beseoglu, Hieronymus D. Boogaarts

Abstract

Background
Obliteration of ruptured intracranial aneurysms is initiated as soon as feasible to prevent rebleeding. A possible disadvantage of immediate aneurysm occlusion is a higher rate of procedural complications. We evaluated whether timing of endovascular aneurysm repair is a risk factor for per-procedural aneurysm re-rupture and if per-procedural aneurysm re-rupture has clinical impact.

Methods
All endovascularly treated, consecutive aneurysmal subarachnoid hemorrhage patients, treated at the Radboud University Medical Center (Nijmegen) and the Academic Medical Center (Amsterdam) between January 2012 and January 2016, were selected. Primary outcome measure was per-procedural aneurysm re-rupture. Secondary outcome was the modified Rankin Scale (mRS) score at six months' follow-up. Predictors of rebleeding were assessed by univariate analysis, determinants for outcome by multivariate analysis.

Results
Per-procedural aneurysm re-rupture occurred in 12 (2.5%) of 471 (mean age 57; 69.4% female) patients. In seven of these, coiling was performed within six hours after ictus, and this was a predictor for per-procedural aneurysm re-rupture (OR 9.0, 95% CI 2.8–29; p<0.001). Procedural re-rupture was related to poor outcome (mRS>2; aOR 7.0, 95% CI 1.9–26; p=0.019, adjusted for age and clinical grade on admission) and increased case-fatality (aOR 7.8 95% CI 2.4–25; p<0.001).

Conclusion
Endovascular coil embolization within six hours after ictus might expose patients to a higher probability of treatment-related aneurysm re-rupture. Early procedural aneurysm re-rupture also results in an increased case-fatality and a reduced chance of returning to daily life. Extra caution therefore, might be warranted if ultra-early aneurysm repair within six hours is contemplated. Alternatively, immediate endovascular intervention following the 'time-is-brain' concept of ischemic stroke, might be considered.
Background

The main aim in treatment of aneurysmal subarachnoid hemorrhage (aSAH) is securing the intracranial aneurysm to prevent spontaneous aneurysmal rebleeding, as this results in 60% case fatality. Some studies have found evidence for ultra-early treatment (<24 hours) or even emergency treatment of ruptured aneurysms in order to reduce aneurysmal rebleeding rates and improve clinical outcome. The benefit has been suggested to be more pronounced for coiling than surgical clipping. Yet, inconsistent results and heterogeneity of most analyses result in a lack of evidence whether earlier endovascular treatment actually improves clinical outcome in patients with aSAH. Aneurysm obliteration within the first hours after initial rupture might also have an adverse effect as the fibrin net covering the aneurysm dome may be insufficiently strong to withstand coil placement and might therefore result in a higher chance of per-procedural aneurysm re-rupture. We aimed to establish whether timing of endovascular aneurysm repair is a risk factor for per-procedural aneurysm re-rupture and whether per-procedural rupture has any clinical impact.

Methods

Study population and inclusion

We included 471 consecutive patients with aSAH from two prospective observational databases, at the neurovascular centers from the Radboud University Medical Center (Radboudumc), Nijmegen, and the Academic Medical Center (AMC), Amsterdam, the Netherlands, between January 2012 and January 2016. The cohort contains no patients from the ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA) study. Only patients with a ruptured intracranial aneurysm who were treated by endovascular coil embolization were included (Figure 7.1). The institutional review boards approved this study.

Data collection and organization of the register

Reporting of the study was according to the STROBE guidelines for observational studies, and adheres to the AHA journals’ implementation of the Transparency and Openness Promotion (TOP) guidelines. The Dutch national neurosurgical society (NVvN) has initiated a physician-driven national outcome register for aSAH in order to improve quality of care (Quality Registry Neurosurgery, QRNS) in 2011. From the prospectively collected data patient characteristics...
(age, sex), clinical (WFNS) and radiological (Fisher grade, aneurysm size) characteristics, treatment modality, complications and outcome were collected. Time of ictus was established by (hetero) anamnesis. Aneurysm size is a known risk factor for per-procedural complication; we defined small aneurysm size as ≤5 mm. The size of the ruptured aneurysm was determined by the largest diameter of the aneurysm.

**Treatment protocol**

A standardized treatment protocol was applied to all patients admitted with aSAH, as described elsewhere. Some regional differences did exist. At Radboudumc, radiological imaging is evaluated and treatment decisions made by hybrid vascular neurosurgeons and in the AMC by interventional neuroradiologists and vascular neurosurgeons in consensus. For patients in poor clinical condition (WFNS grade 5), timing of treatment was variable and could have been postponed in individual cases. At the Radboudumc patients are monitored on the intensive care unit (ICU) prior to aneurysm closure, whereas in Amsterdam, patients are monitored on a specialized brain care unit, and only transferred to the ICU if monitoring or support of vital

**Figure 7.1** Flowchart.
Demonstration of the selection process for the study.
functions is necessary. Until aneurysm closure, at Radboudumc blood pressure is lowered using administration of intravenous labetalol, in patients with a mean arterial pressure >110 mmHg and at the AMC in patients with a mean arterial pressure >135 mmHg. Antifibrinolytic agents are applied when definite aneurysm closure cannot be achieved within 36 hours (Radboudumc).

**Endovascular treatment**

All endovascular treatments were performed under general anesthesia by experienced neuro-interventional specialists, with at least five years of experience. Heparin (2500–3500 IE) was administered after adequate placement of the first coil (AMC), or at the start of the intervention (Radboudumc). Coiling was performed using a coaxial access. In the vast majority of patients, an Excelsior SL-10 microcatheter (Stryker Neurovascular) was used to catheterize the aneurysm. A multitude of micro-guidewires was used in combination with the micro-catheter, depending on personal preference of the interventionalists (Transed 14 or Synchro 14 from Stryker Neurovascular, Traxcess EX from Microvention or Avigo from Medtronic). Balloon catheters were only used in incidental cases with wide-neck aneurysms. For embolization, either Target coils (Stryker Neurovascular) or Micrus coils (Micrus Endovascular, Codman Neurovascular, Johnson & Johnson Co., DePuy Sunthes) were used.

**Definitions and outcome parameters**

The primary outcome of this study was per-procedural aneurysm re-rupture during endovascular treatment. For per-procedural aneurysm re-rupture we used the previously proposed definition: aneurysmal re-rupture attributed to the use of endovascular devices, with extravascular effusion of contrast visible during digital subtraction angiography, regardless of hemodynamic changes. Increase of subarachnoid blood on the CT-scan following the intervention was not sufficient for classification of a procedural re-rupture. Per-procedural re-rupture was distinguished from spontaneous aneurysmal rebleeding. Spontaneous aneurysmal rebleeding was defined as CT-confirmed episodes of pre-treatment rebleeding, in which imaging was prompted by any neurological deterioration, or otherwise clinically suspicious events in comatose patients such as bradycardia, sudden rise in blood pressure or the appearance of fresh blood through external ventricular drainage.

The secondary outcome of the study was clinical outcome at six months after treatment as measured by the modified Rankin scale (mRS), as determined by a specialized nurse who had not been involved in the treatment.
Data analysis

Categorical data are presented as numbers (percentages) and continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the distribution. Categorical data (Fisher-Grade, WFNS and mRS) were dichotomized due to the small number of patients in the re-rupture group into Fisher score 1–3 and 4, good (WFNS 1–3) and poor clinical condition (WFNS 4–5), good (mRS ≤2) and poor (mRS >2) outcome 18. Per-procedural aneurysmal re-rupture was tested for an association with timing of aneurysm closure, age, sex, WFNS grade, Fisher grade and aneurysm size with the t-test or Fisher exact test as appropriate. Known major determinants of outcome (age, WFNS) and per-procedural aneurysm re-rupture were tested in a multivariate logistic regression model 19. The type I error was set at 0.05 and the tests were two-tailed. Patients with missing data or those lost to follow-up were excluded from the analysis (Table 7.1). All statistical analyses were performed using IBM SPSS Statistics version 22.0, release 22.0.0.1 for Windows.

Results

Incidence of procedural perforation and aneurysmal rebleeding

In total there were 471 patients (mean age 56.6; SD ± 13.1 years; 69.4% female) with aSAH. The remaining characteristics of the study population are listed in Table 7.1. Patient inclusion is depicted in Figure 7.1. The median time to aneurysm repair in all patients was 19 hours (IQR 32.5) after ictus. Spontaneous pretreatment aneurysmal rebleeding within the first six hours following ictus occurred in 18 (4.4%) of 405 patients. Per-procedural aneurysm re-rupture occurred in 12 (2.5%) patients (Table 7.2), and were evenly distributed between the two centers. Nine (75.0%) of these 12 patients were treated during office hours (8:00 a.m. and 6:00 p.m.). One of the patients (patient No. five) with a procedural aneurysm re-rupture also experienced a spontaneous aneurysmal re-bleeding prior to intervention.

All 12 procedural aneurysm re-ruptures were caused by perforation of the aneurysm by endovascular devices. In 11 patients perforations were caused by coils and in one patient by a microcatheter. Of 66 patients who were treated within six hours after ictus, seven (10.6%) had per-procedural aneurysm re-rupture. In the patients treated after six hours, five out of 405 (1.2%) patients experienced a re-rupture. Figure 7.2 depicts the occurrence of per-procedural aneurysm re-rupture and spontaneous aneurysmal rebleeding in the interval between ictus and endovascular treatment (≤12 hours).
### Table 7.1 Subarachnoid hemorrhage and aneurysm characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients n=471</th>
<th>Procedural re-rupture n=12</th>
<th>No procedural re-rupture n=459</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean±SD)</strong></td>
<td>56.6±13.1</td>
<td>65.3±12.6</td>
<td>56.3±13.1</td>
<td>p=0.025†</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>327 (69.4%)</td>
<td>10 (83.3%)</td>
<td>317 (69.1%)</td>
<td>p=0.001†</td>
</tr>
<tr>
<td>WFNS grade on admission &gt;3</td>
<td>133 (28.2%)</td>
<td>4 (33.3%)</td>
<td>129 (28.1%)</td>
<td>p=0.231‡</td>
</tr>
<tr>
<td>Fisher grade on admission &gt;3</td>
<td>302 (64.1%)</td>
<td>9 (75%)</td>
<td>293 (63.8%)</td>
<td>p=0.203‡</td>
</tr>
<tr>
<td>Aneurysm diameter ≤5 mm</td>
<td>208 (44.2%)</td>
<td>4 (33.4%)</td>
<td>204 (44.4%)</td>
<td>p=0.198‡</td>
</tr>
</tbody>
</table>

**Time of treatment after ictus, hours**

- ≤6 hours: 66 (14%) 7 (58.3%) 59 (12.9%) p<0.001†
- ≤24 hours: 289 (61.4%) 10 (83.3%) 279 (60.1%) p=0.226‡
- ≤72 hours: 387 (82.2%) 11 (91.7%) 376 (81.9%) p=0.546‡

*Incomplete data n=19 (4%).
† T-test.
‡ Fisher exact test.
N = Number of patients.

---

**Figure 7.2** Procedural aneurysm re-rupture and spontaneous aneurysmal rebleeding.

Number of patients with procedural aneurysm re-rupture and spontaneous aneurysmal rebleeding within the first twelve hours following ictus (in one hourly intervals).
### Table 7.2 Overview of patients with a procedural aneurysm re-rupture

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>WFNS</th>
<th>Aneurysm location</th>
<th>Aneurysm size</th>
<th>Interval between ictus and aneurysm closure</th>
<th>Cause for procedural aneurysm re-rupture</th>
<th>Direct neurological deficit following perforation</th>
<th>mRS at six months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>67</td>
<td>2</td>
<td>aCom</td>
<td>2</td>
<td>2</td>
<td>Coil perforation (#1)</td>
<td>Treatment terminated due to infaust prognosis</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>77</td>
<td>1</td>
<td>pCom</td>
<td>9</td>
<td>1</td>
<td>Microcatheter perforation</td>
<td>Treatment terminated due to infaust prognosis</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>2</td>
<td>pCom</td>
<td>7</td>
<td>1,5</td>
<td>Coil perforation (#1)</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>79</td>
<td>5</td>
<td>AB</td>
<td>6</td>
<td>5</td>
<td>Coil perforation (#2)</td>
<td>Treatment terminated due to infaust prognosis</td>
<td>6</td>
</tr>
<tr>
<td>5*</td>
<td>F</td>
<td>64</td>
<td>5</td>
<td>pCom</td>
<td>14</td>
<td>3</td>
<td>Coil perforation (#1)</td>
<td>Treatment terminated due to infaust prognosis</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>69</td>
<td>1</td>
<td>pCom</td>
<td>6</td>
<td>40</td>
<td>Coil perforation (#2)</td>
<td>Severe neurological impairment</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>47</td>
<td>5</td>
<td>aCom</td>
<td>4</td>
<td>5</td>
<td>Coil perforation (#1)</td>
<td>None</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>49</td>
<td>2</td>
<td>aCom</td>
<td>3</td>
<td>6</td>
<td>Coil perforation (#1)</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>71</td>
<td>2</td>
<td>aCom</td>
<td>6</td>
<td>80</td>
<td>Coil perforation (#2)</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>78</td>
<td>2</td>
<td>ACA</td>
<td>4</td>
<td>23</td>
<td>Coil perforation (#1)</td>
<td>Severe neurological impairment</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>55</td>
<td>5</td>
<td>aCom</td>
<td>6</td>
<td>22</td>
<td>Coil perforation (#2)</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>80</td>
<td>2</td>
<td>pCom</td>
<td>8</td>
<td>20</td>
<td>Coil perforation (#3)</td>
<td>None</td>
<td>3</td>
</tr>
</tbody>
</table>

* Patient who suffered from both spontaneous aneurysmal rebleeding and procedural aneurysm re-rupture.

female (F), male (M), arteria communicans anterior (aCom), arteria communicans posterior (pCom), arteria basilaris (AB), arteria cerebri anterior.
Per-procedural aneurysmal re-rupture

Risk factors for per-procedural re-rupture

Patients with per-procedural re-rupture were older and more often female (Table 7.1). Similarity between the per-procedural re-rupture and non-re-rupture group indicates that emergency endovascular embolization was not initiated by worse clinical status upon admission or increased incidence of pretreatment aneurysmal rebleeding. Factors related to per-procedural aneurysm re-rupture in patients with aSAH are presented in Table 7.1. In patients with per-procedural re-rupture time from ictus to treatment was shorter (5.5 hours, IQR 20.5) than in those without per-procedural re-rupture (19 hours, IQR 86.4; p=0.021). Heparin was antagonized by application of protamine sulfate and complete aneurysm obliteration was performed in all cases. None of the patients with procedural aneurysm re-rupture were treated with balloon-assisted coiling. Univariate analysis identified the following predictors for procedural aneurysmal re-rupture: age (p=0.025), female gender (p=0.001) and endovascular treatment within six hours after subarachnoid hemorrhage (p<0.001) (Table 7.1). The odds ratio (OR) of procedural aneurysmal re-rupture within six hours after ictus was 9.5; 95% CI 2.9–30.9; p<0.001.

Clinical outcome

Information on clinical outcome six months after treatment was available for all 12 (100%) patients in the procedural re-rupture group and for 403 (87.8%) patients in the non-rerupture group (Table 7.3). Patients with procedural aneurysm rupture were more likely to remain dependent (mRS>3; adjusted odds ratio (aOR) 7.0, 95% CI 1.9–26; p=0.019) and risk increased case-fatality (aOR 7.8, 95% CI 2.4–25; p<0.001), both independent of age and clinical grade on admission (Table 7.3). Five of seven (71.4%) patients who had a per-procedural aneurysmal re-rupture within six hours after ictus died during the admission. Four (80%) of these deaths were directly related to the clinical deterioration following intervention. One of the five patients who had procedural aneurysm re-rupture beyond six hours after ictus died.

Procedural re-rupture versus spontaneous aneurysmal rebleeding

Patients who experienced spontaneous aneurysm rebleeding were more often of younger age and presented with higher clinical and radiological grades (WFNS and Fisher grade) when compared to those with procedural aneurysm re-rupture (Table 7.4). However, these parameters failed to reach statistical significance.
### Table 7.3 Patient outcome related to procedural aneurysm re-rupture

<table>
<thead>
<tr>
<th>Outcome after 6 months, cut-off</th>
<th>All patients</th>
<th>Procedural re-rupture</th>
<th>No procedural re-rupture</th>
<th>Univariate analysis</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS≤2</td>
<td>285 (69.0%)</td>
<td>3 (25%)</td>
<td>282 (70.0%)</td>
<td>p=0.001</td>
<td>p=0.019</td>
</tr>
<tr>
<td>mRS=6</td>
<td>51 (12.3%)</td>
<td>6 (50%)</td>
<td>46 (11.4%)</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

*Corrected for WFNS Grade and Age.

mRS = modified Rankin Scale; n = number of patients.

### Table 7.4 Patient characteristics in the procedural re-rupture versus spontaneous rebleeding group

<table>
<thead>
<tr>
<th></th>
<th>Procedural re-rupture</th>
<th>Spontaneous rebleeding</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>65.4±13.2</td>
<td>57.9±12.7</td>
<td>p=0.108</td>
</tr>
<tr>
<td>WFNS grade on admission &gt;3</td>
<td>3 (27.3%)</td>
<td>15 (41.7%)</td>
<td>p=0.280</td>
</tr>
<tr>
<td>Fisher grade on admission &gt;3</td>
<td>8 (72.7%)</td>
<td>32 (88.9%)</td>
<td>p=0.133</td>
</tr>
<tr>
<td>Aneurysm diameter ≤5 mm</td>
<td>4 (36.4%)</td>
<td>13 (36.1%)</td>
<td>p=0.870</td>
</tr>
</tbody>
</table>

* One patient was excluded because she suffered both spontaneous rebleeding and a procedural re-rupture. n = number of patients.

### Discussion

This study shows that emergency (< six hours) endovascular embolization after aneurysm rupture is associated with a higher percentage of per-procedural aneurysm re-rupture, even when performed by experienced neuro-endovascular specialists. Per-procedural perforation was also related to poor clinical outcome and case-fatality.

In current clinical practice, treatment of ruptured intracranial aneurysm is initiated as soon as feasible, based on the hypothesis that early occlusion of the aneurysm reduces rebleeding rates and therefore, could improve patient outcome \(13,14\). A recently published meta-analysis, which included 16 observational cohort studies, suggested that ultra-early endovascular treatment of ruptured aneurysms may result in improved clinical outcome \(4\). However, some of the included studies compared ultra-early treatment with any treatment,
including treatment delayed as long as beyond 72 hours, which may in part disparate results. The decision for treatment beyond 72 hours may have resulted from clinical or aneurysmal characteristics, which may have contributed to poor outcome in the group with late treatment. In the meta-analysis, comparison of the outcome after treatment within 24 hours and between 24–72 hours showed no clinical benefit of early treatment. Adjusted analysis in one study even suggested that ultra-early treatment exposes patients to additional harm. Several explanations for the lack of effectiveness of aneurysm treatment <24 hours have been postulated. Since most rebleeding events take place within the first six hours, with a median interval of 180 minutes, it has been hypothesized that achieving aneurysm occlusion in order to prevent the rebleeding events would prove to be challenging within this time frame.

A significant part of our patients was treated within six hours after ictus, but displayed a high per-procedural re-rupture rate. Our results therefore, could provide an explanation as to why early endovascular treatment (within 24 hours) does not seem to result in a clinical benefit compared to later treatment (24–72 hours). An unstable thrombus during the early course of disease could render the aneurysm more vulnerable during early (< six hours) endovascular coiling. Not only is there an increased risk of perforation during coiling, the diagnostic angiography itself could bear an increased risk for aneurysmal re-rupture when performed within six hours.

Previous studies found that per-procedural aneurysm re-rupture does not lead to reduced clinical outcome or death. The discrepancy between our results and previous studies could be caused by the early phase of disease (< six hours) in which most of the events from our study took place. Early per-procedure aneurysm re-rupture could increase the clinical impact of these events by delaying recovery from early brain injury.

Strengths of our study include the prospective design of two observational databases, representing a homogenous national setting, and its consistency with recommendations on observational studies. However, despite the collaboration between two referral centers, the number of patients with per-procedural aneurysm re-rupture was small. Due to the retrospective study design we could not analyse all potentially relevant factors, such as blood pressure on admission and during the procedure. Moreover, possible imprecision in determining time of ictus might have altered our findings. Finally, this study was observational, so conclusions cannot be drawn on the effects of timing of treatment.

Our results suggest that the spontaneous rebleeding group is younger and had higher WFNS and Fisher grade, but analyses did not reach statistical significance. Similar patient
characteristics between the two groups will complicate clinical decision-making. For patients at risk for spontaneous aneurysmal rebleeding, in whom it is logistically possible to perform emergency aneurysm occlusion, the clinical benefit of early repair might be offset by a higher rate of procedural aneurysm re-rupture (10.6%, within six hours). If the overall net effect of emergency aneurysm occlusion is to make up for the higher rate of procedural aneurysm re-rupture, it might be beneficial to regard aSAH as a neurological emergency analogous to ischemic stroke where the concept of ‘time-is-brain’ nowadays leads to immediate endovascular interventions with extremely short door-to-repair times.

Reversal of heparin anticoagulation and placement of a second microcatheter in the aneurysm to complete the embolization is suggested to limit the consequences, but could not prevent death in most cases from our cohort 16.

Future efforts to reduce the higher probability of treatment-related aneurysm re-rupture might focus on new technical advances such as flow disruption with the Woven Endobridge (WEB)-devices, which can hypothetically decrease per-procedural re-rupture rates by reduced manipulation of the aneurysm dome. Timing of Heparin administration during the procedure, before or after placement of the first coil, may also influence outcome.

The variation in results from previous studies concerning the timing of endovascular aneurysm closure justifies additional observational studies of early treatment. Based on the present data, the overall net effect of early endovascular aneurysm closure is unclear.

**Conclusion**

Endovascular coil embolization within six hours after ictus might expose patients to a higher probability of treatment-related aneurysm re-rupture. Early procedural aneurysm re-rupture also results in an increased case-fatality and a reduced chance of returning to daily life. Extra caution therefore, might be warranted if ultra-early aneurysm repair within six hours is contemplated. Alternatively, immediate endovascular intervention following the ‘time-is-brain’ concept of ischemic stroke, might be considered.

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Per-procedural aneurysmal re-rupture
Summary and conclusion
Summary

The factors involved in the immediate pathophysiological changes following aneurysmal subarachnoid hemorrhage (aSAH) have attracted significant scientific interest; however, a unifying theory has not yet been described (Chapter two). Several new concepts and mechanisms were described and investigated over the last two decades. Some are quite novel and their clinical value (e.g., microcirculatory dysfunction, capillary transit time heterogeneity, or cortical spreading inflammation) has yet to be evaluated in further studies. The clinical impacts of cortical spreading depolarization, depression and ischemia, and early brain injury (EBI) have been documented, while the role of angiographic vasospasms is increasingly being questioned. Furthermore, it remains unclear how these different pathophysiological mechanisms following aSAH are connected. As previously discussed, some of them may be causally connected or present themselves as epiphenomena of an associated process. If these mechanisms have no causal pathophysiological connection and are all individually evoked by the subarachnoid blood and its degradation, multiple treatment strategies are required to address the different pathophysiological mechanisms involved; however, if there is a causal connection between delayed cerebral ischemia (DCI) and EBI, future therapies should address EBI more specifically.

Comparing international incidence rates and life-style factors facilitates the testing of hypotheses regarding the causality of aSAH. Disease-specific incidence rates are often used to evaluate national healthcare programs or policy decisions. Studies from countries with exceptional incidence rates are sometimes disregarded because of the concerns regarding their external validity, however, with the exception of Nordic countries, detailed reports of nationwide aSAH incidence rates are largely unavailable for comparison. The Nordic incidence rates have been considered outliers because smaller cross-sectional studies from other countries have reported very different rates of aSAH. Using a nationwide registry, we monitored the German population (80 million) during 321.2 million person-years of follow up, revealing that the incidence rates of aSAH are much more homogenous than previously reported (Chapter three). Minor differences between the reported incidence rates are likely to result from the prevalence of risk factors between countries, such as smoking and blood pressure, as well as autopsy rates and population structure. Finnish studies were previously excluded from pooled analyses and their use in reference populations has been questioned based on the high reported incidence of aSAH and concerns regarding the external validity of the findings. This means that the PHASES score is based on a limited number of aSAH patients, stratified into multiple subgroups. Aside from the risk of publication bias, this...
approach might also alter conclusions drawn from pooled analyses such as the PHASES risk prediction chart for unruptured intracranial aneurysms, and could consequently lead to misguided treatment decisions.

The complex pathophysiology of aSAH can also cause systemic organ injury. In a retrospective analysis we were able to determine that cardiovascular complications of aSAH are associated with prolonged transportation times to specialized care and increased mortality (Chapter four). Since early admission did not change the surgical management, it could be hypothesized that the early initiation of neuroprotection directed at minimizing EBI-related pathophysiological changes might reduce the risk of DCI and subsequently improve patient outcomes. Treatments aimed at minimizing early adverse cardiovascular events therefore deserve further study.

As rebleeding significantly impairs the prognosis, its prevention is one of the primary goals of acute aSAH management. Aneurysm obliteration, either by a surgical or endovascular approach, definitively prevents rebleeding events, which typically occur within the first six hours following ictus and become more frequent the longer that treatment is delayed. Prior to aneurysm repair, factors associated with rebleeding should be avoided and used in the clinical risk assessment of individual patients. By performing a meta-analysis of the published literature, we revealed that aneurysm size is an important determinant of aneurysmal rebleeding (Chapter five); moreover, we were able to demonstrate a volume-mediated effect of cerebrospinal fluid (CSF) drainage on the probability of rebleeding (Chapter six). This necessitates the meticulous control of the amount of CSF drained prior to aneurysm closure. Alternatively, it can be argued that patients with large aneurysms, or those in need of external ventricular drainage, should undergo emergency treatment rather than ultra-early treatment when feasible. Some studies did indeed state that the early treatment of a ruptured aneurysm is associated with improved clinical outcomes and a reduction in aneurysmal rebleeding rates, with greater benefits using coiling than surgical clipping. Inconsistent results and heterogeneity between most existing analyses mean it is still unclear whether earlier endovascular treatment actually improves outcomes however; in fact, the adjusted analysis in one study even suggested that ultra-early treatment may actually expose patients to additional harm. Indeed, not only is emergency endovascular embolization after aneurysm rupture associated with an increased probability of procedural aneurysm re-rupture, but these events also correlate with an increase in poor patient outcome and mortality overall (Chapter seven). This suggests a shared common etiology between procedural aneurysmal perforation and spontaneous rebleeding events, potentially resulting
from the delay in EBI recovery during the unstable early phase of the disease. This finding adds to the ongoing debate regarding the timing of aneurysm closure, suggesting that extra caution might be warranted if emergency aneurysm repair (within six hours) is contemplated.

Future perspectives

Cerebral circulatory instability during the early course of aSAH complicates its medical treatment and concurrent challenges. Hydrocephalus, logistics, and (non-) modifiable risk factors expose patients to a heterogenic course of disease; therefore, the preference of delaying aneurysm closure until the period of cerebral circulatory instability has passed, maintained throughout the 1960s and 1970s by authorities including Drake and Yaşargil, is understandable. The focus of future treatments should ideally be on stabilizing the early phase of the disease to allow treatment to be delayed; however, the value of pharmacological agents in the prevention of aneurysm rebleeding or the amelioration of DCI have been disproven, leading to a resumption of momentum toward early surgery. There is little dispute that early aneurysm closure reduces management mortality and morbidity rates; however, the logic that earlier aneurysm closure results in superior clinical outcomes can be challenged.

For ischemic stroke, reducing the time to treatment is recommended to improve outcomes. Similar to ischemic stroke, the obliteration of ruptured intracranial aneurysms is often initiated as soon as feasible to prevent aneurysmal rebleeding; however, endovascular coil embolization within six hours of the ictus might expose patients to a higher probability of treatment-related aneurysm re-rupture. Early procedural aneurysm re-rupture results in increased fatalities and a reduced likelihood of returning to everyday life. Future efforts are needed to establish whether the benefits of emergency aneurysm occlusion surpass the negative effects of a higher rate of procedural aneurysm re-rupture. If so, it might be beneficial to regard aSAH as a neurological emergency analogous to ischemic stroke, in which the modern concept of 'time-is-brain' leads to immediate endovascular interventions with extremely short door-to-repair times.

The risk of aneurysmal rebleeding during hospitalization before aneurysmal closure should also be minimized, and the further identification of relevant risk factors will demand the use of high-quality (international) registries. Several modifiable factors for rebleeding known to be affected by an adequate management strategy also require further study. The application of antifibrinolytic drugs (prior to EVD placement) should be discussed, as this medication effectively reduces the incidence of rebleeding; however, the benefits of
antifibrinolytic agents are still inconclusive due to their association with a significantly higher rate of DCI and their failure to improve overall survival and functional outcome. Their efficacy in this situation therefore remains highly speculative. The ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA)-study will investigate whether the ultra-early administration of tranexamic acid leads to favorable functional outcome. Also, by defining the volume of CSF drainage that contributes to aneurysm rebleeding, we identified a group of patients in need of a currently undefined but much-needed treatment protocol. A protocol for a prospective trial evaluating the role of controlled automated CSF drainage is currently under development and the study is planned to commence in the near future.

**Conclusion**

In this thesis, we evaluated several aspects of the acute management of aSAH, which continues to be a critical multifactorial condition involving complex interactions between pathological mechanisms. The heterogenic presentation of patients affected by aSAH poses challenges for the development of a management protocol for the early course of the disease. The primary concern following aSAH is aneurysm closure to prevent aneurysmal rebleeding. Although aneurysm closure is of cardinal importance, the optimal timing of aneurysmal obliteration may not parallel the treatment of other kinds of stroke as emergency endovascular treatments exposes patients with aSAH to a higher rate of procedural aneurysm re-rupture. Adverse events during early treatment should be balanced against the probability of spontaneous aneurysmal rebleeding during a prolonged waiting period. Amongst other factors, aneurysm size, the initiation of CSF-drainage, and the volume of CSF drained prior to aneurysm treatment are predictive of spontaneous rebleeding, and can be used in the clinical decision-making for individual patients.
References


Summary and conclusion
About the author
Curriculum vitae

Jasper Hans van Lieshout was born on August 27th 1988 in Nijmegen, the Netherlands. After completing secondary school at Strabrecht College in Geldrop in 2006, he began medical school at Radboud University, Nijmegen. In 2007, he was selected to participate in a masterclass on internal medicine (at Radboud University), which subsequently enabled him to participate in a research project at the Dana Farber Cancer Institute of Harvard Medical School, Boston, Massachusetts, USA, and the Broad Institute of Harvard University and the Massachusetts Institute of Technology (2009–2010). Upon returning to the Netherlands, he started his medical training at Radboud university medical center, and successfully graduated medical school in 2012. He then began clinical work in the department of neurosurgery at the Elisabeth-TweeSteden Ziekenhuis and later, in 2013, at Radboud university medical center (head: Prof. dr. R.H.M.A. Bartels). In 2014, he commenced neurosurgical training at the department of neurosurgery in the University Clinic in Düsseldorf, NRW, Germany, under the supervision of Prof. dr. H.-J. Steiger. His areas of interests include the skull-base and vascular neurosurgery. He has worked alongside Dr. H.D. Boogaarts on his research since 2013.
List of publications


Words of appreciation
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Considerations for the acute management of aneurysmal subarachnoid hemorrhage

Jasper van Lieshout