

Critical care of the patient with acute subarachnoid hemorrhage

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<https://tinyurl.com/SAH2018>

Disclosures

- Research support from NIAID, NINDS, Alsius, NovoNordisk, Actelion
- DSMB chair for a phase 3 trial of intraventricular nimodipine in SAH (Edge)
- Nicardipine was never submitted to the FDA for approval for SAH, and therefore its use in place of nimodipine is off-label.

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

SAH: What matters?

1. Rapidly identify patients with aneurysmal SAH and secure their aneurysm(s) quickly
2. Lower MAP before securing the aneurysm but not afterwards
3. Detect and manage early complications
 - a. Stress cardiomyopathy
 - b. Neurogenic pulmonary edema
 - c. Cerebral salt wasting

SAH: what matters?

4. Detect vasospasm early
 - a. Clinical
 - b. Electrophysiologic
 - c. Sonographic
 - d. Radiologic
5. Manage clinical vasospasm aggressively
 - a. Augment pressure and flow
 - b. Angioplasty and IA vasodilators
6. Treat at a high-volume center

Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons; and by the Society of NeuroInterventional Surgery

E. Sander Connolly, Jr, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, Vice Chair; J. Ricardo Carhuapoma, MD, FAHA; Colin P. Derdeyn, MD, FAHA; Jacques Dion, MD, FRCPC; Randall T. Higashida, MD, FAHA; Brian L. Hoh, MD, FAHA; Catherine J. Kirkness, PhD, RN; Andrew M. Naidech, MD, MSPH; Christopher S. Ogilvy, MD; Aman B. Patel, MD; B. Gregory Thompson, MD; Paul Vespa, MD, FAAN; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology

Stroke. 2012;43:1711-1737

Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference

**Michael N. Diringer • Thomas P. Bleck • J. Claude Hemphill III •
David Menon • Lori Shutter • Paul Vespa • Nicolas Bruder • E. Sander Connolly Jr. •
Giuseppe Citerio • Daryl Gress • Daniel Hänggi • Brian L. Hoh •
Giuseppe Lanzino • Peter Le Roux • Alejandro Rabinstein • Erich Schmutzhard •
Nino Stocchetti • Jose I. Suarez • Miriam Treggiari • Ming-Yuan Tseng •
Mervyn D. I. Vergouwen • Stefan Wolf • Gregory Zipfel**

Complications of aneurysmal SAH

- rebleeding
- cerebral vasospasm
- volume disturbances
- osmolar disturbances
- seizures
- cardiovascular complications
- CNS infections
- other complications of critical illness

Critical care issues: rebleeding

- Unsecured aneurysms:
 - 9% – 17% rebleed on day 0, then
 - 1.5%/day for next 13 days [∴ up to 36% for 2 weeks]
- Antifibrinolytic therapy (e.g., aminocaproic acid)
 - may be useful between presentation and early surgery
- Blood pressure management
 - labetalol, hydralazine, nicardipine
- Analgesia
- Minimal or no sedation to allow examination

Predictors of 1-year outcome after coiling for poor-grade subarachnoid aneurysmal hemorrhage

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Anne L. Boch · Chantal Colonne · Lise Lejean · Lamine Abdenmour ·
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Abstract

Objective To describe features in patients admitted to the intensive care unit (ICU) for poor-grade aneurysmal subarachnoid hemorrhage (SAH) and to identify predictors of 12-month outcome.

Methods We conducted a controlled observational study of 51 consecutive patients treated with endovascular coiling within 96 h of rupture for poor-grade aneurysmal SAH (20 men and 31 women, age 54 ± 12 years). We recorded co-morbidities; initial severity; aneurysm location; occurrence of acute hydrocephalus, initial seizures, and/or neurogenic lung edema; troponin values, Fisher grade; computed tomography (CT) findings; treatment intensity; and occurrence of vasospasm. The brain injury marker S100B was assayed daily over the first 8 days. Glasgow Outcome Scores (GOS) were recorded at ICU discharge, at 6 and 12 months. The main outcome criterion was the 1-

year GOS score, which we used to classify patients as having a poor outcome (GOS 1–3) or a good outcome (GOS 4–5).

Results Overall, clinical status after 1 year was very good (GOS 5) in 41% of patients and good (GOS 4) in 16%. Neither baseline characteristics nor interventions differed significantly between patients with good outcome (GOS 4–5) and those with poor outcome (GOS 1–3). Persistent intracranial pressure elevation and higher mean 8-day S100B value significantly and independently predicted the 1-year GOS outcome ($P = 0.008$ and $P = 0.001$, respectively).

Conclusions Patients in poor clinical condition after SAH have more than a 50:50 chance of a favorable outcome after 1 year. High mean 8-day S100B value and persistent intracranial hypertension predict a poor outcome (GOS 1–3) after 1 year.

Table 1 Baseline clinical characteristics by 1-year outcome

	GOS 1–3 (n = 22)	GOS 4–5 (n = 29)
Age (mean ± SD)	54 ± 13	53 ± 12
Gender		
Women	11(50)	20(69)
Men	11(50)	9(31)
Arterial hypertension	9(41)	9(32)
History of diabetes	0(0)	1(4)
History of smoking	5(23)	10(34)
History of heart failure	0(0)	1(4)
Number of bleeding episodes		
1	18 (82)	26(90)
2	4(18)	3(10)
Initial glasgow coma score		
7–12	12(55)	12(41)
<7	10(45)	17(59)
Baseline Fisher score		
2	0(0)	1(4)
3	3(14)	2(7)
4	10(45)	14(48)
5	9(41)	12(41)
SAPS II (mean ± SD)	57 ± 10	52 ± 9
Aneurysm location		
VB system	0(0)	1(4)
Ca + ACA	12(55)	15(52)
ICA + PCA	7(31)	10(34)
MCA	3(14)	3(10)

Table 1 Baseline clinical characteristics by 1-year outcome

	GOS 1–3 (n = 22)	GOS 4–5 (n = 29)
Number of aneurysms per patient		
1	19(86)	22(76)
2	1(5)	2(7)
3	2(9)	3(10)
≥4	0(0)	2(7)
Acute hydrocephalus	11(33)	22(67)
Initial seizures	5(23)	11(38)
Baseline S100B, µg/l (mean ± SD)	0.46 ± 0.35	0.46 ± 0.54
Mean 8-day S100B, µg/l (mean ± SD)*	0.63 ± 0.46	0.23 ± 0.16
Baseline troponin > 0.15 µg/l	14(64)	19(66)
Baseline troponin, µg/l		
Median	1.20	0.27
Mean ± SD	9.50 ± 32.8	1.53 ± 2.68
Neurogenic lung edema at admission	7(32)	5(17)
Time from bleeding to treatment, days		
0	12(55)	10(34)
1	7(31)	9(32)
≥2	3(14)	10(34)

Conclusions Patients in poor clinical condition after SAH have more than a 50:50 chance of a favorable outcome after 1 year. High mean 8-day S100B value and persistent intracranial hypertension predict a poor outcome (GOS 1–3) after 1 year.

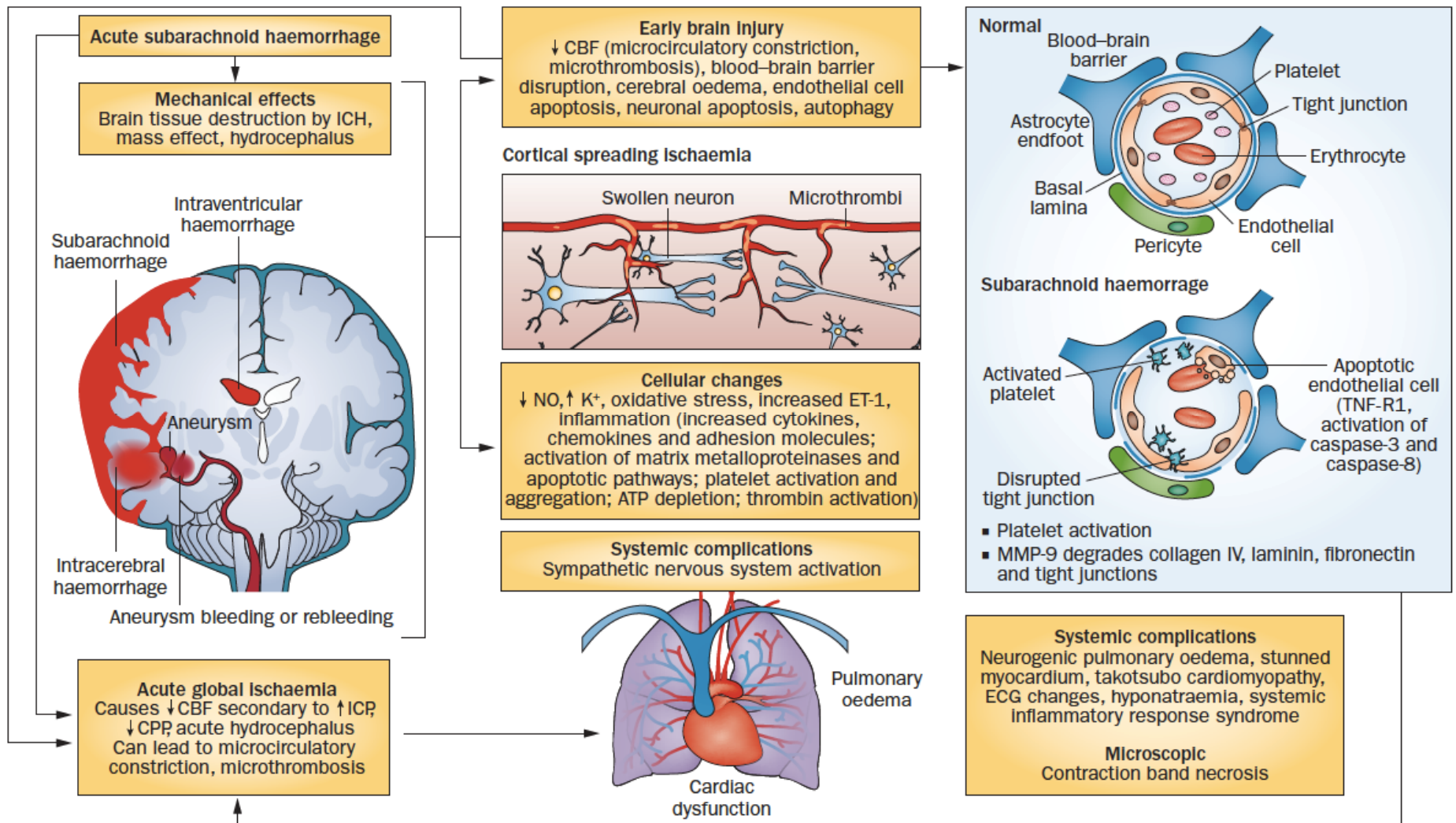
	Rebleeding	Vasospasm	Perihemorrhage ischemia	Ischemia resulting from aneurysm treatment	Increase intracranial pressure	Microcirculatory spasm	Microembolism	Blood-brain barrier dysfunction	Cortical spreading ischemia
0 min	initial event								
60 min	High probability	High probability	High probability		High probability				
2-12 h	High probability	Considerable probability	High probability	High probability	High probability	High probability	High probability	High probability	
24-48 h	High probability	Low probability	High probability	High probability	Moderate probability	Considerable probability	Considerable probability	High probability	Low probability
3-7 days	Considerable probability	Considerable probability	Low probability	Low probability	Considerable probability			Considerable probability	High probability
7-9 days	Considerable probability	High probability	Low probability	Low probability	High probability			Considerable probability	High probability
10-14 days	Moderate probability	Considerable probability	Low probability	Low probability	Considerable probability			Moderate probability	Low probability
2-4 weeks	Moderate probability	Low probability	Low probability	Low probability	Considerable probability			Moderate probability	
4-8 weeks	Moderate probability	Low probability	Low probability	Low probability	High probability			Low probability	

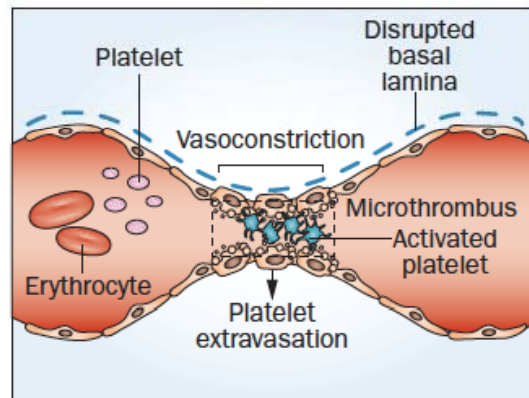
Delayed neurological deterioration after subarachnoid haemorrhage

R. Loch Macdonald

Abstract | Subarachnoid haemorrhage (SAH) causes early brain injury (EBI) that is mediated by effects of transient cerebral ischaemia during bleeding plus effects of the subarachnoid blood. Secondary effects of SAH include increased intracranial pressure, destruction of brain tissue by intracerebral haemorrhage, brain shift, and herniation, all of which contribute to pathology. Many patients survive these phenomena, but deteriorate days later from delayed cerebral ischaemia (DCI), which causes poor outcome or death in up to 30% of patients with SAH. DCI is thought to be caused by the combined effects of angiographic vasospasm, arteriolar constriction and thrombosis, cortical spreading ischaemia, and processes triggered by EBI. Treatment for DCI includes prophylactic administration of nimodipine, and current neurointensive care. Prompt recognition of DCI and immediate treatment by means of induced hypertension and balloon or pharmacological angioplasty are considered important by many physicians, although the evidence to support such approaches is limited. This Review summarizes the pathophysiology of DCI after SAH and discusses established treatments for this condition. Novel strategies—including drugs such as statins, sodium nitrite, albumin, dantrolene, cilostazol, and intracranial delivery of nimodipine or magnesium—are also discussed.

Macdonald, R. L. *Nat. Rev. Neurol.* **10**, 44–58 (2014); published online 10 December 2013; corrected online 17 December 2013;
doi:10.1038/nrneurol.2013.246





Microcirculatory
constriction
Microthrombosis

Angiographic vasospasm
 ↑ Haemoglobin, oxidative stress and inflammation lead to endothelial cell and perivascular nerve injury, leading to
 ↑ NO, endothelin, leading to membrane depolarization, open voltage-gated calcium channels and activation of TRP channels

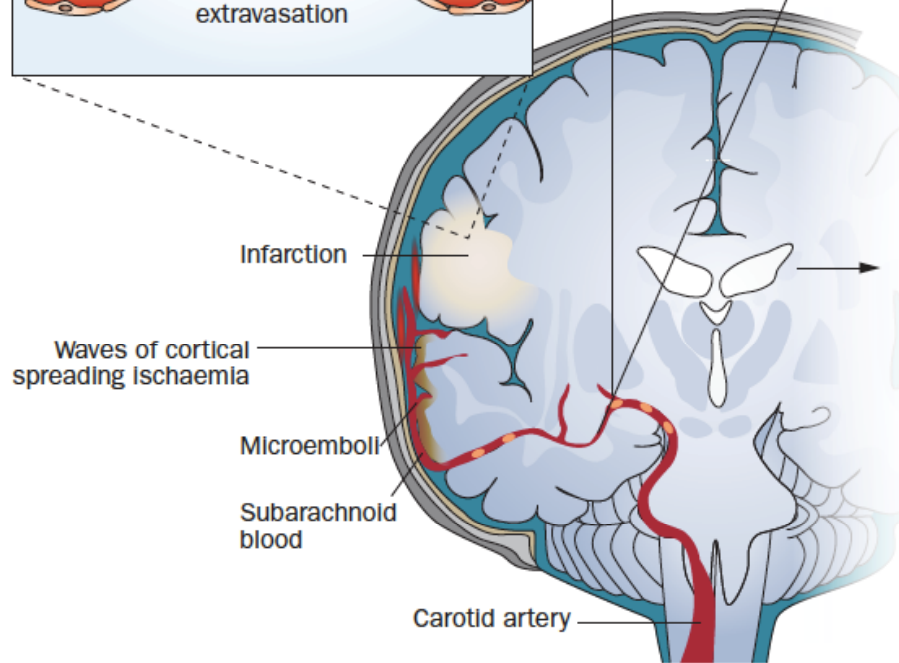
Cortical spreading ischaemia

This diagram shows a cross-section of the cortex with a spreading wave of ischaemia. It features a swollen neuron and microthrombi in the blood vessels. Labels include: Swollen neuron and Microthrombi.

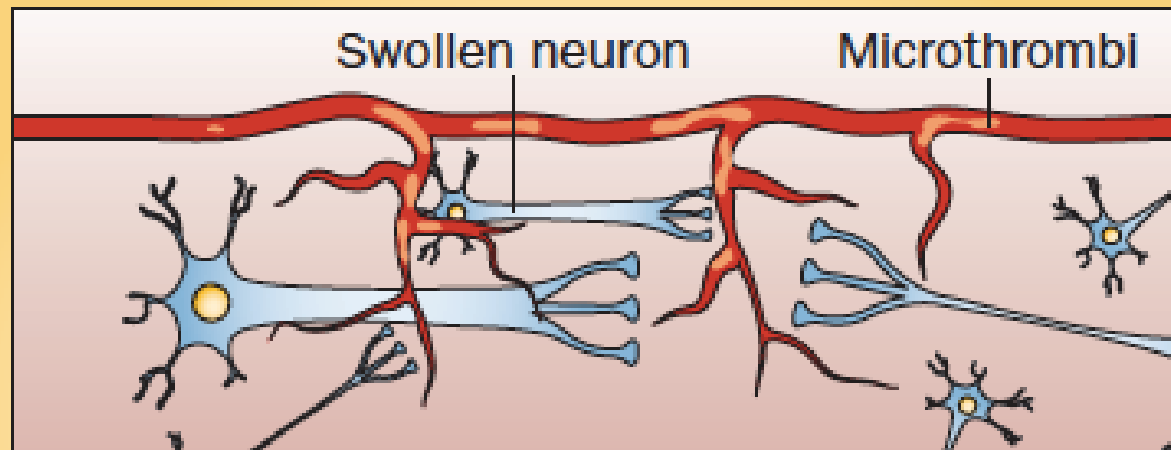
Spreading depressions, neuronal swelling, distorted dendritic spines, neuronal depolarization, glutamate release and depression, associated with pathological spreading wave of vasoconstriction, caused by ↑ K, ↑ haemoglobin and inhibition of NO synthase that are present after SAH and possibly mediated by increased astrocyte endfeet calcium that activates large-conductance calcium-activated potassium channels

Delayed neurological complications
 Seizures, infection, complications of aneurysm repair, aneurysm rebleeding, hydrocephalus, brain swelling, intracranial haematoma, increased ICP, reduced CPP

Delayed systemic complications
 Infection, fever, pulmonary oedema, cardiac failure, organ failure, drug adverse effects, hyponatraemia, hypercarbia, hypoglycaemia, low haemoglobin, systemic inflammatory response syndrome



Cortical spreading Ischaemia



Spreading depressions, neuronal swelling, distorted dendritic spines, neuronal depolarization, glutamate release and depression, associated with pathological spreading wave of vasoconstriction, caused by $\uparrow K$, \uparrow haemoglobin and inhibition of NO synthase that are present after SAH and possibly mediated by increased astrocyte endfeet calcium that activates large-conductance calcium-activated potassium channels

Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations

Jens P. Dreier,^{1,*} Johannes Woitzik,^{5,*} Martin Fabricius,^{7,*} Robin Bhatia,⁹ Sebastian Major,¹ Christoph Drenckhahn,¹ Thomas-Nicolas Lehmann,² Asita Sarrafzadeh,² Lisette Willumsen,⁸ Jed A. Hartings,¹⁰ Oliver W. Sakowitz,⁶ Jörg H. Seemann,³ Anja Thieme,⁴ Martin Lauritzen⁷ and Anthony J. Strong⁹

Progressive ischaemic damage in animals is associated with spreading mass depolarizations of neurons and astrocytes, detected as spreading negative slow voltage variations. Speculation on whether spreading depolarizations occur in human ischaemic stroke has continued for the past 60 years. Therefore, we performed a prospective multicentre study assessing incidence and timing of spreading depolarizations and delayed ischaemic neurological deficit (DIND) in patients with major subarachnoid haemorrhage (SAH) requiring aneurysm surgery. Spreading depolarizations were recorded by electrocorticography with a subdural electrode strip placed on cerebral cortex for up to 10 days. A total of 2110 h recording time was analysed. The clinical state was monitored every 6 h. Delayed infarcts after SAH were verified by serial CT scans and/or MRI. Electrocorticography revealed 298 spreading depolarizations in 13 of the 18 patients (72%). A clinical DIND was observed in seven patients 7.8 days (7.3, 8.2) after SAH. DIND was time-locked to a sequence of recurrent spreading depolarizations in every single case (positive and negative predictive values: 86 and 100%, respectively). In four patients delayed infarcts developed in the recording area. As in the ischaemic penumbra of animals, delayed infarction was preceded by progressive prolongation of the electrocorticographic depression periods associated with spreading depolarizations to >60 min in each case. This study demonstrates that spreading depolarizations have a high incidence in major SAH and occur in ischaemic stroke. Repeated spreading depolarizations with prolonged depression periods are an early indicator of delayed ischaemic brain damage after SAH. In view of experimental evidence and the present clinical results, we suggest that spreading depolarizations with prolonged depressions are a promising target for treatment development in SAH and ischaemic stroke.

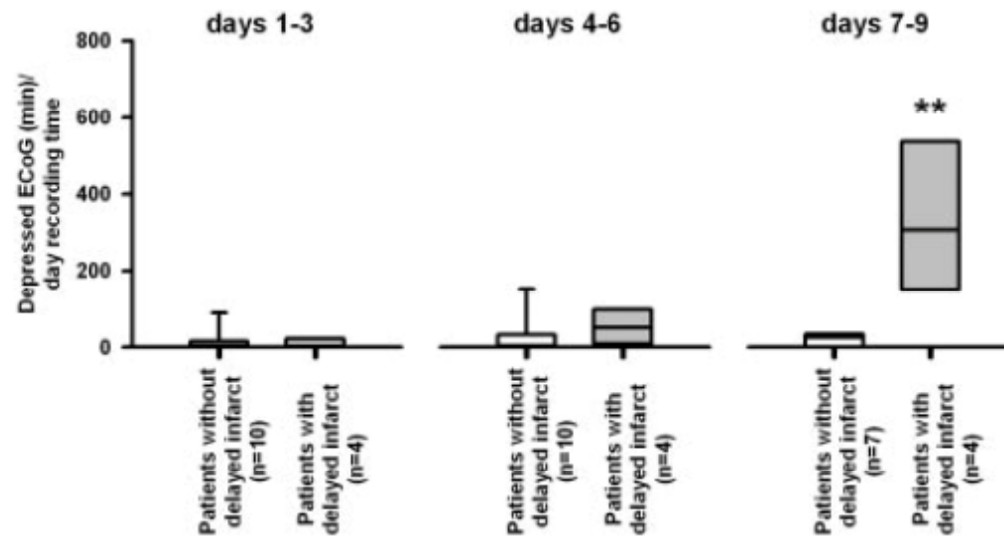


Fig. 7 Delayed brain infarcts are associated with prolonged electrocorticographic depression. Patients with delayed CT-/MRI-proven infarcts showed significantly prolonged electrocorticographic (ECoG) depression periods during infarct development at Days 7–9 after SAH (** $P = 0.006$), whereas early after SAH, no significant difference was found between patients who later developed a delayed infarct and those who did not. Prolongation of the recovery phase of spreading depolarization is one of the electrocorticographic hallmarks of penumbral spreading depolarizations in animals.

The Burden of the Systemic Inflammatory Response Predicts Vasospasm and Outcome after Subarachnoid Hemorrhage

Rajat Dhar · Michael N. Diringer

Abstract

Introduction Subarachnoid hemorrhage (SAH) can trigger immune activation sufficient to induce the systemic inflammatory response syndrome (SIRS). This may promote both extra-cerebral organ dysfunction and delayed cerebral ischemia, contributing to worse outcome. We ascertained the frequency and predictors of SIRS after spontaneous SAH, and determined whether degree of early systemic inflammation predicted the occurrence of vasospasm and clinical outcome.

Methods Retrospective analysis of prospectively collected data on 276 consecutive patients admitted to a neurosciences intensive care unit with acute, non-traumatic SAH between 2002 and 2005. A daily SIRS score was derived by summing the number of variables meeting standard criteria (HR >90, RR >20, Temperature >38°C, or <36°C, WBC count <4,000 or >12,000). SIRS was considered present if two or more criteria were met, while SIRS burden over the first four days was calculated by averaging daily scores. Regression modeling was used to determine the relationship among SIRS burden (after controlling for confounders including infection, surgery, and corticosteroid use), symptomatic vasospasm, and outcome, determined by hospital disposition.

Results SIRS was present in over half the patients on admission and developed in 85% within the first four days. Factors associated with SIRS included poor clinical grade,

thick cisternal blood, larger aneurysm size, higher admission blood pressure, and surgery for aneurysm clipping. Higher SIRS burden was independently associated with death or discharge to nursing home (OR 2.20/point, 95% CI 1.27–3.81). All of those developing clinical vasospasm had evidence of SIRS, with greater SIRS burden predicting increased risk for delayed ischemic neurological deficits (OR 1.77/point, 95% CI 1.12–2.80).

Conclusions Systemic inflammatory activation is common after SAH even in the absence of infection; it is more frequent in those with more severe hemorrhage and in those who undergo surgical clipping. Higher burden of SIRS in the initial four days independently predicts symptomatic vasospasm and is associated with worse outcome.

Keywords Subarachnoid hemorrhage · Inflammation · Vasospasm · Sepsis syndrome

Introduction

Activation of the systemic immune response after subarachnoid hemorrhage (SAH) is frequently manifested by elevated levels of circulating cytokines, the major effectors of systemic inflammation [1]. The clinical manifestations of this process have been termed the *Systemic Inflammatory Response Syndrome* (SIRS) a constellation of findings

The Burden of the Systemic Inflammatory Response Predicts Vasospasm and Outcome after Subarachnoid Hemorrhage

Rajat Dhar · Michael N. Diringer

Conclusions Systemic inflammatory activation is common after SAH even in the absence of infection; it is more frequent in those with more severe hemorrhage and in those who undergo surgical clipping. Higher burden of SIRS in the initial four days independently predicts symptomatic vasospasm and is associated with worse outcome.

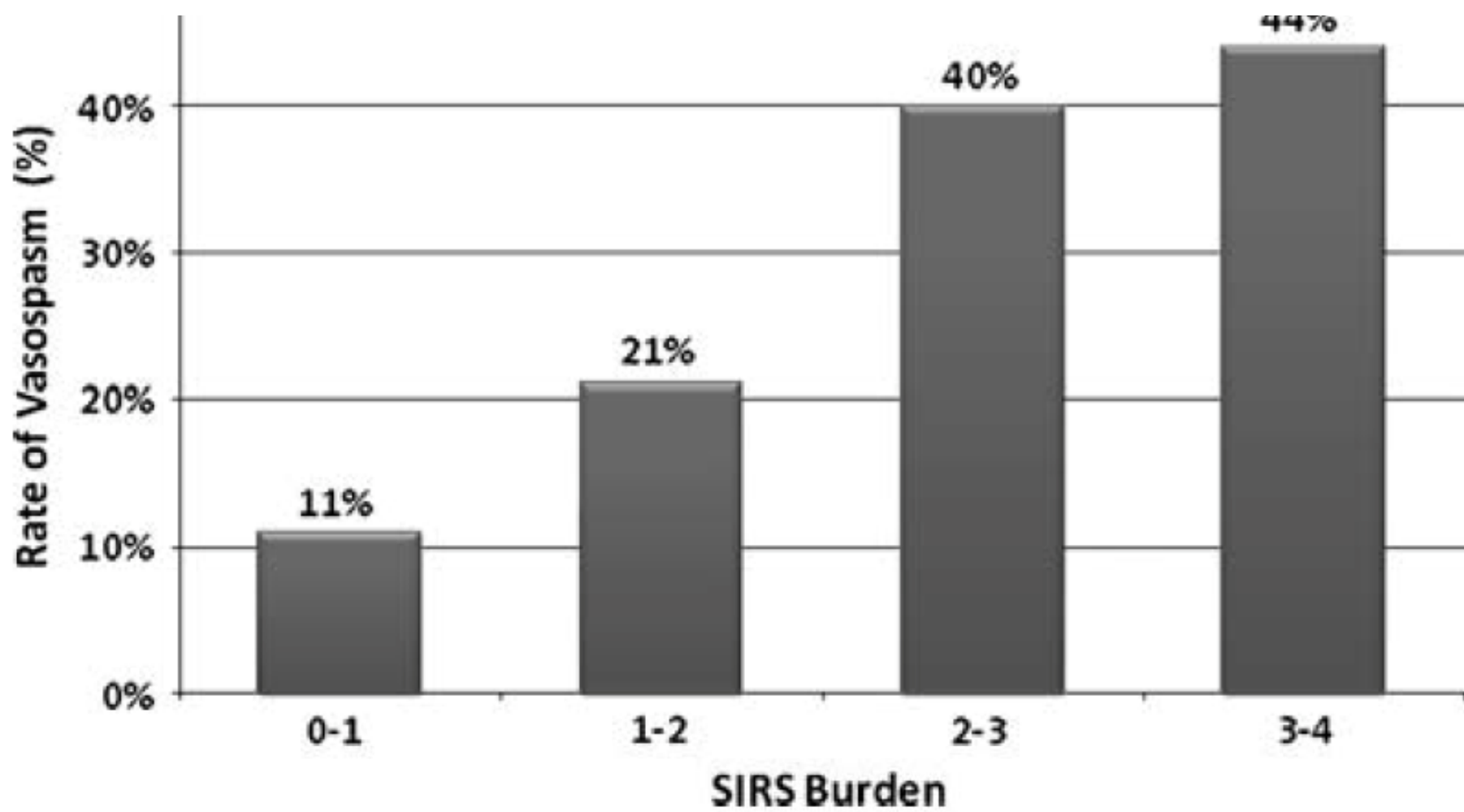


Fig. 1. Rate of Vasospasm by SIRS Burden in Patients with Traumatic Brain Injury

The Utility of Serum Procalcitonin in Distinguishing Systemic Inflammatory Response Syndrome from Infection After Aneurysmal Subarachnoid Hemorrhage

Emir Festic · Jason Siegel · Matthew Stritt ·
William D. Freeman

Conclusions Procalcitonin of 0.2 ng/mL or greater was demonstrated to be very specific for sepsis among patients with aSAH. Further studies should validate this result and establish its clinical applicability.

Table 4 Predictive characteristics of PCT measurements

All PCT measurements	Odds ratio (95 % CI)	<i>p</i> value	ROC
All infections	25.2 (2.7, 233)	0.001	0.74
Major infections only	33.3 (4.3, 261)	0.001	0.96
Minor infections only	4.1 (0.8, 22.0)	0.11	0.60
<i>Baseline PCT</i>			
All infections	35 (2.2, 571)	0.022	0.85
Major infections only	72 (3.2, 1,624)	0.011	0.99
Minor infections only	0	1	0.59
<i>Repeat PCT for SIRS</i>			
All infections	0	0.25	0.69
Major infections only	14 (0.8, 235)	0.097	0.92
Minor infections only	3.4 (0.29, 41)	0.58	0.46

A comparison of 3 radiographic scales for the prediction of delayed ischemia and prognosis following subarachnoid hemorrhage

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Conclusions. Although the modified Fisher and Claassen scales have yet to be prospectively validated, the authors' findings suggest that the clinical performance of these systems is superior to that of the Fisher scale.
(DOI: 10.3171/JNS/2008/109/8/0199)

Hyperglycemia in Patients Undergoing Cerebral Aneurysm Surgery: Its Association With Long-term Gross Neurologic and Neuropsychological Function

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CONCLUSION: In patients at high risk for ischemic brain injury, intraoperative hyperglycemia, of a magnitude commonly encountered clinically, was associated with long-term changes in cognition and gross neurologic function.

Mayo Clin Proc. 2008;83(4):406-417

Strict Glucose Control Does Not Affect Mortality after Aneurysmal Subarachnoid Hemorrhage

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Conclusions: The initiation of a tight glucose control regimen lowered average glucose levels but had no effect on overall in-hospital mortality.

Table 2. Multivariate Comparison of Factors Related to Mortality

	Odds Ratio	5% Confidence Lower	95% Confidence Upper	<i>P</i> Value
Significant predictors				
Other bleed (IVH, IPH)	2.658	1.603	4.407	< 0.001
Moderate hypoglycemia	3.818	1.396	10.441	0.009
Average glucose	1.045	1.034	1.056	< 0.001
Length of stay	0.876	0.840	0.915	< 0.001
Other factors				
Male	0.974	0.554	1.711	0.926
Caucasian	1.327	0.680	2.590	0.407
Multiple aneurysms	0.993	0.450	2.192	0.987
Craniotomy	0.817	0.469	1.425	0.477
Posterior circulation	1.398	0.743	2.628	0.299
Admission glucose	1.004	1.000	1.009	0.064
Vasospasm	1.397	0.754	2.588	0.288
Protocol	1.602	0.868	2.956	0.132

Table 3. Multivariate Comparison of Factors Related to Vasospasm

	Odds Ratio	5% Confidence Lower	95% Confidence Upper	<i>P</i> Value
Significant Predictors				
Craniotomy	1.757	1.195	2.582	0.004
Other bleed (IVH, IPH)	1.541	1.084	2.190	0.016
Average glucose	0.984	0.972	0.995	0.004
Length of stay	1.057	1.039	1.076	< 0.001
Protocol	1.784	1.220	2.610	0.003
Other factors				
Male	0.775	0.535	1.123	0.178
Caucasian	1.180	0.786	1.774	0.425
Multiple aneurysms	1.128	0.700	1.816	0.621
Moderate hypoglycemia	1.396	0.666	2.924	0.377
Admission glucose	1.001	0.998	1.005	0.472
Death	1.386	0.716	2.683	0.333

Neurosurgical Patients

Federico Bilotta, M.D., Ph.D.,* Remo Caramia, M.D.,† Francesca P. Paoloni, B.Sci.,‡ Roberto Delfini, M.D.,§ Giovanni Rosa, M.D.||

Results: Hypoglycemia episodes were more frequent in patients receiving intensive insulin therapy, median (min–max): 8 (0–23) *versus* 3 (0–4); $P < 0.0001$. The length of stay in the ICU was shorter (6 *vs.* 8 days; $P = 0.0001$), and the infection rate was lower (25.7% *vs.* 39.3%; $P = 0.0018$). Glasgow outcome scale score and overall survival at 6 months were similar in the two groups.

Conclusions: Intensive insulin therapy in patients admitted to a postoperative neurosurgical ICU after brain surgery is associated with iatrogenic hypoglycemia, but it can also reduce the infection rate and shorten the ICU stay.

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CLINICAL STUDIES

TRANSCRANIAL DOPPLER FOR PREDICTING DELAYED CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

OBJECTIVE: Transcranial Doppler (TCD) is widely used to monitor the temporal course of vasospasm after subarachnoid hemorrhage (SAH), but its ability to predict clinical deterioration or infarction from delayed cerebral ischemia (DCI) remains controversial. We sought to determine the prognostic utility of serial TCD examination after SAH.

METHODS: We analyzed 1877 TCD examinations in 441 aneurysmal SAH patients within 14 days of onset. The highest mean blood flow velocity (mBFV) value in any vessel before DCI onset was recorded. DCI was defined as clinical deterioration or computed tomographic evidence of infarction caused by vasospasm, with adjudication by consensus of the study team. Logistic regression was used to calculate adjusted odds ratios for DCI risk after controlling for other risk factors.

RESULTS: DCI occurred in 21% of patients ($n = 92$). Multivariate predictors of DCI included modified Fisher computed tomographic score ($P = 0.001$), poor clinical grade ($P = 0.04$), and female sex ($P = 0.008$). After controlling for these variables, all TCD mBFV thresholds between 120 and 180 cm/s added a modest degree of incremental predictive value for DCI at nearly all time points, with maximal sensitivity by SAH day 8. However, the sensitivity of any mBFV more than 120 cm/s for subsequent DCI was only 63%, with a positive predictive value of 22% among patients with Hunt and Hess grades I to III and 36% in patients with Hunt and Hess grades IV and V. Positive predictive value was only slightly higher if mBFV exceeded 180 cm/s.

CONCLUSION: Increased TCD flow velocities imply only a mild incremental risk of DCI after SAH, with maximal sensitivity by day 8. Nearly 40% of patients with DCI never attained an mBFV more than 120 cm/s during the course of monitoring. Given the poor overall sensitivity of TCD, improved methods for identifying patients at high risk for DCI after SAH are needed.

Continuous EEG Monitoring in Patients With Subarachnoid Hemorrhage

Jan Claassen,*† Stephan A. Mayer,† and Lawrence J. Hirsch*

Abstract: Patients with subarachnoid hemorrhage (SAH) are at risk for seizures and delayed cerebral ischemia, both of which can be detected with continuous EEG monitoring (cEEG). Ischemia can be detected with EEG at a reversible stage. CEEG may be most useful in patients with poor grade SAH, as the neurological exam is of limited utility in these stuporous or comatose patients. Seizures have been detected in 19% of SAH patients undergoing cEEG, with the vast majority (95%) of these seizures being nonconvulsive and without any detectable clinical correlate. Applying quantitative analysis to the cEEG (relative alpha variability, post-stimulation alpha/delta ratio) allows reliable detection of ischemia from vasospasm, with EEG changes often preceding changes in the clinical exam and other non-continuous monitoring techniques by up to two days. In patients at risk for developing vasospasm, cEEG monitoring, preferably with quantitative EEG analysis, should be started as early as possible and carried out for up to 14 days after the SAH. CEEG findings may lead to therapeutic (e.g., antiepileptic medication, hypertensive therapy, angioplasty) or additional diagnostic interventions such as angiography, CT or MRI.

Key Words: Continuous EEG monitoring, Subarachnoid hemorrhage, Nonconvulsive status epilepticus, Neurological intensive care unit, Vasospasm ischemia detection, Quantitative EEG.

(*J Clin Neurophysiol* 2005;22: 92–98)

patients who often have impaired consciousness to further improve morbidity of this devastating disease. CEEG has the potential to help monitor the clinical state of obtunded patients, detect delayed cerebral ischemia (DCI) from vasospasm, and unmask nonconvulsive status epilepticus (NCSE) (Table 1). However, CEEG monitoring is labor intensive in that EEG technicians are constantly needed to maintain EEG leads to ensure a high-quality recording and electroencephalographers have to review large amounts of EEG data. Furthermore, EEG leads may interfere with imaging studies such as computed tomography (CT) or MRI, which are frequently needed in patients after SAH. This article summarizes the data available on the preliminary experience of CEEG monitoring in SAH patients. For a detailed discussion on the drawbacks and limitations of CEEG monitoring in general, please refer to the article by Hirsch (2004) in this issue of the *Journal of Clinical Neurophysiology*.

DETECTING ICTAL ACTIVITY

Seizures are common in all types of acute brain injury. Older studies have reported generalized tonic clonic seizures at the onset of bleeding in 6% to 25% of SAH patients (Butzkueven et al., 2000; Hart et al., 1981; Rhoney et al.,

Radiographic diagnosis of vasospasm

- Only half of patients with angiographic vasospasm have clinical findings related to the arteries involved
- DSA is currently the standard method
 - Good definition of large and medium vessels
 - Allows angioplasty and intra-arterial therapy
- CTA for the diagnosis of vasospasm is increasing in use
 - Distal spasm may be more difficult to detect by CTA
- What about ‘microvasospasm?’

Critical care issues: vasospasm and delayed ischemic damage

- Prophylaxis
 - clot removal
 - volume repletion
 - prophylactic volume expansion not useful
 - nimodipine 60 mg q4h x 14 days
 - relative risk of stroke reduced 0.69 (0.58-0.84)
 - Probably neuroprotection rather than a vascular effect
 - nicardipine 0.075 mg/kg/hr is probably equivalent

NEWTON: Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage

Daniel Hänggi · Nima Etmann · R. Loch Macdonald · Hans Jakob Steiger ·
Stephan A. Mayer · François Aldrich · Michael N. Düringer · Brian L. Hoh ·
J. Mocco · Poul Strange · Herbert J. Faleck · Michael Miller

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Abstract

Background Aneurysmal subarachnoid hemorrhage (aSAH) is associated with high morbidity and mortality. EG-1962 is a sustained-release microparticle formulation of nimodipine that has shown preclinical efficacy when administered intraventricularly or intracisternally to dogs with SAH, without evidence of toxicity at doses in the anticipated therapeutic range. Thus, we propose to administer EG-1962 to humans in order to assess safety and tolerability and determine a dose to investigate efficacy in subsequent clinical studies.

For the NEWTON Investigators.

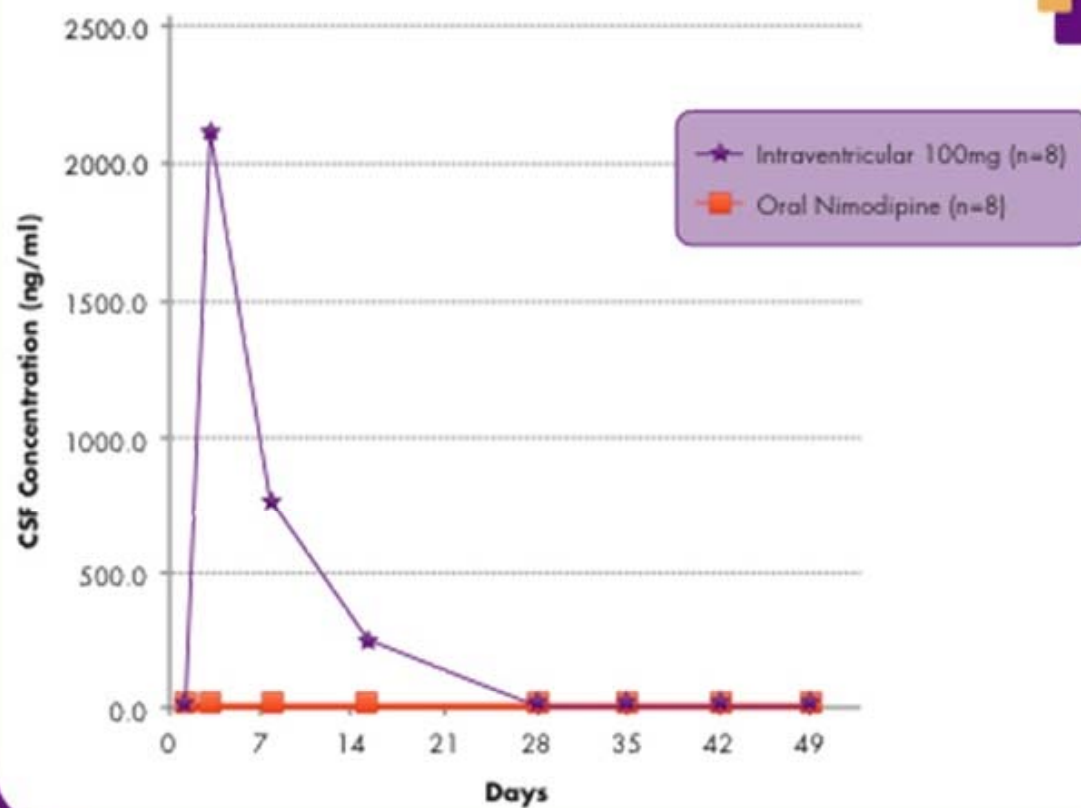
Trial registration: www.clinicaltrials.gov Identifier: NCT01893190

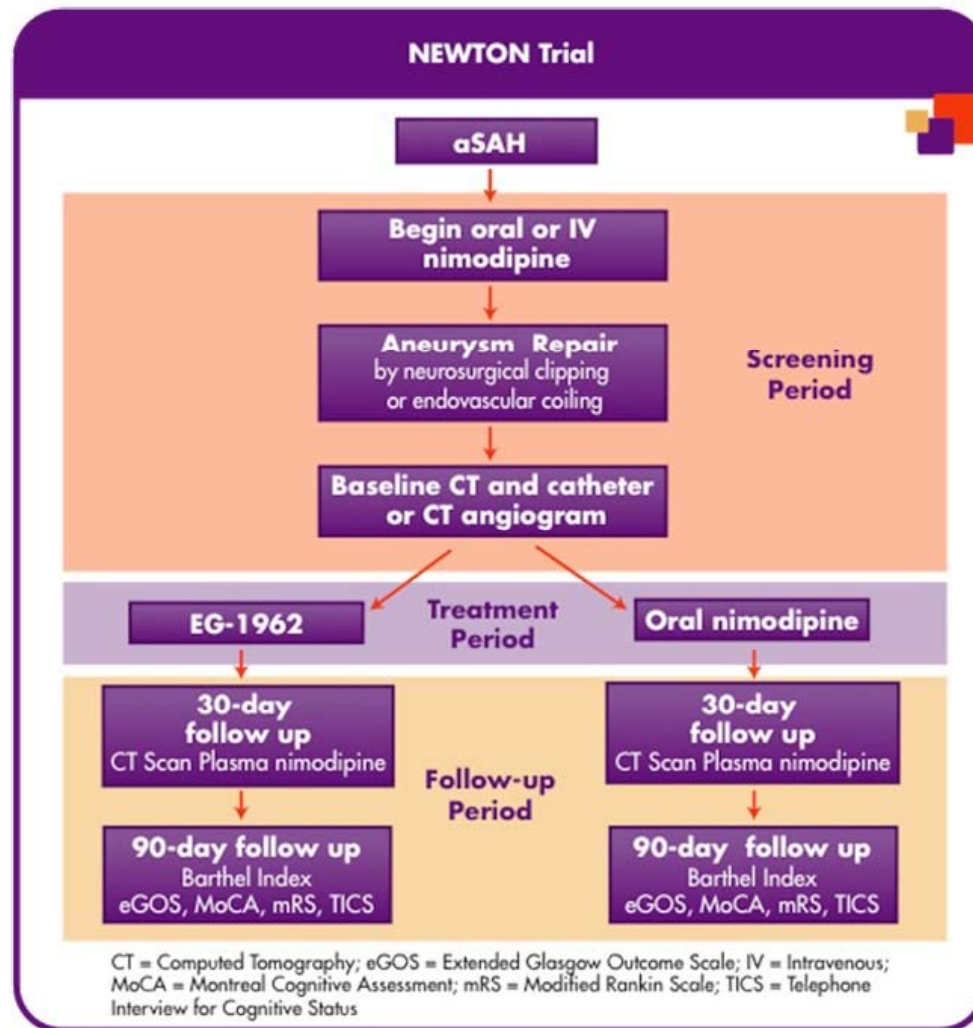
Electronic supplementary material The online version of this article (doi:10.1007/s12028-015-0112-2) contains supplementary material, which is available to authorized users.

Methods We describe a Phase 1/2a multicenter, controlled, randomized, open-label, dose escalation study to determine the maximum tolerated dose (MTD) and assess the safety and tolerability of EG-1962 in patients with aSAH. The study will comprise two parts: a dose escalation period (Part 1) to determine the MTD of EG-1962 and a treatment period (Part 2) to assess the safety and tolerability of the selected dose of EG-1962. Patients with a ruptured saccular aneurysm treated by neurosurgical clipping or endovascular coiling will be considered for enrollment. Patients will be randomized to receive either EG-1962 (study drug: nimodipine microparticles) or oral nimodipine in the approved dose regimen (active control) within 60 h of aSAH.

Results Primary objectives are to determine the MTD and the safety and tolerability of the selected dose of intraventricular EG-1962 as compared to enteral nimodipine. The secondary objective is to determine release and distribution by measuring plasma and CSF concentrations of

Intraventricular Delivery CSF Concentration





STATIN USE WAS NOT ASSOCIATED WITH LESS VASOSPASM OR IMPROVED OUTCOME AFTER SUBARACHNOID HEMORRHAGE

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OBJECTIVE: The development of delayed ischemia caused by cerebral vasospasm remains a common cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage. Preliminary studies suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may decrease the risk of vasospasm, but additional study is required.

METHODS: Beginning in May 2006, our treatment protocol for patients presenting with subarachnoid hemorrhage was altered to routinely include the use of 80 mg of simvastatin per day for 14 days. Before this time, only patients with other indications for statins were treated. The charts of 203 consecutive patients over a period of 27 months were retrospectively reviewed, and 150 patients were included in the analysis, of whom 71 patients received statins. These patients were compared with 79 untreated patients to determine whether or not the use of statins was associated with a reduction in the occurrence of vasospasm, delayed infarction, or poor outcome (death, vegetative state, or severe disability).

RESULTS: Patients who were treated with statins and those who were not had similar baseline characteristics, although more patients in the former group were managed with endovascular coil embolization. There were no statistically significant differences in the proportion of patients developing at least moderate radiographic vasospasm (41% with statins versus 42% without, $P = 0.91$), symptomatic vasospasm (32% with statins versus 25% without, $P = 0.34$), delayed infarction (23% with statins versus 28% without, $P = 0.46$), or poor outcome (39% with statins versus 35% without, $P = 0.61$). After adjustment for differences in baseline characteristics, including the method of aneurysm treatment, statins were still not significantly protective.

CONCLUSION: The addition of statins to standard care was not associated with any reduction in the development of vasospasm or improvement in outcomes after aneurysmal subarachnoid hemorrhage. If there is a benefit to statin use, it may be smaller than suggested by previous studies. However, further randomized controlled trials are awaited.

KEY WORDS: Cerebral aneurysm, Simvastatin, Statin, Subarachnoid hemorrhage, Transcranial Doppler, Vasospasm



Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial

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Summary

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This online publication has been corrected.

The corrected version first appeared at *thelancet.com/neurology* on June 16, 2014

See [Comment](#) page 639

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Background The benefit of statins in patients with acute aneurysmal subarachnoid haemorrhage is unclear. We aimed to determine whether simvastatin 40 mg could improve the long-term outcome in patients with this disorder.

Methods In this international, multicentre, randomised, double-blind trial, we enrolled patients aged 18–65 years with confirmatory evidence of an aneurysmal subarachnoid haemorrhage and presenting less than 96 h from ictus from 35 acute neurosurgical centres in nine countries. Patients were randomly allocated (1:1) to receive either simvastatin 40 mg or placebo once a day for up to 21 days. We used a computer-generated randomisation code to randomise patients in every centre by blocks of ten (five simvastatin, five placebo). Participants and investigators were masked to treatment assignment. The primary outcome was the distribution of modified Rankin Scale (mRS) score obtained by questionnaire at 6 months. Analyses were done on the intention-to-treat population. This trial has been completed and is registered with Current Controlled Trials, number ISRCTN75948817.

Findings Between Jan 6, 2007, and Feb 1, 2013, apart from the period between May 15, 2009, and Feb 8, 2011, when recruitment was on hold, 803 patients were randomly assigned to receive either simvastatin 40 mg (n=391) or placebo (n=412). All patients were included in the intention-to-treat population. 782 (97%) patients had outcome data recorded at 6 months, of whom 560 (72%) were classed as having a favourable outcome, mRS 0–2 (271 patients in the simvastatin group vs 289 in the placebo group). The primary ordinal analysis of the mRS, adjusted for age and World Federation of Neurological Surgeons grade on admission, gave a common odds ratio (OR) of 0·97, 95% CI 0·75–1·25; $p=0\cdot803$. At 6 months, we recorded 37 (10%) deaths in the simvastatin group compared with 35 (9%) in the placebo group (log-rank $p=0\cdot592$). 70 (18%) serious adverse events were reported in the simvastatin group compared with 74 (18%) in the placebo group. No suspected unexpected serious adverse reactions were reported.

Interpretation The STASH trial did not detect any benefit in the use of simvastatin for long-term or short-term outcome in patients with aneurysmal subarachnoid haemorrhage. Despite demonstrating no safety concerns, we conclude that patients with subarachnoid haemorrhage should not be treated routinely with simvastatin during the acute stages.

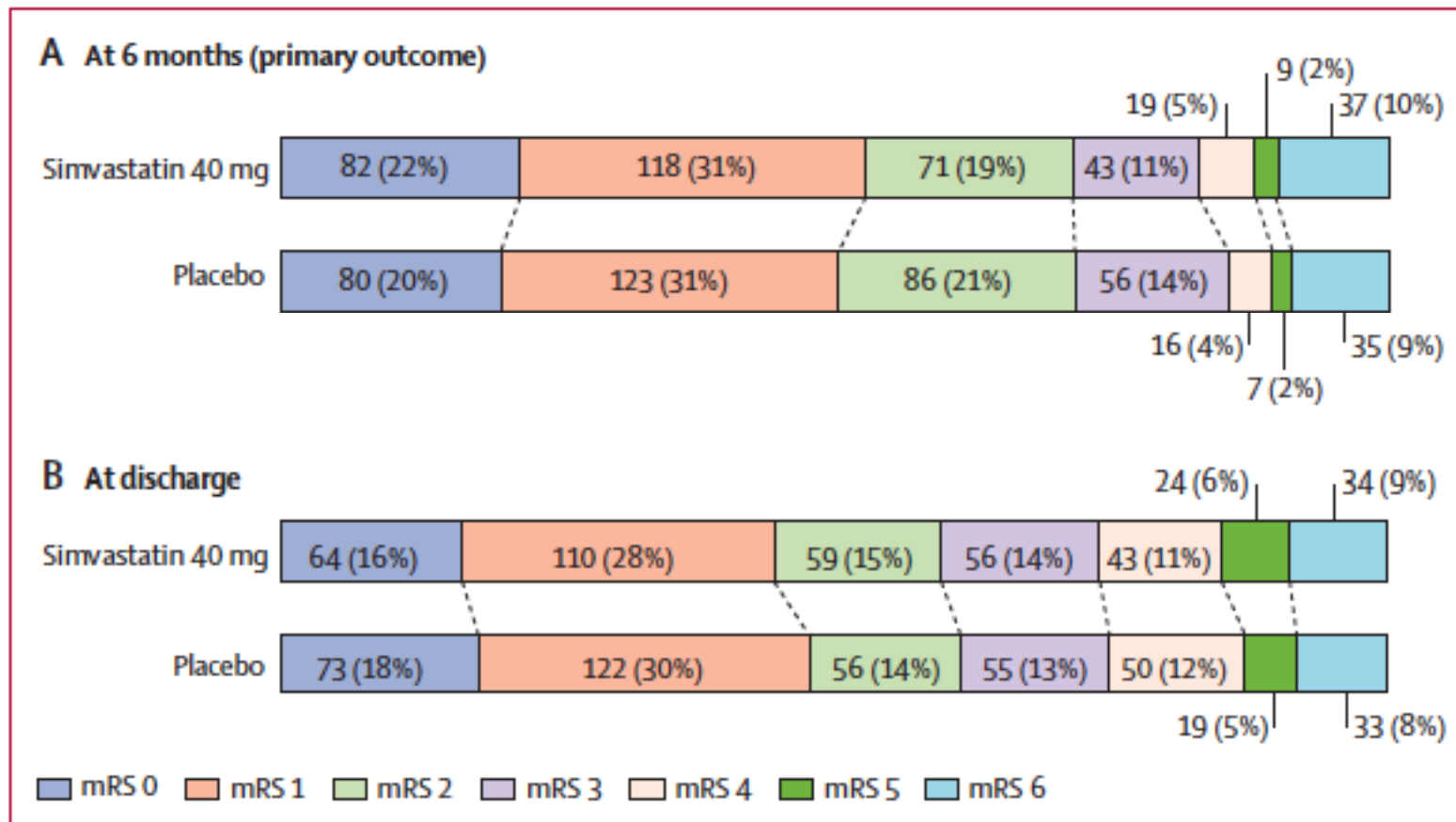


Figure 2: Distribution of scores on the mRS scale

(A) At 6 months. (B) At discharge. mRS=modified Rankin Scale.

Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage

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Objective: Patients with subarachnoid hemorrhage (SAH) frequently develop delayed cerebral ischemia and may be especially vulnerable to the effects of anemia. However, the potentially harmful effects of allogeneic red blood cells are increasingly being recognized. The optimal transfusion threshold is unknown, but current practice most often uses a liberal approach. We assessed the association between anemia or transfusion and subsequent adverse outcomes.

Design: Retrospective cohort study.

Setting: Neuroscience intensive care unit of a university hospital.

Patients: A total of 245 consecutive patients with aneurysmal SAH.

Interventions: None.

Measurements: Logistic regression models were used to adjust for baseline differences in age, severity of neurologic impairment, and amount of blood on computed tomography. Patients were dichotomized based on whether symptomatic vasospasm was diagnosed.

Main Results: Individually, anemia (nadir hemoglobin <10 g/dL) and the use of transfusions were both associated with the combined outcome of death, severe disability, or delayed infarction (odds ratio [OR] for anemia, 2.7; 95% confidence interval [CI] 1.5–5; $p < .01$; OR for transfusion, 4.8; 95% CI, 2.5–9.1; $p < .01$). When both variables were together introduced into a logistic regression model, only transfusion remained significantly predictive (OR, 4.3; 95% CI, 1.5–9.3; $p < .01$). The relationship between anemia and adverse outcomes was stronger among patients diagnosed with vasospasm, whereas for transfusion, it was stronger among patients without vasospasm. Transfusion also was associated with the development of nosocomial infections (OR, 3.2; 95% CI, 1.7–5.5; $p < .01$). There was no statistically significant difference in complications based on the duration of blood storage before transfusion.

Conclusions: Although anemia is predictive of adverse outcomes in patients with SAH, this observation cannot be considered justification for a liberal transfusion strategy. Appropriate transfusion thresholds may vary depending on the presence or absence of clinical vasospasm. Randomized trials that compare liberal and restrictive transfusion strategies in patients with SAH are needed. (Crit Care Med 2008; 36:2070–2075)

KEY WORDS: anemia; critical care; delayed infarction; intensive care; nosocomial infection; subarachnoid hemorrhage; transfusion; vasospasm

Relationship Between Transfusion and Secondary Outcomes: Vasospasm, ARDS, Infection

Of the 64 patients with clinical vasospasm, 46 (72%) received at least 1 unit of RBCs. However, in the majority of cases (29/46), the first transfusion occurred after the diagnosis of vasospasm was established.

Effect of Hypervolemic Therapy on Cerebral Blood Flow After Subarachnoid Hemorrhage

A Randomized Controlled Trial

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Eric C. Raps, MD†; Robert A. Solomon, MD

Background and Purpose—Cerebral blood flow (CBF) is reduced after subarachnoid hemorrhage (SAH), and symptomatic vasospasm is a major cause of morbidity and mortality. Volume expansion has been reported to increase CBF after SAH, but CBF values in hypervolemic (HV) and normovolemic (NV) subjects have never been directly compared.

Methods—On the day after aneurysm clipping, we randomly assigned 82 patients to receive HV or NV fluid management until SAH day 14. In addition to 80 mL/h of isotonic crystalloid, 250 mL of 5% albumin solution was given every 2 hours to maintain normal (NV group, n=41) or elevated (HV group, n=41) cardiac filling pressures. CBF (¹³³xenon clearance) was measured before randomization and approximately every 3 days thereafter (mean, 4.5 studies per patient).

Results—HV patients received significantly more fluid and had higher pulmonary artery diastolic and central venous pressures than NV patients, but there was no effect on net fluid balance or on blood volume measured on the third postoperative day. There was no difference in mean global CBF during the treatment period between HV and NV patients ($P=0.55$, random-effects model). Symptomatic vasospasm occurred in 20% of patients in each group and was associated with reduced minimum regional CBF values ($P=0.04$). However, there was also no difference in minimum regional CBF between the 2 treatment groups.

Conclusions—HV therapy resulted in increased cardiac filling pressures and fluid intake but did not increase CBF or blood volume compared with NV therapy. Although careful fluid management to avoid hypovolemia may reduce the risk of delayed cerebral ischemia after SAH, prophylactic HV therapy is unlikely to confer an additional benefit. (*Stroke*. 2000;31:383-391.)

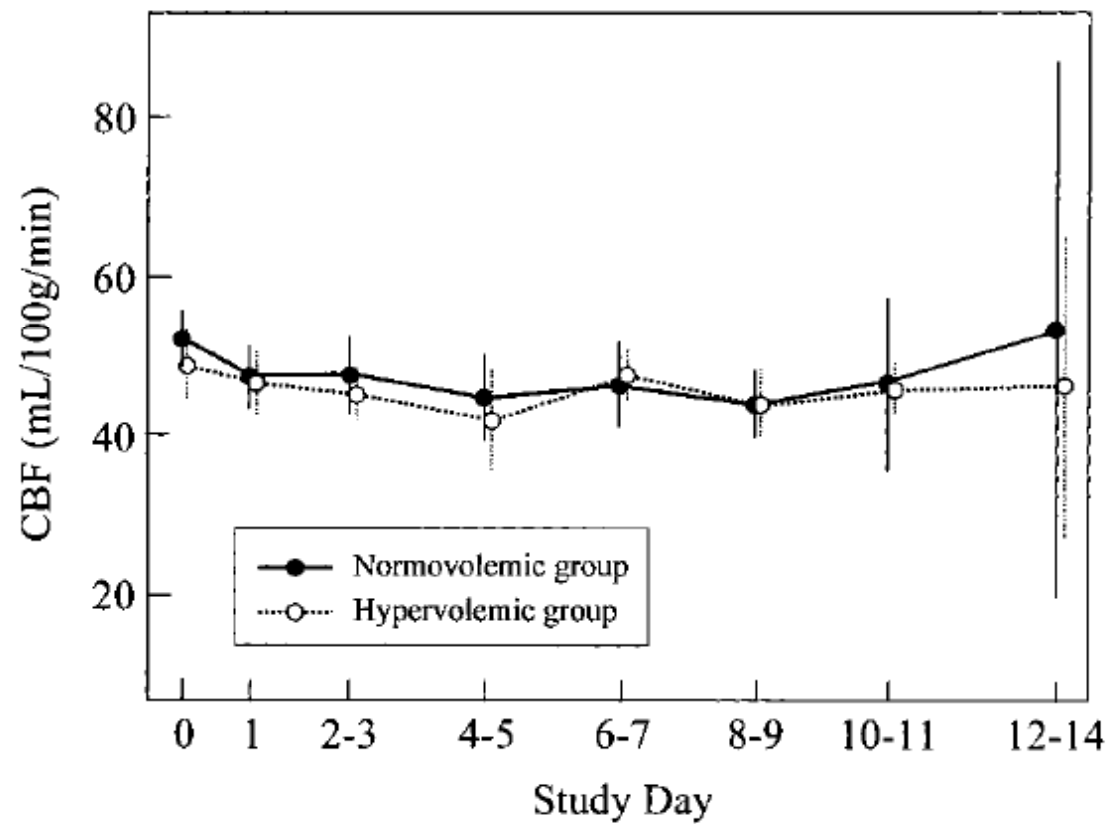


Figure 2. Mean global CBF (gCBF) in the hypervolemic and normovolemic treatment groups plotted over the 14-day study period. Error bars represent 95% CIs.

Can we prevent delayed neurologic deterioration after SAH?

- Systemic nimodipine is associated with a substantial reduction in disability, although not a change in vascular caliber
 - The mechanism(s) involved remain uncertain
 - Intraventricular nimodipine under study
- Avoiding volume depletion probably helps
- Nitrites as (nitric oxide donors?) might work
- Interfering with spreading depolarization might work
- Don't stop statins, but don't start them either.

Critical care issues: vasospasm and delayed ischemic damage

- Management
 - volume expansion
 - rarely achieved
 - induced hypertension
 - cardiac output augmentation
 - dopamine or dobutamine or milrinone
 - intra-aortic balloon pump
 - angioplasty
 - verapamil or nicardipine (no longer use papaverine)
 - intrathecal or intraventricular NO donors
 - magnesium?

Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial



Sanne M Dorhout Mees, Ale Algra, W Peter Vandertop, Fop van Kooten, Hans A J M Kuijsten, Jelis Boiten, Robert J van Oostenbrugge, Rustam Al-Shahi Salman, Pablo M Lavados, Gabriel J E Rinkel, Walter M van den Bergh

Summary

Background Magnesium sulphate is a neuroprotective agent that might improve outcome after aneurysmal subarachnoid haemorrhage by reducing the occurrence or improving the outcome of delayed cerebral ischaemia. We did a trial to test whether magnesium therapy improves outcome after aneurysmal subarachnoid haemorrhage.

Methods We did this phase 3 randomised, placebo-controlled trial in eight centres in Europe and South America. We randomly assigned (with computer-generated random numbers, with permuted blocks of four, stratified by centre) patients aged 18 years or older with an aneurysmal pattern of subarachnoid haemorrhage on brain imaging who were admitted to hospital within 4 days of haemorrhage, to receive intravenous magnesium sulphate, 64 mmol/day, or placebo. We excluded patients with renal failure or bodyweight lower than 50 kg. Patients, treating physicians, and investigators assessing outcomes and analysing data were masked to the allocation. The primary outcome was poor outcome—defined as a score of 4–5 on the modified Rankin Scale—3 months after subarachnoid haemorrhage, or death. We analysed results by intention to treat. We also updated a previous meta-analysis of trials of magnesium treatment for aneurysmal subarachnoid haemorrhage. This study is registered with controlled-trials.com (ISRCTN 68742385) and the EU Clinical Trials Register (EudraCT 2006-003523-36).

Findings 1204 patients were enrolled, one of whom had his treatment allocation lost. 606 patients were assigned to the magnesium group (two lost to follow-up), 597 to the placebo (one lost to follow-up). 158 patients (26·2%) had poor outcome in the magnesium group compared with 151 (25·3%) in the placebo group (risk ratio [RR] 1·03, 95% CI 0·85–1·25). Our updated meta-analysis of seven randomised trials involving 2047 patients shows that magnesium is not superior to placebo for reduction of poor outcome after aneurysmal subarachnoid haemorrhage (RR 0·96, 95% CI 0·86–1·08).

Interpretation Intravenous magnesium sulphate does not improve clinical outcome after aneurysmal subarachnoid haemorrhage, therefore routine administration of magnesium cannot be recommended.

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See Online/Comment

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(W M van den Bergh MD), University Medical Center Utrecht, Utrecht, The Netherlands; Neurosurgical Center Amsterdam, Academic Medical Center Amsterdam and VU University Medical Center, Amsterdam, The Netherlands (Prof W P Vandertop MD); Department of Neurology, Erasmus Medical Center Rotterdam, Rotterdam,

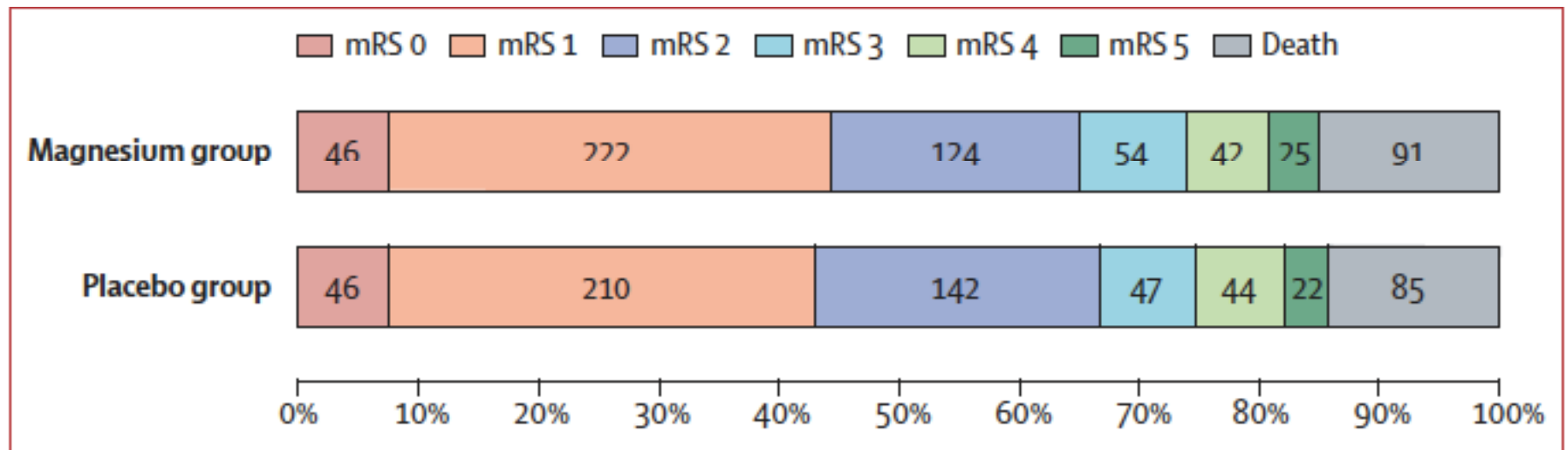


Figure 2: Distributions of mRS score in the magnesium and placebo groups

Data are number of patients with each mRS score. Tested with Mann-Whitney *U* test; $p=0.95$. mRS=modified Rankin Scale score.

Nitrite Infusions to Prevent Delayed Cerebral Vasospasm in a Primate Model of Subarachnoid Hemorrhage

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Andre Dejam, MD, PhD

George Grimes, PhD

Mark T. Gladwin, MD

Edward H. Oldfield, MD

INTRACRANIAL ANEURYSM RUPTURE affects an estimated 10 individuals in a population of 100 000 annually.¹⁻³ Half survive to reach the hospital and receive surgical and/or endovascular intervention.^{1,3} However, half of the patients whose aneurysm is successfully treated develop delayed cerebral vasospasm.^{4,5} Despite the use of currently available management modalities (nimodipine and hypertension-hypervolemia-hemodilution [triple-H] therapy), cerebral vasospasm severely disables or kills half of the affected patients.^{3,5-7} A growing body of experimental⁸⁻¹⁹ and clinical²⁰⁻²⁴ evidence suggests that decreased availability of nitric oxide in the cerebral artery wall is associated with vasospasm development. Nitric oxide plays a dominant role in the dilation of vessels and in the regulation of cerebral blood flow.

Nitric oxide levels are decreased after subarachnoid hemorrhage due to (1) toxicity of oxyhemoglobin to neurons

Context Delayed cerebral vasospasm causes permanent neurological deficits or death in at least 15% of patients following otherwise successful treatment for ruptured intracranial aneurysm. Decreased bioavailability of nitric oxide has been associated with the development of cerebral vasospasm.

Objective To determine whether infusions of nitrite will prevent delayed cerebral vasospasm.

Design, Setting, and Subjects A total of 14 anesthetized cynomolgus monkeys had an autologous blood clot placed around the right middle cerebral artery. Cerebral arteriography was performed before clot placement and on days 7 and 14 to assess vasospasm. The study was conducted from August 2003 to February 2004.

Interventions A 90-mg sodium nitrite intravenous solution infused over 24 hours plus a 45-mg sodium nitrite bolus daily (n=3); a 180-mg sodium nitrite intravenous solution infused over 24 hours (n=3); or a control saline solution infusion (n=8). Each was infused continuously for 14 days.

Main Outcome Measures Nitrite, S-nitrosothiol, and methemoglobin levels in blood and cerebrospinal fluid and degree of arteriographic vasospasm.

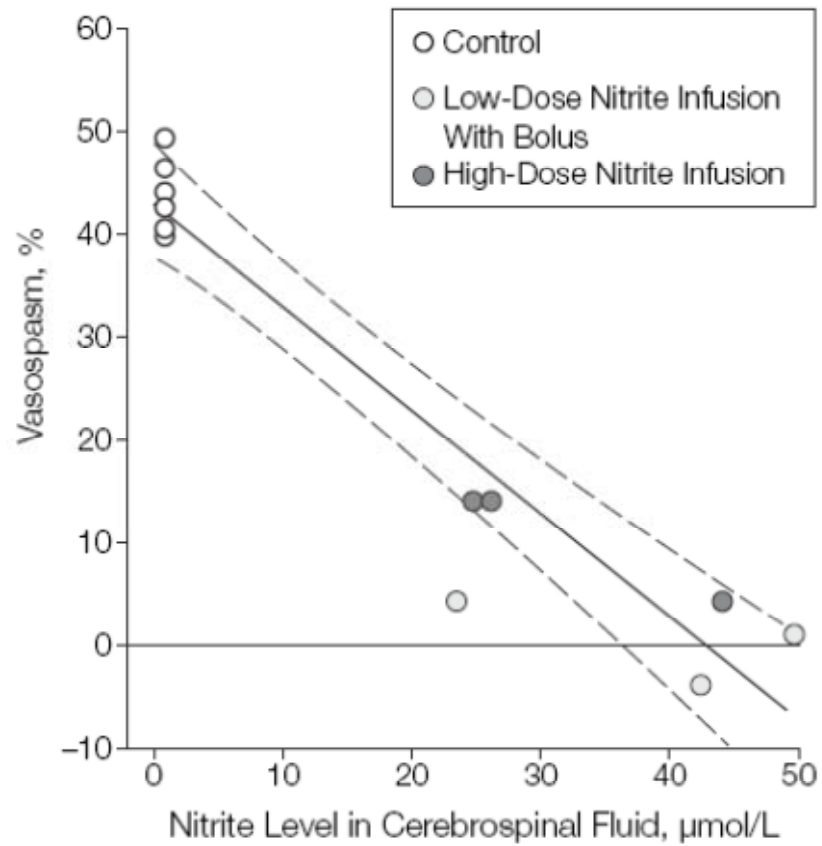
Results In control monkeys, mean (SD) cerebrospinal fluid nitrite levels decreased from 3.1 (1.5) $\mu\text{mol/L}$ to 0.4 (0.1) $\mu\text{mol/L}$ at day 7 and to 0.4 (0.4) $\mu\text{mol/L}$ at day 14 ($P=.03$). All 8 control monkeys developed significant vasospasm of the right middle cerebral artery, which was complicated by stroke and death in 1 animal. Sodium nitrite infusions increased the nitrite and methemoglobin levels ($<2.1\%$ of total hemoglobin) in the blood and cerebrospinal fluid without evoking systemic hypotension. Nitrite infusion prevented development of vasospasm (no animals developed significant vasospasm; mean [SD] reduction in right middle cerebral artery area on day 7 after subarachnoid hemorrhage of 8% [9%] in nitrite-treated monkeys vs 47% [5%] in saline-treated controls; $P<.001$). There was a negative correlation between the concentration of nitrite in cerebrospinal fluid and the degree of cerebral vasospasm ($P<.001$). Pharmacological effects of nitrite infusion were also associated with the formation of S-nitrosothiol in cerebrospinal fluid. There was no clinical or pathological evidence of nitrite toxicity.

Conclusion Subacute sodium nitrite infusions prevented delayed cerebral vasospasm in a primate model of subarachnoid hemorrhage.

JAMA. 2005;293:1477-1484

www.jama.com

Figure 4. Relationship Between Degree of Vasospasm and Nitrite Levels in Cerebrospinal Fluid at Day 7



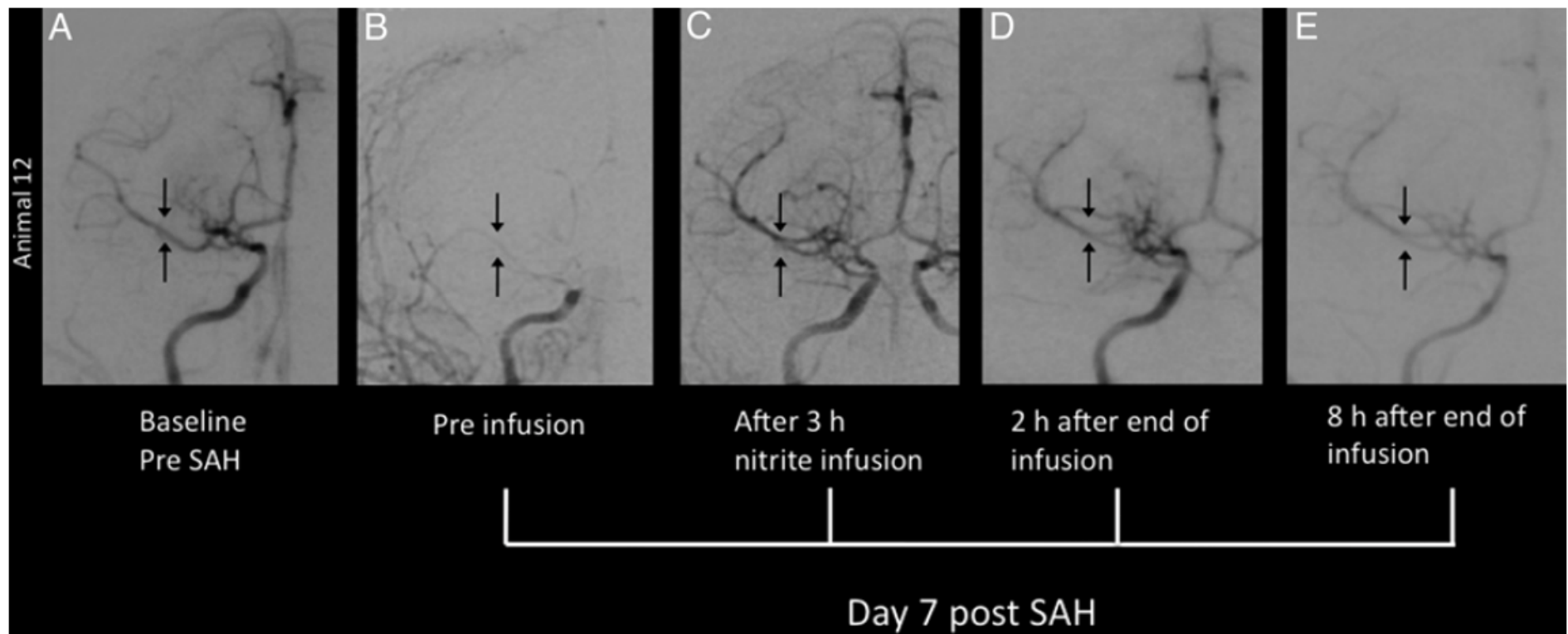


FIG. 3. Representative arteriograms, anteroposterior views, of the right cerebral arteries of monkeys treated intravenously with NaNO_2 . A: Baseline arteriogram before SAH clot placement. B: Arteriogram on Day 7 after SAH and before infusion of NaNO_2 showing severe vasospasm of the right MCA. C: After 3 hours of continuous intravenous NaNO_2 infusion, the degree of vasospasm was significantly decreased. D: Two hours after ceasing the infusion, the therapeutic effect persisted. E: Eight hours after infusion, the spasm of the right MCA returned. Arrows indicate the right MCA.

J Neurosurg 115:1213–1220, 2011

Safety and pharmacokinetics of sodium nitrite in patients with subarachnoid hemorrhage: a Phase IIA study

Clinical article

J Neurosurg 119:634–641, 2013

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Object. Intravenous sodium nitrite has been shown to prevent and reverse cerebral vasospasm in a primate model of subarachnoid hemorrhage (SAH). The present Phase IIA dose-escalation study of sodium nitrite was conducted to determine the compound's safety in humans with aneurysmal SAH and to establish its pharmacokinetics during a 14-day infusion.

Methods. In 18 patients (3 cohorts of 6 patients each) with SAH from a ruptured cerebral aneurysm, nitrite (3 patients) or saline (3 patients) was infused. Sodium nitrite and saline were delivered intravenously for 14 days, and a dose-escalation scheme was used for the nitrite, with a maximum dose of 64 nmol/kg/min. Sodium nitrite blood levels were frequently sampled and measured using mass spectroscopy, and blood methemoglobin levels were continuously monitored using a pulse oximeter.

Results. In the 14-day infusions in critically ill patients with SAH, there was no toxicity or systemic hypotension, and blood methemoglobin levels remained at 3.3% or less in all patients. Nitrite levels increased rapidly during intravenous infusion and reached steady-state levels by 12 hours after the start of infusion on Day 1. The nitrite plasma half-life was less than 1 hour across all dose levels evaluated after stopping nitrite infusions on Day 14.

Conclusions. Previous preclinical investigations of sodium nitrite for the prevention and reversal of vasospasm in a primate model of SAH were effective using doses similar to the highest dose examined in the current study (64 nmol/kg/min). Results of the current study suggest that safe and potentially therapeutic levels of nitrite can be achieved and sustained in critically ill patients after SAH from a ruptured cerebral aneurysm. Clinical trial registration no.: NCT00873015 (ClinicalTrials.gov).

(<http://thejns.org/doi/abs/10.3171/2013.3.JNS13266>)

Cerebral salt wasting: pathophysiology

- volume depletion puts SAH patients at risk for stroke from vasospasm
 - Wijdicks et al (1985) showed that volume restriction (as one would do for patients with SIADH) doubled the rates of stroke and death attributable to vasospasm

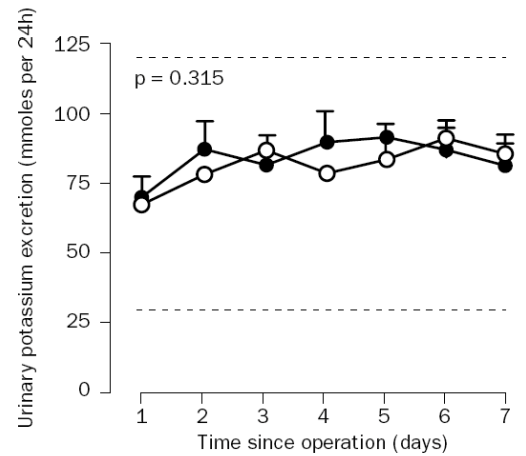
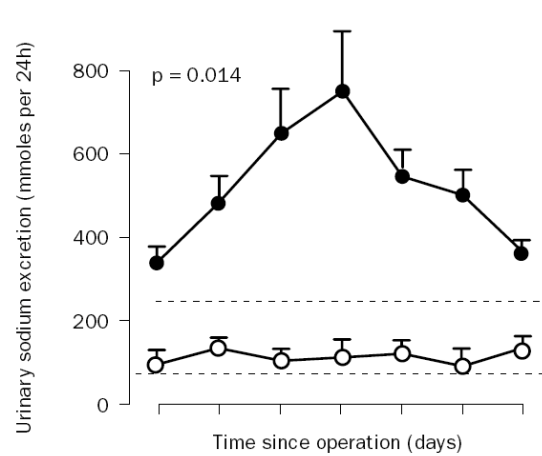
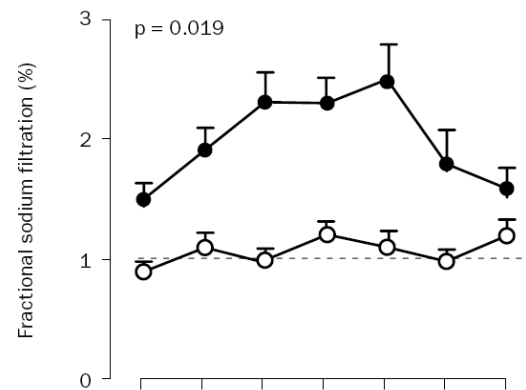
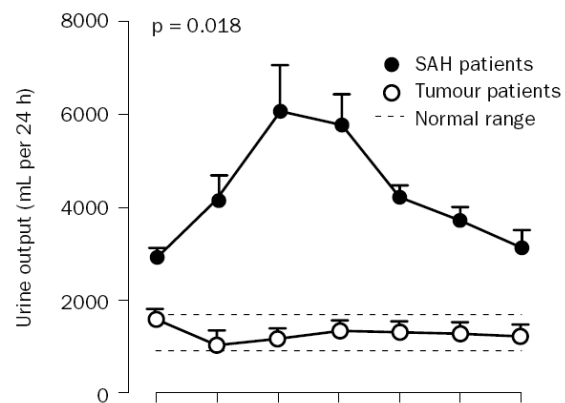


Figure 1: Mean (SE) daily urine output, fractional sodium filtration excretion of sodium, and excretion of potassium in patients with subarachnoid haemorrhage (SAH) and tumours

Is it cerebral or renal salt wasting?

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Euolemia in SIADH and ECV depletion in RSW are the only variables that differentiate SIADH from RSW on first encounter, but clinical assessment of ECV is inaccurate.⁶ Treatment for RSW, however, can be initiated if FEphosphate is >20% on first encounter.² Moreover, exceptions and misconceptions have fueled this controversy, although it can be concluded that RSW is a clinical entity that is more common than is perceived and must now be considered in those without cerebral disease.^{1,2}

Cerebral salt wasting: management

- replete plasma volume
 - signs of volume depletion masked by high catecholamine state
 - volume restriction (as for SIADH) contraindicated

Cerebral salt wasting: management

- prevent or treat the hypotonic state with additional sodium
 - furosemide/saline rarely adequate
 - often requires hypertonic saline
 - measure urine osmolality
 - administer fluid of higher osmolality
 - 1.8% saline = 616 mOsm/L
 - 3% saline = 1027 mOsm/L
- 5% albumin may be beneficial
 - RCCT by Mayer *et al* Neurosurgery 1998;42:759-67

Critical care issues: neurogenic pulmonary edema

- Symptomatic pulmonary edema occurs in about 20% of SAH patients
 - detectable oxygenation abnormalities occur in 80%
- Potential mechanisms:
 - hypersympathetic state
 - cardiogenic pulmonary edema
 - neurogenic pulmonary edema
- Management



Fig. 2. The cast of a vein has regular indentations that divide it into segments. Note the large round nuclear impressions that are characteristic of cast veins. Bar represents 10 μm .

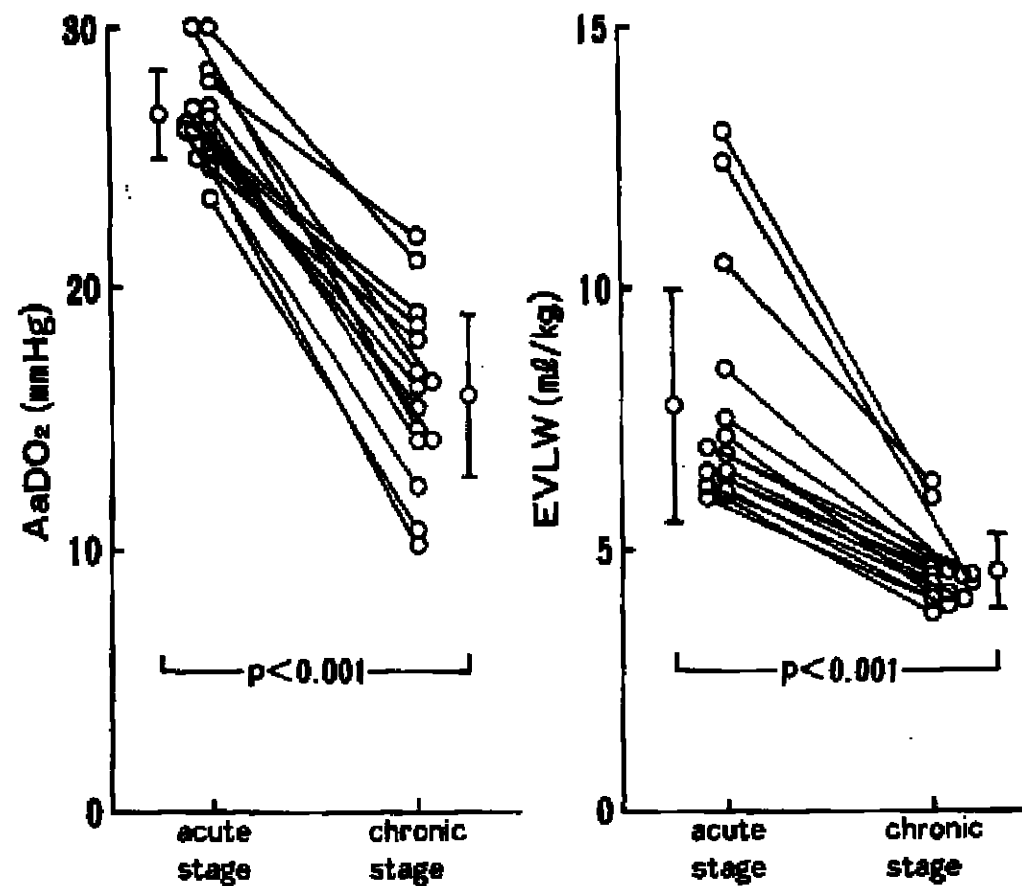


FIG. 3. Changes in alveolar-arterial oxygen difference (AaDO₂) and extravascular lung water (EVLW) in the acute and chronic stages in Group I. The values of AaDO₂ and EVLW in the acute stage were significantly higher than those in the chronic stage.

Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction

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Object. Neurogenic stunned myocardium in aneurysmal subarachnoid hemorrhage (SAH) is associated with a wide spectrum of reversible left ventricular wall motion abnormalities and includes a subset of patients with a pattern of apical akinesia and concomitant sparing of basal segments called “tako-tsubo cardiomyopathy.”

Methods. After obtaining institutional review board approval, the authors retrospectively identified among all patients admitted to the Mayo Clinic’s Neurological Intensive Care Unit between January 1990 and January 2005 those with aneurysmal SAH who had met the echocardiographic criteria for tako-tsubo cardiomyopathy. Among 24 patients with SAH-induced reversible cardiac dysfunction, the authors identified eight with SAH-induced tako-tsubo cardiomyopathy. All eight patients were women with a mean age of 55.5 years (range 38.6–71.1). Seven patients presented with a poor-grade SAH, reflected by a Hunt and Hess grade of III or IV. Four patients underwent aneurysm clip application, and four underwent endovascular coil occlusion. The initial mean ejection fraction (EF) was 38% (range 25–55%), and the mean EF at recovery was 55% (range 40–68%). Cerebral vasospasm developed in six patients, but cerebral infarction developed in only three patients.

Conclusions. The authors describe the largest cohort with aneurysmal SAH-induced tako-tsubo cardiomyopathy. In the SAH population, tako-tsubo cardiomyopathy predominates in postmenopausal women and is often associated with pulmonary edema, prolonged intubation, and cerebral vasospasm. Additional studies are warranted to understand the complex mechanism involved in tako-tsubo cardiomyopathy and its intriguing relationship to neurogenic stunned myocardium.

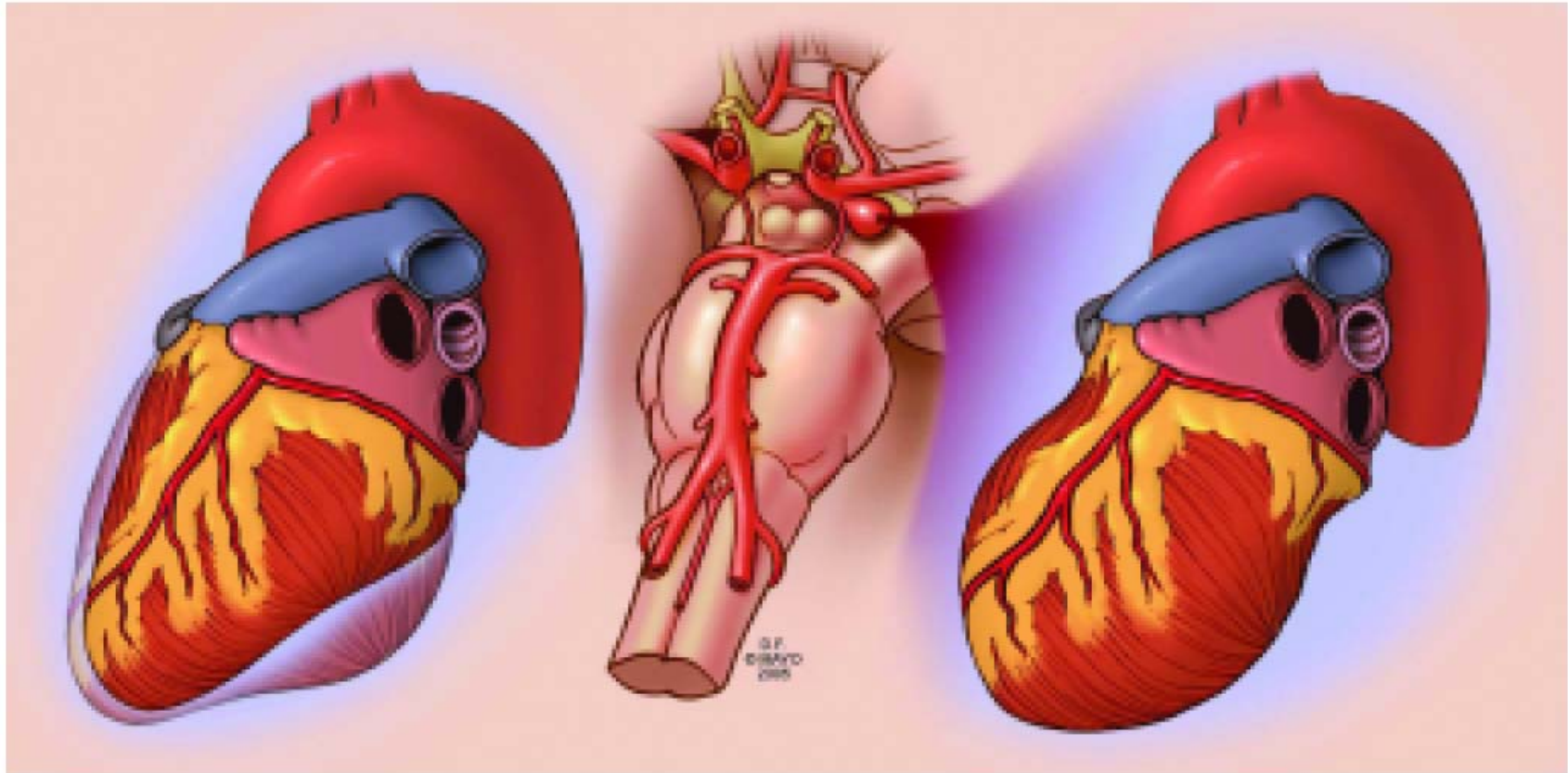


FIG. 2. Illustration of the heart depicting a normal (*left*) and abnormal (*right*) cardiac contraction. After aneurysmal SAH, the cardiac contraction becomes abnormal, with apical and midventricle akinesia consistent with tako-tsubo cardio-

Implications of Early Versus Late Bilateral Pulmonary Infiltrates in Patients with Aneurysmal Subarachnoid Hemorrhage

Andreas H. Kramer · Thomas P. Bleck ·
Aaron S. Dumont · Neal F. Kassell ·
Claire Olson · Bart Nathan

Conclusions Bilateral pulmonary infiltrates after SAH most often occur within three days of aneurysm rupture. However, only infiltrates occurring beyond this time are independently associated with poor outcome. Increased emphasis on the prevention of late pulmonary complications has the potential to improve outcomes in SAH.

Cardiac Troponin I and Acute Lung Injury After Subarachnoid Hemorrhage

Andrew M. Naidech · Sarice L. Bassin · Rajeev K. Garg ·
Michael L. Ault · Bernard R. Bendok · H. Hunt Batjer ·
Charles M. Watts · Thomas P. Bleck

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Abstract

Introduction There are few predictors of acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) after subarachnoid hemorrhage (SAH). We hypothesized that cardiac troponin I, which is associated with cardiovascular morbidity, would also predict ALI.

Methods We prospectively enrolled 171 consecutive patients with SAH. Troponin was routinely measured on admission and the next day and subsequently if abnormal. We prospectively recorded the maximum troponin, in-hospital events, and clinical endpoints. ALI and ARDS were defined by standard criteria.

Results Acute lung injury was found in 10 patients (6%), ARDS in an additional 14 (8%), and pulmonary edema without lung injury in 9 (5%). Maximum troponin was different in patients without lung injury or pulmonary edema (0.03 [0.02–0.12] mcg/l), ALI (0.17 [0.04–1.4]), or ARDS (0.31 [0.9–1.8], $P < 0.001$). In ROC analysis, a cutoff of 0.04 mcg/l had 91% sensitivity and 42% specificity for ALI

or ARDS (AUC = 0.75, $P < 0.001$). Troponin was associated with ALI or ARDS after accounting for neurologic grade in multivariate models without further contribution from pneumonia, packed red cell transfusion, gender, tobacco use, coronary artery disease, vasospasm, depressed ejection fraction on echocardiography, or CT grade. Lung injury was associated with worse functional outcome at 14 days, but not at 28 days or 3 months.

Conclusion Troponin I is associated with the development of ALI after SAH.

Keywords Subarachnoid hemorrhage ·
Acute lung injury · Troponin

Introduction

Subarachnoid hemorrhage (SAH) is a neurologic emergency with high morbidity and mortality. While the most

FEVER BURDEN AND FUNCTIONAL RECOVERY AFTER SUBARACHNOID HEMORRHAGE

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OBJECTIVE: Fever is associated with worse outcome after subarachnoid hemorrhage, but there are few prospective data to quantify this relationship.

METHODS: We prospectively enrolled consecutive aneurysmal or cryptogenic subarachnoid hemorrhage patients and recorded the highest core temperature each calendar day for Day 0 (the day of hemorrhage) through Day 13. Fever burden was defined as the daily highest core temperature minus 100.4°F, summed from admission through Day 13 (temperatures <100.4°F did not contribute to or subtract from fever burden). Outcomes were assessed at 14 days or at the time of hospital discharge with the National Institutes of Health Stroke Scale and modified Rankin Scale, and at 28 days and 3 months with the modified Rankin Scale. Improvement was analyzed with repeated measures analysis of variance.

RESULTS: We prospectively enrolled 94 patients. From 14 days to 28 days to 3 months, functional improvement was related to cumulative fever burden, admission neurological grade, aneurysm obliteration procedure, admission computed tomographic score, vasospasm, and external ventricular drainage. Good-grade patients had worse functional outcomes with increased fever burden, and poor-grade patients improved more over time when fever burden was higher (time by World Federation of Neurological Surgeons grade by fever burden interaction, $P < 0.001$). Patients with vasospasm ($P = 0.04$) and patients with higher computed tomographic scores ($P = 0.002$) had worse 14-day outcomes but improved more over time. Bacteremia and ventriculitis were uncommon ($\leq 5\%$) and were not associated with higher fever burden.

CONCLUSION: Cumulative fever burden was associated with worse outcomes in good-grade patients and potential late recovery in poor-grade patients. Effective fever control in febrile subarachnoid hemorrhage patients may improve functional outcomes and hasten recovery.

KEY WORDS: Fever, Outcomes, Recovery, Subarachnoid hemorrhage, Vasospasm

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DOI: 10.1227/01.NEU.0000320453.61270.0F

www.neurosurgery-online.com

Most patients in the neurointensive care unit (NICU) have a fever during their stay (1), especially those with intracranial disease (11). Only about half of the fevers in NICU patients are explained by infection, however, and in nearly one-third of pa-

tients, no definite cause is found (7). Some intensive care unit data associate a noninfective fever with a benign prognosis (5), but fever is associated with worse neurological outcome in ischemic stroke (2), especially when it occurs within the first 24 hours (4). The highest recorded temperature is associated with prolonged NICU length of stay, and

Seizures in SAH patients

- about 6% of patients suffer a seizure at the time of the hemorrhage
 - distinction between a convulsion and decerebrate posturing may be difficult
- postoperative seizures occur in about 1.5% of patients despite anticonvulsant prophylaxis
- remember to consider other causes of seizures (e.g., alcohol withdrawal)

Seizures in SAH patients

- patients developing delayed ischemia may seize following reperfusion by angioplasty
- late seizures occur in about 3% of patients

Deep Venous Thrombosis Prophylaxis

Paul Vespa · The Participants in the International Multi-disciplinary Consensus
Conference on the Critical Care Management of Subarachnoid Hemorrhage

Abstract Although clinicians are generally advised to use prophylactic therapy to reduce the risk for developing deep venous thrombosis in patients after repair of ruptured aneurysms, limited data are available to guide specific therapeutic decisions. An electronic literature search was conducted to identify English-language articles that addressed prophylactic treatment for deep venous thrombosis after subarachnoid hemorrhage published between 1980 and March 2011. A total of 12 articles were included in this review, including seven original research studies and one meta-analysis. The incidence of deep venous thrombosis varied among studies, with the highest incidence reported with prospective ultrasound screening. Poor-grade patients are at highest risk. Mechanical prophylactic methods appear to be modestly effective as monotherapy, without significant risk for the typical patient with subarachnoid hemorrhage. Unfractionated heparin is moderately effective but carries a small risk of intracranial hemorrhage. Low molecular weight heparin has been

linked to an increased risk for intracranial hemorrhage. Limited data are available to direct the timing and duration of prophylactic therapies.

Keywords Anticoagulation · Heparin · Intracranial hemorrhage · Sequential compression devices

Introduction

Subarachnoid hemorrhage (SAH) frequently leads to decreased mobility for variable periods of time, often in the setting of enhanced systemic inflammation and coagulation [1–3], especially grade 4–5 patients. These factors lead to a prothrombotic state, with increased risk for deep venous thrombosis (DVT) and pulmonary embolism. Hunt and Hess grade, total hospital stay, and number of days in intensive care have been reported to be significant predictors of DVT in patients after aneurysmal SAH [4].

Although DVT prophylaxis has been recommended as a

Critical care issues: hydrocephalus

- Diagnosis
 - clinical
 - radiologic
- Management
 - ventriculostomy
 - infection reduction
 - shunting

High-Volume Centers

P. Vespa · Michael N. Dinger · The Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

Abstract Outcome from trauma, surgery, and a variety of other medical conditions has been shown to be positively affected by providing treatment at facilities experiencing a high volume of patients with those conditions. An electronic literature search was made to identify English-language articles available through March 2011, addressing the effect of patient treatment volume on outcome for patients with subarachnoid hemorrhage. Limited data were identified, with 16 citations included in the current review. Over 60% of hospitals fall into the lowest case-volume quartile. Outcome is influenced by patient volume, with better outcome occurring in high-volume centers treating >60 cases per year. Patients treated at low-volume hospitals are less likely to experience definitive treatment. Furthermore, transfer to high-volume centers may be inadequately arranged. Several factors may influence the better outcome at high-volume centers, including the availability of neurointensivists and interventional neuroradiologists.

Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

A systematic review

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¹ *Conclusions.* Despite the shortcomings of this study, the mortality rate was lower in hospitals with a larger case-load. Limitations of the meta-analysis are the not uniform cutoff values and uncertainty about case mix.
(<http://thejns.org/doi/abs/10.3171/2013.9.JNS13640>)

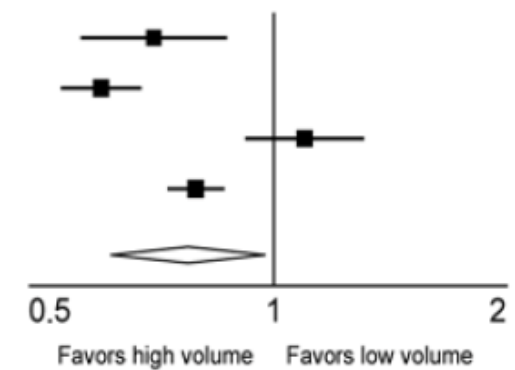
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Study name

Statistics for each study

Odds ratio and 95% CI

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Johnston, 2000	0.690	0.550	0.865	-3.209	0.001
Cross et al., 2003	0.586	0.517	0.664	-8.381	0.000
Hattori et al., 2007	1.100	0.915	1.322	1.016	0.310
Leake et al., 2011	0.786	0.719	0.859	-5.323	0.000
Overall	0.767	0.604	0.972	-2.190	0.029



Hospital Case Volume Is Associated With Mortality in Patients Hospitalized With Subarachnoid Hemorrhage

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BACKGROUND: Prior studies have suggested that hospital case volume may be associated with improved outcomes after subarachnoid hemorrhage (SAH), but contemporary national data are limited.

OBJECTIVE: To assess the association between hospital case volume for SAH and in-hospital mortality.

METHODS: Using the Get With The Guidelines-Stroke registry, we analyzed patients with a discharge diagnosis of SAH between April 2003 and March 2012. We assessed the association of annual SAH case volume with in-hospital mortality by using multivariable logistic regression adjusting for relevant patient, hospital, and geographic characteristics.

RESULTS: Among 31,973 patients with SAH from 685 hospitals, the median annual case volume per hospital was 8.5 (25th-75th percentile, 6.7-12.9) patients. Mean in-hospital mortality was 25.7%, but was lower with increasing annual SAH volume: 29.5% in quartile 1 (range, 4-6.6), 27.0% in quartile 2 (range, 6.7-8.5), 24.1% in quartile 3 (range, 8.5-12.7), and 22.1% in quartile 4 (range, 12.9-94.5). Adjusting for patient and hospital characteristics, hospital SAH volume was independently associated with in-hospital mortality (adjusted odds ratio 0.79 for quartile 4 vs 1, 95% confidence interval, 0.67-0.92). The quartile of SAH volume also was associated with length of stay but not with discharge home or independent ambulatory status.

CONCLUSION: In a large nationwide registry, we observed that patients treated at hospitals with higher volumes of SAH patients have lower in-hospital mortality, independent of patient and hospital characteristics. Our data suggest that experienced centers may provide more optimized care for SAH patients.

KEY WORDS: Comprehensive stroke centers, Referral bias, Quality of care

B

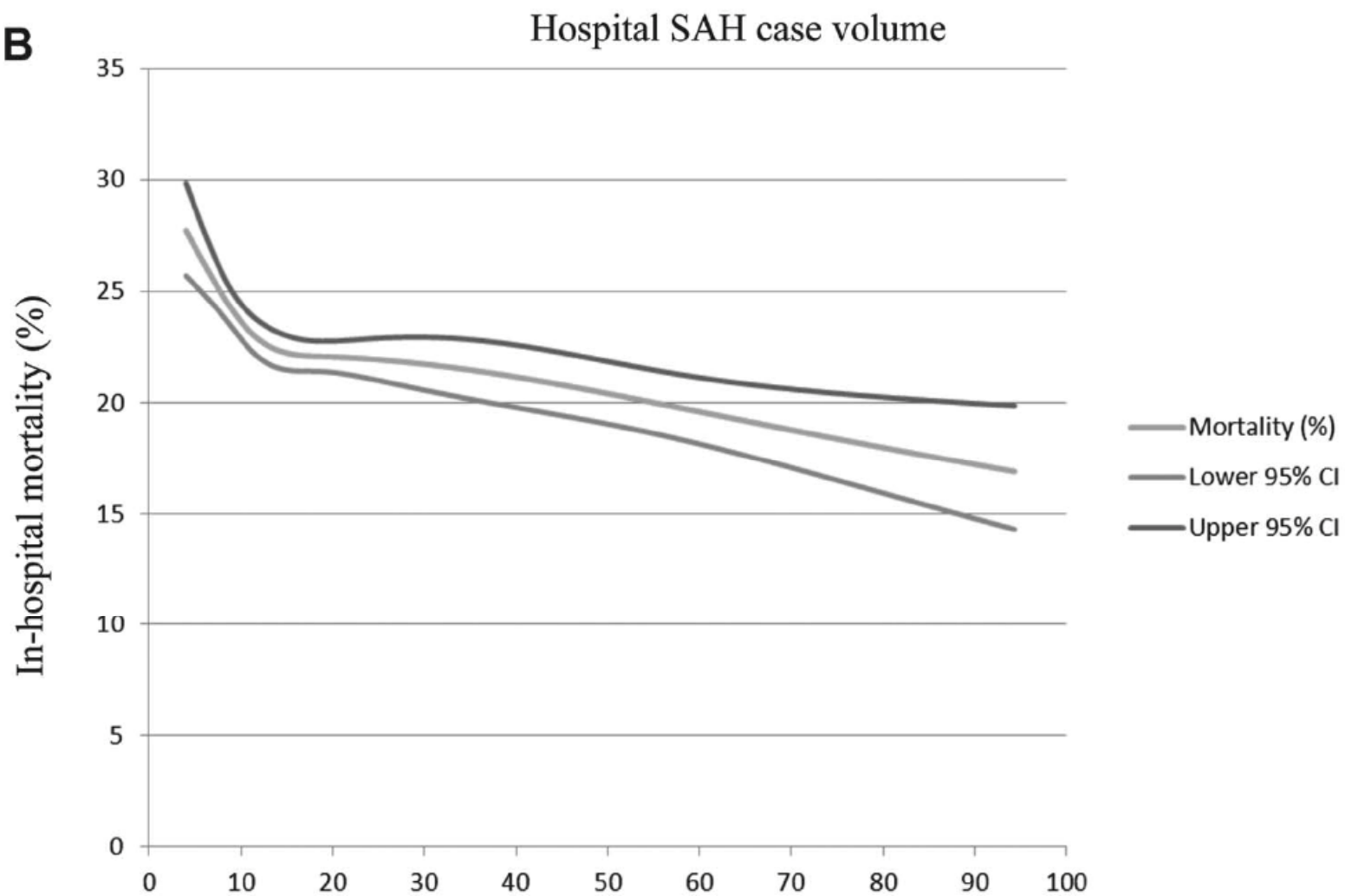


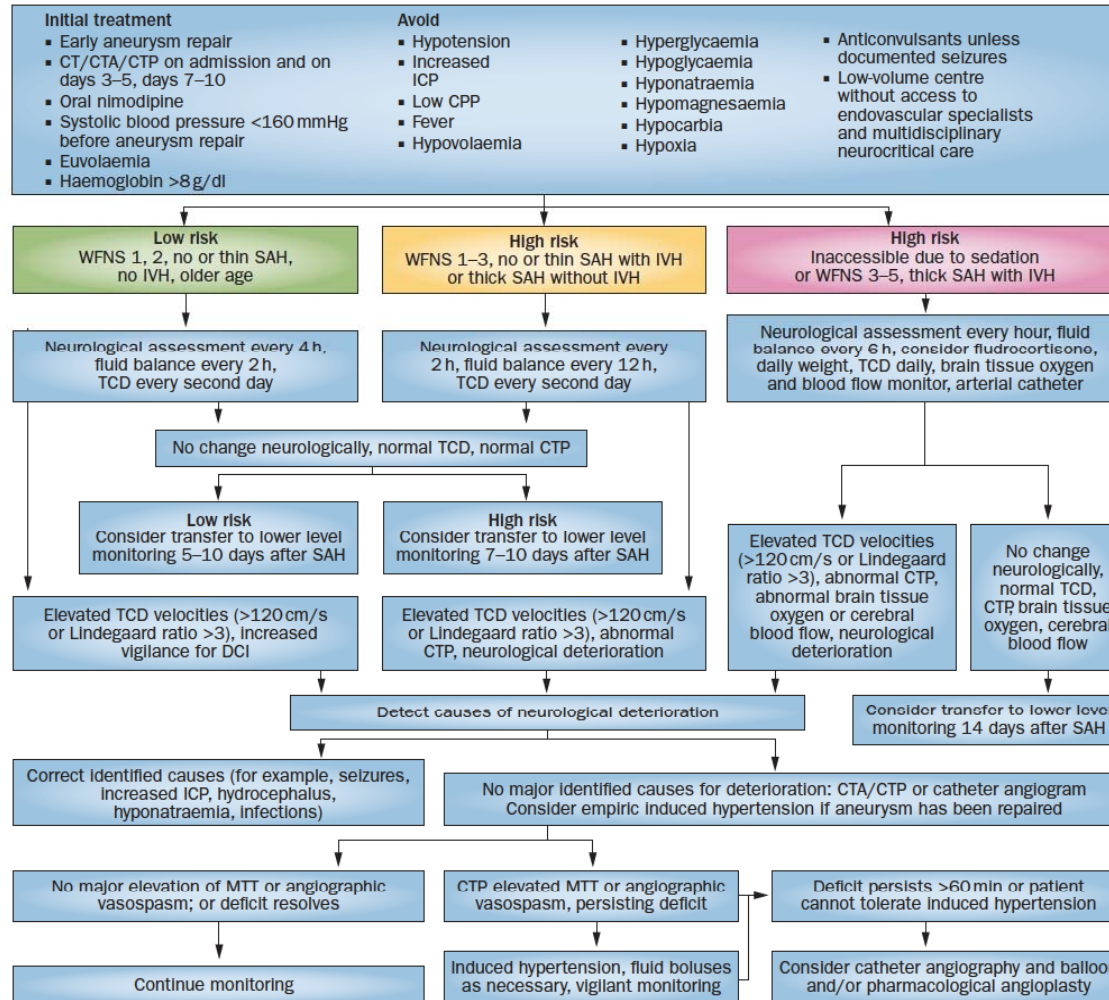
TABLE 3. Unadjusted and Adjusted OR and 95% CI for In-hospital Mortality by Annual Hospital SAH Case Volume^a

In-hospital Mortality	Unadjusted		Adjusted for Patient Factors ^b		Adjusted for Patient and Hospitals Factors ^c	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Highest vs lowest quartile	0.69 (0.61-0.77)	<.001	0.85 (0.75-0.97)	.018	0.79 (0.67-0.92)	.003
Medium high vs lowest quartile	0.76 (0.67-0.87)	<.001	0.88 (0.77-1.02)	.087	0.87 (0.75-1.01)	.078
Medium low vs lowest	0.90 (0.78-1.04)	.161	0.95 (0.82-1.11)	.539	0.95 (0.82-1.11)	.507
SAH volume (per 5 units/y)	0.95 (0.93-0.97)	<.001	0.98 (0.96-0.99)	.007	0.97 (0.95-0.99)	<.001

^aCI, confidence interval; IV, intravenous; OR, odds ratio; MI, myocardial infarction; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

^bAdjusted for age, female (vs male), race (black, Hispanic, other vs white), history of atrial fibrillation/flutter, prosthetic heart valve, previous stroke/TIA, coronary artery disease or prior MI, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, heart failure and smoking, arrived at off-hours, and care unit.

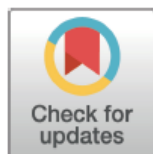
^cAdjusted for patient factors plus hospital region, size, annual number of ischemic stroke discharges, annual IV tPA volume, teaching status, primary stroke center status, and rural (vs urban) location.



SAH prognosis

- Sudden death prior to medical attention in about 20%
- Of the remainder, with early surgery
 - 58% regained premorbid level of function
 - as high as 67% in some centers
 - 9% moderately disabled
 - 2% vegetative
 - 26% dead

RESEARCH



Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study



OPEN ACCESS



SAHIT

Subarachnoid Hemorrhage International Trialists

[Background](#) [Calculate](#) [Reference](#)

Prediction models for 3 month outcome after aSAH

Definitions

Age should be entered as the patient's age in years.

Hypertension should be defined or considered present if there is a known history of hypertension, the patient was taking antihypertensive medications prior to admission or there are other clinically apparent signs consistent with essential hypertension such as very high blood pressure on admission or electrocardiogram, echocardiogram, kidney or other end-organ signs or laboratory findings consistent with a history of hypertension.

Neurological or clinical grade of the patient is based on the grade when they are admitted to hospital and prior to aneurysm repair. This model includes studies that determined the neurological grade before aneurysm repair but before and after resuscitation including insertion of an external ventricular drain. Thus, you should use the neurological grade determined before aneurysm repair. The model uses the World Federation of Neurological Surgeons (WFNS) scale that is based on the modified Glasgow coma score and presence or absence of focal motor deficit (including aphasia) as outlined below.{Teasdale, 1988 #17556;Drake, 1988 #8208;Teasdale, 1974 #34155} If the Hunt and Hess system is used, an approximate conversion method is shown.{Hunt, 1968 #10458}

Size is defined as the largest diameter of the aneurysm. This is usually the length from the aneurysm neck at the aneurysm origin from the parent artery to the end of the dome of the aneurysm.

Location follows the ISAT categorization as such:

ACA - Anterior cerebral artery, including Anterior communication, proximal to A comm, pericallosal.

ICA - Internal carotid artery, including proximal to or ophthalmic region, posterior communication region, and the bifurcation.

MCA - Middle cerebral artery.

PCA - Posterior circulation artery, including vertebro-basilar artery and branches.

Fisher grade should be calculated using the cranial computed tomographic scan obtained when the patient presented with subarachnoid hemorrhage and before aneurysm repair:

1 - No SAH or intraventricular hemorrhage.

2 - Diffuse deposition of thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) < 1 mm thick.

3 - Vertical layers of blood ≥ 1 mm thick or localized clots (clots defined as $> 3 \times 5$ mm).

4 - Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots.

Method of repair indicates whether the ruptured aneurysm was repaired by neurosurgical clipping, endovascular coiling or not repaired. The data from which this model is constructed leads to the recommendation that aneurysms repaired with adjunctive surgical methods in addition to clipping including bypass and trapping are classified as neurosurgical clipping and stent-assisted coiling, flow diverters and such are classified as endovascular coiling.

Admission Characteristics

Core

Age (0-99):

Hypertension:

WFNS Grade:

Neuro

Size (mm):

Location:

Fisher Grade:

Full

Repair Modality:

Interpreting Results

After inputting known characteristics, the Results section will load between 1 and 3 graphs consisting of 3 bars. The first illustrates the probability of mortality, the second of an unfavourable outcome and the third of a favourable outcome. The description below each graph outlines the corresponding confidence intervals for the mortality and unfavourable outcome graphs.

Results

Core Characteristics:

With a 95% confidence interval, the error for mortality is between 20% and 27% and for unfavourable outcome it is between 46% and 54%.

Neuro Characteristics:

With a 95% confidence interval, the error for mortality is between 29% and 39% and for unfavourable outcome it is between 92% and 95%.

Full Characteristics:

With a 95% confidence interval, the error for mortality is between 40% and 58% and for unfavourable outcome it is between 94% and 96%.

PREDICTORS OF GLOBAL COGNITIVE IMPAIRMENT 1 YEAR AFTER SUBARACHNOID HEMORRHAGE

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OBJECTIVE: We sought to determine the frequency, risk factors, and impact on functional outcome and quality of life (QOL) of global cognitive impairment 1 year after subarachnoid hemorrhage.

METHODS: We prospectively evaluated global cognitive status 3 and 12 months after hospitalization with the Telephone Interview for Cognitive Status in 232 subarachnoid hemorrhage survivors. Cognitive impairment was defined as a score of 30 or less (scaled 0 = worst, 51 = best). Logistic regression was performed to calculate adjusted odds ratios (AORs) for impairment at 1 year. Basic activities of daily living were evaluated with the Barthel Index, instrumental activities of daily living were assessed with the Lawton scale, and QOL was evaluated with the Sickness Impact Profile.

RESULTS: The frequency of cognitive impairment was 27% at 3 months and 21% at 12 months. After the effects of age, education, and race/ethnicity were controlled for, risk factors for cognitive impairment at 12 months included anemia treated with transfusion (AOR, 3.4; $P = 0.006$), any temperature level higher than 38.6°C (AOR, 2.7; $P = 0.016$), and delayed cerebral ischemia (AOR, 3.6; $P = 0.01$). Among cognitively impaired patients at 3 months, improvement at 1 year occurred in 34% and was associated with more than 12 years of education and the absence of fever higher than 38.6°C during hospitalization ($P = 0.015$). Patients with cognitive impairment at 1 year had worse concurrent QOL and less ability to perform instrumental and basic activities of daily living (all $P < 0.001$).

CONCLUSION: Global cognitive impairment affects more than 20% of subarachnoid hemorrhage survivors at 1 year, is predicted by fever, anemia treated with transfusion, and delayed cerebral ischemia, and adversely affects functional recovery and QOL.

KEY WORDS: Anemia, Cerebral aneurysm, Cognitive impairment, Delayed cerebral ischemia, Fever, Subarachnoid hemorrhage

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www.neurosurgery-online.com

Cognitive impairment has been reported in up to 50% of survivors of subarachnoid hemorrhage (SAH) and is associated with functional disability and poor

other cognitive domains, such as executive functioning, visuospatial functioning, and visual memory (13, 19, 21, 26, 35).

Several demographic and clinical variables

TABLE 3. Adjusted odds ratios for cognitive impairment at 12 months^a

	AOR	95% CI	P value
Fever >38.6°C	2.7	1.2–6.0	0.016
Hunt-Hess grade 3–5	2.2	1.0–4.7	0.055
Hyperglycemia	2.2	0.9–5.5	0.089
Anemia	3.4	1.4–8.0	0.006
Delayed cerebral ischemia	3.6	1.4–9.6	0.01

^a AOR, adjusted odds ratio; CI, confidence interval. Values are adjusted for age, education, and ethnicity.

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