Published in final edited form as:

Neurosurgery. 2013 May ; 72(5): 702–708. doi:10.1227/NEU.0b013e318285c3db.

The Relationship Between Delayed Infarcts and Angiographic Vasospasm After Aneurysmal Subarachnoid Hemorrhage

Robert J. Brown, M.D., Abhay Kumar, M.D., Rajat Dhar, M.D., Tomoko R. Sampson, M.D., and Michael N. Diringer, M.D.

Neurocritical Care Section, Department of Neurology, Washington University School of Medicine, Saint Louis, Missouri, USA

Abstract

Background—Delayed cerebral ischemia is common after aneurysmal subarachnoid hemorrhage (aSAH) and is a major contributor to poor outcome. Yet, while generally attributed to arterial vasospasm, neurologic deterioration may also occur in the absence of vasospasm.

Objective—To determine the relationship between delayed infarction and angiographic vasospasm and compare the characteristics of infarcts related vs. those unrelated to vasospasm.

Methods—A retrospective review of patients with aSAH admitted from July 2007 through June 2011. Patients were included if they were admitted within 48 hours of SAH, had a CT scan both 24–48 hours following aneurysm treatment and 7 days after SAH, and had a catheter angiogram to evaluate for vasospasm. Delayed infarcts seen on late CT but not post-procedurally were attributed to vasospasm if there was moderate or severe vasospasm in the corresponding vascular territory on angiography. Infarct volume was measured by perimeter tracing.

Results—Of 276 aSAH survivors, 134 had all imaging requisite for inclusion. 54 (34%) had moderate or severe vasospasm, of which 17 (31%) had delayed infarcts, compared to only 3 (4%) of 80 patients without vasospasm ($p < 0.001$). There were a total of 29 delayed infarcts in these 20 patients; 21 were in a territory with angiographic vasospasm while 8 (28%) were not. Infarct volume did not differ between vasospasm-related (18 ± 25 cc) and vasospasm-unrelated (11 ± 12 cc) infarcts ($p = 0.54$), but infarcts in the absence of vasospasm were more likely watershed (50% vs. 10%, $p = 0.03$).

Conclusion—Delayed infarcts following aSAH can occur in territories without angiographic vasospasm and are more likely watershed in distribution.

Keywords

Cerebral vasospasm; Delayed cerebral ischemia; Stroke; Subarachnoid hemorrhage

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for a disproportionate amount of morbidity and mortality relative to other types of stroke.¹ A substantial portion of this morbidity is from delayed cerebral ischemia (DCI), which is defined as a delayed

Corresponding Author: Michael N. Diringer, Division of Neurocritical Care Section, Department of Neurology, Washington University School of Medicine, 660 South Euclid, Campus Box 8111, St. Louis, MO 63110.

Disclosure:

Supported in part by: NIH (NINDS) 5P50NS05597704, Barnes-Jewish Hospital Foundation. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

neurological decline presumed secondary to cerebral ischemia or the development of a new cerebral infarction.² Cerebral infarction, with or without symptoms, occurs in 12–20% of aSAH survivors and is a major predictor of poor outcome.^{3–6}

Angiographic vasospasm refers to arterial narrowing seen on cerebral catheter angiography. It occurs in up to 70% of aSAH patients and has been associated with cerebral infarction.⁷ However, about half of patients with angiographic vasospasm do not experience DCI or infarction, and some cases of DCI and infarction occur in the absence of vasospasm.⁸ Furthermore, clinical trials have found that a significant reduction in vasospasm did not translate into improvements in clinical outcomes including cerebral infarction.^{9,10} These data have called into question the primary and causative relationship between vasospasm and cerebral infarction and have led to further investigation into other possible mechanisms of ischemia and neuronal injury after SAH.¹¹

Other potential causes of cerebral infarction following aSAH include microvascular dysfunction, thromboembolic disease, cortical spreading depolarization (CSD), and inflammation.^{12–14} These varied etiologies may lead to differences in infarct characteristics including size and location. Furthermore, as they are distinct entities, risk factors and patient characteristics may differ between them.

We assessed the relationship between angiographic vasospasm and DCI-related infarction and further characterized the nature of delayed infarcts. We hypothesized that a substantial portion of infarcts could not be explained by large-vessel angiographic vasospasm and that these infarcts may have different characteristics including volume and location.

Methods

Patients with aSAH diagnosed by computed tomography (CT) or cerebrospinal fluid (CSF) analysis and angiography were identified from a prospectively collected database of patients admitted to the Neurology/Neurosurgery Intensive Care Unit (NNICU) at Barnes-Jewish Hospital between July 2007 and June 2011. Patients were included if they: were admitted within 48 hours of aneurysmal rupture; had a screening catheter angiogram 6–8 days after rupture; and had CT scans both 24–48 hours after their aneurysm-securing procedure and again at least 7 days after rupture (termed the late CT). Patients were excluded if they survived fewer than 7 days after initial rupture or if a vascular malformation or other cause of hemorrhage was identified.

Patient Management

All patients were cared for in the NNICU. Ruptured aneurysms were treated with clipping or coiling within 24 hours of admission. All patients received enteral nimodipine. Euvolemia was maintained by daily adjustments of intravenous fluids to keep fluid intake and output balanced, but prophylactic hypervolemia was not used. Neurological deterioration was promptly evaluated and if no other cause was identified, patients underwent cerebral angiography and hemodynamic augmentation with vasopressors.¹⁵ The attending neurointerventionalist and neurosurgeon jointly determined if endovascular interventions were performed. In the absence of neurological decline, patients routinely underwent cerebral angiography screening around day 7 after SAH. Transcranial Doppler ultrasound was not performed.

Data Collection

Admission CTs were reviewed to obtain the modified Fisher and IVH scores.^{16,17} Late CTs were reviewed for well-defined hypodensities; if a hypodensity was seen, the post-procedure scan was reviewed. Hypodensities seen only on the late CT and not otherwise explained

(e.g. ventriculostomy tract, hematoma reabsorption, or surgical intervention) were considered infarcts from DCI and termed “delayed infarcts”.

The volumes of all delayed infarcts were measured by perimeter tracing. This technique involves tracing the hypodensity on each slice to obtain an area, adding these areas together, and multiplying by slice thickness to obtain the volume. Infarcts were categorized as “cortical” if the hypodensity was restricted to the cortex, “deep” if the hypodensity involved only white matter and/or deep structures, and “both” if the hypodensity involved cortex and white matter/deep structures.¹⁸ Infarcts were also categorized into one of the following vascular territories: anterior cerebral (ACA), middle cerebral (MCA), posterior cerebral (PCA), vertebrobasilar, anterior watershed, and posterior watershed. Vascular territory was determined by the reviewer with the use of a vascular territory map.¹⁹ All CT scans were analyzed by one of two investigators (AK and RJB) who demonstrated excellent inter-rater reliability for the detection of delayed infarcts ($\kappa = 0.94$, $n=15$).

The reports of all angiograms performed during a patient’s hospitalization were reviewed to determine presence and location of vasospasm. Severity of vasospasm was determined by one of three experienced attending neuroradiologists. Delayed infarction was attributed to vasospasm if at least moderate vasospasm was present on any angiogram in the corresponding vascular territory. Watershed infarcts were attributed to vasospasm if there was moderate or severe vasospasm in either of the major blood vessels supplying the watershed territory.

The database and patient charts were retrospectively reviewed to obtain clinical data including history of vascular risk factors, admission GCS and WFNS scores,²⁰ and the need for ventriculostomy. We also obtained information regarding aneurysm location and aneurysm treatment (i.e. clipping or coiling).

Statistical Analysis

Characteristics of patients who experienced delayed infarcts were compared to those who did not have delayed infarcts. Additionally, of patients with delayed infarcts, characteristics of those whose infarcts were related to vasospasm were compared to those whose infarcts were unrelated to vasospasm. Finally, the nature of infarcts themselves was compared between those infarcts related to vasospasm and those occurring in the absence of vasospasm. Binary variables were compared using Fisher’s exact test. Continuous variables, including infarct volumes, were compared via t-test or the Mann-Whitney-U test if non-normality was determined. Differences in infarct location were assessed via logistic regression.

Results

We identified 276 patients with confirmed aSAH who survived at least 7 days after the initial hemorrhage; 134 patients met all inclusion criteria. The majority of those excluded lacked a post-procedural CT scan (Figure 1). 89% of included subjects were classified as modified Fisher 3 or 4 and 31% presented in poor clinical status (WFNS grade 4 or 5, see Table 1). 54 of the 134 patients (34%) had moderate or severe angiographic vasospasm in at least 1 vascular territory. Twenty out of the 134 patients (15%) developed a delayed cerebral infarct after exclusion of procedural infarcts. The rate of delayed infarction in those with vasospasm was considerably higher (31%) than in those without any vasospasm (4%, $p<0.001$), although in one of these patients with vasospasm the infarct was actually in a vascular territory that was not affected by vasospasm. On univariate analysis, vasospasm was the only identified risk factor for delayed infarction in this cohort (Table 1). We did not find modified Fisher grade to predict infarction, although both groups had a high proportion

of grades 3 and 4, while higher IVH score and female gender had only non-significant trends towards higher rates of infarction.

Patients

Fifteen of the 20 patients with delayed infarcts had infarcts related to vasospasm while 4 had infarcts unrelated to vasospasm, and one patient had infarcts both related and unrelated to vasospasm. Table 2 compares characteristics of the 15 patients who only had infarcts related to vasospasm to the four patients who only had infarcts unrelated to vasospasm. An MCA aneurysm was the most common aneurysm association with vasospasm-unrelated infarcts (75%), while aneurysms in the anterior circle of Willis tended to be more common with vasospasm-related infarcts ($p=0.272$). There were no other significant differences between patients whose infarcts were associated with vasospasm and those whose infarcts were not.

Infarcts

There were a total of 29 delayed infarcts (Table 3). Twenty-one infarcts were associated with proximal arterial vasospasm, while eight (28%) were seen in the absence of any vasospasm. Half of the infarcts related to vasospasm were in the ACA territory, while no infarcts unrelated to vasospasm occurred in the ACA territory. Rather, 50% of vasospasm-unrelated infarcts were in “watershed” territories compared to only 10% of vasospasm-related infarcts ($p=0.03$). Infarcts related to vasospasm were not larger than those unrelated to vasospasm and were evenly divided between cortical and subcortical regions.

Discussion

In this selected cohort, 25% of patients with delayed cerebral infarction after aSAH had no significant vasospasm. Furthermore, over a quarter of all delayed infarcts could not be explained by vasospasm in the corresponding vascular territory. Infarcts unrelated to vasospasm were more likely located in watershed territories, while vasospasm-related infarcts were more likely in a vascular distribution. Otherwise, vasospasm-unrelated infarcts did not differ in size or location from infarcts associated with vasospasm.

The first published images of cerebral vasospasm were reported by Ecker and Riemenschneider in 1951.²¹ Their publication was followed by a heated debate regarding the role of this angiographic phenomenon in the development of delayed ischemia.²² However, Fisher silenced the debate in 1977 with his report of 50 aSAH patients showing a strong correlation between angiographic vasospasm and the development of delayed (between days 4 and 14) neurological deficits.²³ Following Fisher’s publication, the main focus in the management of aSAH patients after securing the aneurysm involves the prevention and treatment of vasospasm. Nimodipine became standard of care in the 1980s after studies showed it lead to a significant reduction in both cerebral infarction and poor outcome in aSAH patients.²⁴ However, despite this demonstrated efficacy, nimodipine did not reduce the frequency of angiographic vasospasm.

Over 2 decades have passed since this study, and nimodipine remains the sole medication established to improve outcomes in aSAH patients. This may be due to an overemphasis on the prevention of vasospasm. For example, clazosentan, an endothelin inhibitor, significantly reduces the incidence of angiographic vasospasm but does not reduce the incidence of cerebral infarction or improve outcome.^{9,10} Our study, which showed that in 25% of the patients with infarcts they were unrelated to vasospasm, provides a possible explanation for this discrepancy and suggests mechanisms independent of vasospasm may play a role in the development of delayed cerebral infarction.

Several other mechanisms have been proposed as potential causes of DCI and infarction in aSAH. One possibility is microcirculatory dysfunction, impaired vascular reactivity or “microspasm.” In the setting of proximal vasospasm, compensatory dilation of downstream arterioles would preserve cerebral blood flow, such that anything except for the most severe spasm would require a concomitant impairment in small vessel vasodilation for ischemia to occur. In fact, one study showed reduced, rather than increased, cerebral blood volume in the setting of vasospasm, suggesting impairment in autoregulatory function.²⁵ Another proposed mechanism for infarcts unrelated to vasospasm is the occurrence of cerebral thromboembolic events following aSAH. Both an increased platelet consumption and increased CSF thrombin production have been associated with DINDs and infarction.^{26,27} In addition, transcranial Doppler studies indicate a high incidence of embolic signals.¹³ It is possible that territorial infarcts in our study unrelated to angiographic vasospasm were a result of either microvascular dysfunction or thromboembolic disease. Moreover, patients with moderate or severe vasospasm who did not develop infarcts may have had sufficient autoregulatory function as to be able to maintain adequate cerebral blood flow.

Another intriguing putative explanation for vasospasm-unrelated infarcts is the phenomenon of cortical spreading depression (CSD). Shown experimentally many years ago, when using cortical EEG electrodes, CSD occurs frequently following aSAH and other types of brain injury.¹⁴ CSD is an increasingly recognized cause of ischemia and has recently been associated with DCI in the absence of angiographic vasospasm.²⁸ If CSD is a significant cause of vasospasm-unrelated infarcts, the infarcts would be expected to be mostly cortical. Indeed, one study looking at small cortical infarcts on magnetic resonance imaging found that 70% were not associated with significant vasospasm.²⁹ However, we did not find vasospasm-independent infarcts to occur more frequently in cortical regions. This finding may suggest that CSD was not a substantial cause of infarction in our study, or may be due to the decreased sensitivity of CT for detecting these types of infarcts.

Finally, there is growing evidence that inflammation plays a role in DCI after aSAH.^{30–34} The systemic inflammatory response syndrome (SIRS) is present in the vast majority of aSAH patients and predicts poor outcome.³⁵ The presence of subarachnoid blood activates the release of the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor- α .^{36–37} Elevated levels of myeloperoxidase correlate with clinical signs of delayed ischemia.³⁸

A strength of this study is the precise correlation of each infarct to results of cerebral angiography. In fact, 17 of the 20 patients with delayed infarcts had angiographic vasospasm, yet 2 of these patients had infarcts in territories that were not affected by vasospasm. Proximal vasospasm, while present, was not the cause of these patient’s infarcts. Comparing rates of vasospasm to rates of infarction only at a patient-level would miss this discrepancy. Of note, we considered infarcts in territories with mild vasospasm to be unrelated to vasospasm. As vessel narrowing of this degree is not flow-limiting, it is unlikely to significantly affect perfusion. This is supported by a CT perfusion study that showed reductions in perfusion proportional to the degree of vasospasm.⁸ Furthermore, when analyzing watershed infarcts, although we did not have data on degree of collaterals, we evaluated for even a moderate degree of vasospasm in either contributing vessel to ensure that vasospasm was not a factor in these types of infarcts.

Another strength of this study was our rigorous methodology to exclude procedural infarcts. The rate of stroke following SAH varies substantially in the literature depending on the methods of ascertainment. Our rate of 15% agrees with other studies that specifically excluded procedural infarcts.⁴ Studies showing substantially higher rates are likely adulterated by procedure-related infarcts. In fact, a study in 2010 found 69 of 174 patients

undergoing surgical clipping experienced a procedure-related infarct.³⁹ Inadvertently including procedure-related infarcts in the analysis would overestimate the frequency of delayed infarcts as well as overcall the number of vasospasm-unrelated infarcts. While this rigorous approach limited the number of patients eligible for analysis, we felt it critical in properly carrying out this study.

Limitations

Due to the retrospective nature of this study and its design, it has a number of important limitations that must be considered when interpreting the results. The inclusion criteria and the need for imaging at three time windows introduced selection bias. Of the 276 patients with aSAH, just under half were eventually included in the analysis. This leaves a smaller subgroup to be analyzed, likely those who were sicker and more symptomatic (and therefore more likely to undergo repeat imaging). Our findings best reflect this patient population and not necessarily the SAH patient who remains asymptomatic and never undergoes repeat imaging.

The majority were excluded for not having post-procedural CT scans. To be included, these scans had to have been performed 24–48 hours after the aneurysmal securing procedure. Scans performed too soon would have decreased sensitivity for detecting an infarct, while scans performed greater than 48 hours would be within the “DCI window.” Still it is possible that a peri-procedural infarct may have been missed and the infarct classified as due to DCI and unrelated to vasospasm.

Similarly, angiographic vasospasm may have been missed. However, the chances of that occurring are relatively small since we routinely perform angiograms on all patients, whether symptomatic or not 6–8 days after aSAH. In addition, patients routinely underwent angiography any time there was a suspicion of clinical worsening.

Conclusion

This study provides further support for the multifactorial nature of DCI and infarction in aSAH. Focusing solely on the prevention and treatment of cerebral vasospasm may not benefit patients whose infarcts appear to be unrelated to angiographic vasospasm. Infarcts unrelated to vasospasm are similar in size to infarcts related to vasospasm, but are more likely watershed. Whether there are multiple distinct etiologies that lead to delayed infarction or whether it is an interaction between several mechanisms needs to be further evaluated.

References

1. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology*. 1998; 50(5):1413–1418. [PubMed: 9595997]
2. Vergouwen MD, Vermeulen M, van Gijn J, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010; 41(10):2391–2395. [PubMed: 20798370]
3. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007; 38(8):2315–2321. [PubMed: 17569871]
4. Schmidt JM, Wartenberg KE, Fernandez A, et al. Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. *J Neurosurg*. 2008; 109(6): 1052–1059. [PubMed: 19035719]

5. Rabinstein AA, Friedman JA, Weigand SD, et al. Predictors of Cerebral Infarction in aneurysmal subarachnoid hemorrhage. *Stroke*. 2004; 35(8):1862–1866. [PubMed: 15218156]
6. Fergusen S, Macdonald RL. Predictors of Cerebral Infarction in Patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2007; 60(4):658–667. [PubMed: 17415202]
7. Crowley RW, Medal R, Dumont AS, et al. Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage. *Stroke*. 2011; 42(4):919–923. [PubMed: 21350201]
8. Dankbaar JW, Rijdsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Neuroradiology*. 2009; 51(12):813–819. [PubMed: 19623472]
9. Macdonald RL, Kassell NF, Mayer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke*. 2008; 39(11):3015–3021. [PubMed: 18688013]
10. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomized, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011; 10(7):618–625. [PubMed: 21640651]
11. Vergouwen M, Vermeulen M, Roos Y. Delayed Cerebral Ischemia after aneurysmal subarachnoid hemorrhage: Is angiographic vasospasm an epiphenomenon? *Stroke*. 2009; 40(2):e39. [PubMed: 19074477]
12. Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2000; 31(7):1621–1627. [PubMed: 10884463]
13. Azarpazhooh MR, Velayati A, Chambers BR, Nejad HM, Nejad PS. Microembolic signals in subarachnoid hemorrhage. *J Clin Neurosci*. 2009; 16(3):390–393. [PubMed: 19138849]
14. Dreier JP, Major S, Manning A, et al. Cortical spreading ischemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid hemorrhage. *Brain*. 2009; 132:1866–1881. [PubMed: 19420089]
15. Miller JA, Dacey RG Jr, Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke*. 1995; 26(12):2260–2266. [PubMed: 7491647]
16. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB, et al. Computed tomographic diagnosis of intraventricular hemorrhage. *Radiology*. 1982; 143(1):91–96. [PubMed: 6977795]
17. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery*. 2006; 59(1):21–27. [PubMed: 16823296]
18. Rabinstein AA, Weigand S, Atkinson JL, Wijdicks EF. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke*. 2005; 36(5):992–997. [PubMed: 15831836]
19. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of the human brain: cerebral hemispheres. *Neurology*. 1998; 50(6):1699–1708. [PubMed: 9633714]
20. Teasdale GM, Drake CG, Hunt W, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. *J Neurol Neurosurg Psychiatry*. 1988; 51(11):1457. [PubMed: 3236024]
21. Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. *J Neurosurg*. 1951; 8(6):660–667. [PubMed: 14889314]
22. Millikan CH. Cerebral vasospasm and ruptured intracranial aneurysm. *Arch Neurol*. 1975; 32(7):433–449. [PubMed: 1137510]
23. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm-the clinical manifestations. *Neurosurgery*. 1977; 1(3):245–248. [PubMed: 615969]
24. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ*. 1989; 298(6674):636–642. [PubMed: 2496789]

25. Yundt KD, Grubb RK Jr, Diringer MN, Powers WJ. Autoregulatory vasodilation of parenchymal vessels is impaired during cerebral vasospasm. *J Cereb Blood Flow Metab.* 1998; 18(4): 419–424. [PubMed: 9538907]
26. Hirashima Y, Hamada H, Kurimoto M, Origasa H, Endo S. Decrease in platelet count as an independent risk factor for symptomatic vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2005; 102(5):882–887. [PubMed: 15926714]
27. Kasuya H, Shimizu T, Takakura K. Thrombin activity in CSF after SAH is correlated with the degree of SAH, the persistence of clot and the development of vasospasm. *Acta Neurochira (Wien).* 1998; 140(6):579–584.
28. Woitzik J, Dreier JP, Hecht N, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. *J of Cereb Blood Flow and Metab.* 2012; 32(2):203–212. [PubMed: 22146193]
29. Weidauer S, Vatter H, Beck J, et al. Focal laminar cortical infarcts following aneurysmal subarachnoid hemorrhage. *Neuroradiology.* 2008; 50:1–8. [PubMed: 17922121]
30. Provencio JJ. Inflammation in subarachnoid hemorrhage and delayed deterioration associated with vasospasm: a review. *Acta neurochirurgica Supplement.* 2013; 115:233–8. Epub 2012/08/15. 10.1007/978-3-7091-1192-5_42 [PubMed: 22890674]
31. Nyquist PA, Wang H, Suffredini AF. Protein biomarkers in patients with subarachnoid hemorrhage, vasospasm, and delayed ischemic neurological deficits. *Acta neurochirurgica Supplement.* 2013; 115:23–5. Epub 2012/08/15. 10.1007/978-3-7091-1192-5_6 [PubMed: 22890638]
32. Lim M, Bower RS, Wang Y, Sims L, Bower MR, Camara-Quintana J, et al. The predictive value of serum myeloperoxidase for vasospasm in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgical review.* 2012; 35(3):413–9. discussion 9. Epub 2012/03/01. 10.1007/s10143-012-0375-4 [PubMed: 22370810]
33. Echigo R, Shimohata N, Karatsu K, Yano F, Kayasuga-Kariya Y, Fujisawa A, et al. Trehalose treatment suppresses inflammation, oxidative stress, and vasospasm induced by experimental subarachnoid hemorrhage. *Journal of translational medicine.* 2012; 10:80. Epub 2012/05/02. 10.1186/1479-5876-10-80 [PubMed: 22546323]
34. Chou SH, Feske SK, Simmons SL, Konigsberg RG, Orzell SC, Marckmann A, et al. Elevated Peripheral Neutrophils and Matrix Metalloproteinase 9 as Biomarkers of Functional Outcome Following Subarachnoid Hemorrhage. *Translational stroke research.* 2011; 2(4):600–7. Epub 2011/12/31. 10.1007/s12975-011-0117-x [PubMed: 22207885]
35. Dhar R, Diringer MN. The burden of the systemic inflammatory response predicts vasospasm and outcome after subarachnoid hemorrhage. *Neurocritical care.* 2008; 8(3):404–12. Epub 2008/01/16. 10.1007/s12028-008-9054-2 [PubMed: 18196475]
36. Gruber A, Rossler K, Graninger W, et al. Ventricular cerebrospinal fluid and serum concentrations of sTNF-R-I, IL-1ra, and IL-6 after aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol.* 2000; 12(4):297–306. [PubMed: 11147377]
37. Fassbender K, Hodapp B, Rossol S, et al. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. *J Neurol Neurosurg Psychiatry.* 2001; 70(4):534–7. [PubMed: 11254783]
38. Schoch B, Regel JP, Wichert M, et al. Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. *Neurosurgery.* 2007; 60(5):828–36. [PubMed: 17460517]
39. Umredkar A, Gupta SK, Khandelwal N, et al. Intracerebral infarcts following clipping of intracranial aneurysms: incidence, clinical correlation and outcome. *Brit J of Neurosurg.* 2010; 24(2):156–162. [PubMed: 20210531]

Figure 1.
Patient flow at each stage

Table 1

Patients with and without delayed infarcts

	All Patients (n=134)	Delayed infarct (n=20)	No Infarct (n=114)	p-value	OR (CI)
Age (Mean $\pm$ SD)	55 $\pm$ 14	54 $\pm$ 10	55 $\pm$ 14	0.798	
Male Gender	29 (22%)	1 (5%)	28(24%)	0.074	0.16 (0.02,1.27)
EVD	93 (69%)	13 (65%)	80(70%)	0.611	0.79(0.29,2.15)
Smoker	81 (60%)	15 (75%)	66(58%)		
Hypertension	62 (47%)	8 (40%)	53(47%)		
Diabetes	8 (6%)	1 (5%)	7(6%)		
Prior stroke	6 (5%)	1 (5%)	5(4%)		
WFNS Grade 1–3	92 (69%)	12 (60%)	80 (70%)		
WFNS Grade 4–5	42 (31%)	8 (40%)	34 (30%)	0.435	1.57(.59,4.18)
MFS 0–2	15 (11%)	1 (5%)	14 (12%)		
MFS 3–4	119 (89%)	19 (95%)	100 (88%)	0.469	2.66(.33–21.44)
IVH Score (median, range)	2 (0–12)	3.5 (0–10)	2 (0–12)	0.209	1.08 (0.94, 1.25) ^b
Coiled	67(50%)	7 (35%)	60 (53%)		
Clipped	67 (50%)	13 (65%)	54 (47%)	0.225	2.06(.77–5.55)
Angiographic spasm	54 (40%)	17 (85%)	37 (32%)	<0.001	11.79(3.25,42.78)
Discharge Disposition					
Home or rehab	116 (86%)	16 (80%)	100 (88%)		
Chronic Care	13 (10%)	2 (10%)	11 (10%)	0.875	1.14(0.23,5.61)
Dead	5 (4%)	2 (10%)	3 (2%)	0.134	4.17(0.65,26.91)

OR: odd's ratio; M: male; EVD: external ventriculostomy drain; WFNS: world federation of neurological surgeons; MFS: modified fisher scale; IVH: intraventricular hemorrhage

Table 2Patients with VSP-related and VSP-unrelated infarcts^a

	Delayed infarct with VSP (n=15)	Delayed infarct without VSP (n=4)
Age (Mean $\pm$ SD)	53 $\pm$ 11	57 $\pm$ 9
Hydrocephalus	10 (67%)	2 (50%)
Smoker	10 (67%)	4 (100%)
Hypertension	6 (40%)	1 (25%)
WFNS Grade 4–5	6 (43%)	1 (25%)
MFS 3–4	14 (93%)	4 (100%)
IVH Score (median, range)	3 (0–10)	4 (0–4)
Aneurysm Clipped	9 (60%)	3 (75%)
Aneurysm Location		
ICA/A Com	8 (53.3%)	1 (25%)
P Com	4 (26.7%)	1 (25%)
MCA	2 (13.3%)	2 (50%)
Basilar	1 (6.7%)	0 (0%)
Discharge Disposition		
Home or Rehab	11 (73%)	3 (75%)
Chronic Care	3 (20%)	0
Dead	1 (7%)	1 (25%)

^aVSP: vasospasm; WFNS: world federation of neurological surgeons; MFS: modified fisher scale; IVH: intraventricular hemorrhage; ICA: internal carotid artery; A Com: anterior communicating artery; P Com: posterior communicating artery; MCA: middle cerebral artery

Table 3Infarct characteristics^a

	Delayed infarct w/VSP (n=21)	Delayed Infarct w/o VSP (n=8)	P-value
Volume (mean ± SD)	18 ± 25	11 ± 12	0.542
Infarct location			0.871 ^b
Isolated Cortical	8 (38%)	3 (38%)	
Deep	6 (29%)	3 (38%)	
Combined	7 (33%)	2 (25%)	
Infarct territory			
ACA	11 (52%)	0 (0%)	
MCA	7 (33%)	2 (25%)	
PCA	1 (5%)	2 (25%)	
Watershed	2 (10%)	4 (50%)	0.033 ^c

^aVSP, vasospasm; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery;^bDerived using multiple logistic regression^cDerived using Fisher's exact test comparing watershed to non-watershed infarcts