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

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BACKGROUND: Delayed cerebral ischemia is common after aneurysmal subarachnoid hemorrhage (aSAH) and is a major contributor to poor outcome. Yet, although generally attributed to arterial vasospasm, neurological 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 to vasospasm vs those unrelated.

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 computed tomography scan both 24 to 48 hours following aneurysm treatment and ≥7 days after SAH, and had a catheter angiogram to evaluate for vasospasm. Delayed infarcts seen on late computed tomography 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. Fifty-four (34%) had moderate or severe vasospasm, of whom 17 (31%) had delayed infarcts, compared with only 3 (4%) of 80 patients without vasospasm ($P < .001$). There were a total of 29 delayed infarcts in these 20 patients; 21 were in a territory with angiographic vasospasm, but 8 (28%) were not. Infarct volume did not differ between vasospasm-related (18 ± 25 mL) and vasospasm-unrelated (11 ± 12 mL) infarcts ($P = .54$), but infarcts in the absence of vasospasm were more likely watershed (50% vs 10%, $P = .03$).

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

KEY WORDS: Cerebral vasospasm, Delayed cerebral ischemia, Stroke, Subarachnoid hemorrhage

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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 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% to 20% of aSAH survivors and is a major predictor of poor outcome.[3-6]

ABBREVIATIONS: ACA, anterior cerebral artery; **aSAH,** aneurysmal subarachnoid hemorrhage; **CSD,** cortical spreading depression; **DCI,** delayed cerebral ischemia

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, and inflammation.[12-14] These varied etiologies may lead to differences in infarct characteristics including size and location. Furthermore, because 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.

PATIENTS AND 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 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 to 8 days after rupture, and had CT scans both 24 to 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 Neurology/Neurosurgery Intensive Care Unit. 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 whether endovascular interventions were performed. In the absence of neurological decline, patients routinely underwent cerebral angiography screening at about day 7 after SAH. Transcranial Doppler ultrasound was not performed.

Data Collection

Admission CTs were reviewed to obtain the modified Fisher and intraventricular hemorrhage scores.[16,17] Late CTs were reviewed for well-defined hypodensities; if a hypodensity was seen, the postprocedure scan was reviewed. Hypodensities seen only on the late CT and not otherwise explained (eg, 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 artery (ACA), middle cerebral artery, posterior cerebral artery, 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 1 of 2 investigators (A.K. and R.J.B.) who demonstrated excellent interrater 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 the presence and location of vasospasm. Severity of vasospasm was determined by 1 of 3 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 Glasgow Coma Score and World Federation of Neurological Surgeons scores,[20] and the need for ventriculostomy. We also obtained information regarding aneurysm location and aneurysm treatment (ie, clipping or coiling).

Statistical Analysis

Characteristics of patients who experienced delayed infarcts were compared with those who did not have delayed infarcts. Additionally, of patients with delayed infarcts, characteristics of those whose infarcts were related to vasospasm were compared with 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 by using the Fisher exact test. Continuous variables, including infarct volumes, were compared via t test or the Mann-Whitney U test if nonnormality 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 postprocedural CT scan (Figure 1). Eighty-nine percent of included subjects were classified as modified Fisher 3 or 4, and 31% presented in poor clinical status (World Federation of Neurological Surgeons grade 4 or 5; see Table 1). Fifty-four of the 134 patients (34%) had moderate or severe angiographic vasospasm in at least 1 vascular territory. Twenty 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%, $P < .001$), although in 1 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

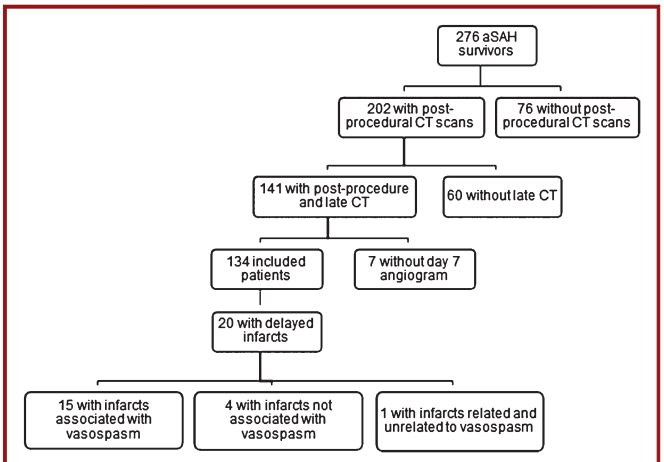

FIGURE 1. *Patient flow at each stage. aSAH, aneurysmal subarachnoid hemorrhage.*

(Table 1). We did not find modified Fisher grade to predict infarction, although both groups had a high proportion of grades 3 and 4, whereas higher intraventricular hemorrhage score and female sex had only non significant trends toward higher rates of infarction.

Patients

Fifteen of the 20 patients with delayed infarcts had infarcts related to vasospasm, whereas 4 had infarcts unrelated to vasospasm, and 1 patient had infarcts both related and unrelated to vasospasm. Table 2 compares characteristics of the 15 patients who only had infarcts related to vasospasm with the 4 patients who only had infarcts unrelated to vasospasm. A middle cerebral artery aneurysm was the most common aneurysm association with vasospasm-unrelated infarcts (75%), whereas aneurysms in the anterior circle of Willis tended to be more common with vasospasm-related infarcts (P = .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, whereas 8 (28%) were seen in the absence of any vasospasm. Half of the infarcts related to vasospasm were in the ACA territory, whereas no infarcts unrelated to vasospasm occurred in the ACA territory. Rather, 50% of vasospasm-unrelated infarcts were in "watershed" territories compared with only 10% of vasospasm-related infarcts (P = .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

TABLE 1. Patients With and Without Delayed Infarcts[a,b]

	All Patients (n = 134)	Delayed Infarct (n = 20)	No Infarct (n = 114)	*P*	OR (CI)
Age, mean ± SD	55 ± 14	54 ± 10	55 ± 14	.798	
Male sex	29 (22)	1 (5)	28 (24)	.074	0.16 (0.02,1.27)
EVD	93 (69)	13 (65)	80 (70)	.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)		
Previous 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)	.435	1.57 (0.59,4.18)
MFS 0-2	15 (11)	1 (5)	14 (12)		
MFS 3-4	119 (89)	19 (95)	100 (88)	.469	2.66 (0.33-21.44)
IVH score, median (range)	2 (0-12)	3.5 (0-10)	2 (0-12)	.209	1.08 (0.94, 1.25)[c]
Coiled	67 (50)	7 (35)	60 (53)		
Clipped	67 (50)	13 (65)	54 (47)	.225	2.06 (0.77-5.55)
Angiographic spasm	54 (40)	17 (85)	37 (32)	<.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)	.875	1.14 (0.23,5.61)
Dead	5 (4)	2 (10)	3 (2)	.134	4.17 (0.65,26.91)

[a]CI, confidence interval; EVD, external ventriculostomy drain; IVH, intraventricular hemorrhage; MFS, modified Fisher scale; OR, odds ratio; rehab, rehabilitation; SD, standard deviation; WFNS, World Federation of Neurological Surgeons.
[b]Values are n (%), unless otherwise stated.
[c]OR reflects a one point increase in IVH score.

TABLE 2. Patients With VSP-related and VSP-unrelated Infarcts[a,b]

	Delayed Infarct With VSP (n = 15)	Delayed Infarct Without VSP (n = 4)
Age, mean ± SD	53 ± 11	57 ± 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)

[a]A Com, anterior communicating artery; ICA, internal carotid artery; IVH, intraventricular hemorrhage; MFS, modified Fisher scale; MCA, middle cerebral artery; P Com, posterior communicating artery; SD, standard deviation; VSP, vasospasm; WFNS, World Federation of Neurological Surgeons.
[b]Values are n (%), unless otherwise stated.

vasospasm in the corresponding vascular territory. Infarcts unrelated to vasospasm were more likely located in watershed territories, whereas 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.

TABLE 3. Infarct Characteristics[a,b]

	Delayed Infarct With VSP (n = 21)	Delayed Infarct Without VSP (n = 8)	*P*
Volume, mean ± SD	18 ± 25	11 ± 12	.542
Infarct location			.871[c]
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)	.033[d]

[a]ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; VSP, vasospasm.
[b]Values are n (%), unless otherwise stated.
[c]Derived using multiple logistic regression.
[d]Derived using the Fisher exact test comparing watershed with nonwatershed infarcts.

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] Since Fisher's publication, the main focus in the management of aSAH patients after securing the aneurysm involved the prevention and treatment of vasospasm. Nimodipine became standard of care in the 1980s after studies showed it led 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, the infarcts 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 increased platelet consumption and increased CSF thrombin production have been associated with delayed ischemic neurological deficits 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 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 electroencephalography 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 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 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 with 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. Because 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 the 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 that 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. Although this rigorous approach limited the number of patients eligible for analysis, we felt that it was critical in properly conducting this study.

Limitations

Because of 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 3 time windows introduced selection bias. Of the 276 patients with aSAH, just less than 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 postprocedural CT scans. To be included, these scans had to have been performed 24 to 48 hours after the aneurysmal securing procedure. Scans performed too soon would have decreased sensitivity for detecting an infarct, whereas scans performed greater than 48 hours would be within the "DCI window." Still it is possible that a periprocedural 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 because we routinely perform angiograms on all patients, whether symptomatic or not 6 to 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.

Disclosures

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COMMENTS

This is a retrospective review of 134 patients with aneurysmal subarachnoid hemorrhage (SAH) who were selected from a total of 276 (49% of the total) patients. The findings are consistent with previous studies showing that infarctions detected days after SAH are almost always associated with moderate or severe angiographic vasospasm.[1] The interesting finding was that some of the infarctions in patients with angiographic vasospasm were not in territories of vasospastic arteries, and a few infarcts were in patients with no angiographic vasospasm. As with any retrospective review, there are several limitations to this analysis, as well as many possible explanations for the findings, none of which can be ruled out with certainty. The infarctions that are not in the territory of vasospastic arteries may be in brain regions of low cerebral blood flow due to poor collateral circulation. Another issue is that delayed neurological deterioration is treated with induced hypertension, and there is some evidence that treating the patient with vasopressors that are potent vasoconstrictors might cause ischemia.[2] Furthermore, other processes postulated to cause delayed ischemia (cortical spreading ischemia, microthromboemboli, and such) may cause the infarctions. These processes seem to be associated with angiographic vasospasm, however, because the delayed infarctions are uncommon in patients with no angiographic vasospasm. Whether the relation between angiographic vasospasm and other possible mechanisms of delayed cerebral ischemia is causal or due to common underlying pathophysiological mechanisms is an interesting scientific question. In previous studies, we also found some difficulty in figuring out what the cause of delayed infarction was; thus, the opinion of the reader interpreting the studies also matters.[3] The data in Table 3 remind me of what we saw in reviewing baseline, 24 to 48 hours postaneurysm securing and 6 week computed tomographic (CT) scans and baseline and vasospasm interval catheter angiograms of about 400 patients in CONSCIOUS-1. There was a group of patients with infarctions, often watershed or posterior cerebral artery territory appearing in a delayed fashion. We would review the CT scan done 24 to 48 hours

after the aneurysm securing procedure, trying to see if there were early signs of ischemia where the infarct eventually was seen and the clinical data to see if there were technical difficulties with the catheter angiograms or the patient had increased intracranial pressure and possible transient herniation and such. We would argue about whether it was in a vascular territory or was venous. Then we would conclude we had no idea what the cause of the infarct was. Overall, this is a very well done study. Although only half of the patient population could be studied, data collection was quite complete and rigorously analyzed. All patients underwent catheter angiography during the delayed cerebral ischemia interval, which is remarkable. In our institution, patients with aneurysmal SAH may never have a catheter angiogram, given the quality of CT angiography. For example, an older patient who undergoes neurosurgical clipping and has no postoperative deterioration or complications does not have a catheter angiogram for surgery or need one in follow-up. I check the clipping with intraoperative angiography through the superficial temporal artery and/or indocyanine green angiography and I do not care if we miss a 2-mm unruptured aneurysm that might be detected by postoperative catheter angiography, because it would not be treated anyway. In conclusion, the authors add another well-done, comprehensive analysis of infarctions after SAH.

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Over the past 4 years there has been a marked shift in our thinking concerning the etiology of delayed cerebral infarction (DCI) after aneurysmal subarachnoid hemorrhage (SAH). For more than half a century, DCI was attributed primarily to arterial narrowing ("vasospasm"), based on the initial description of this phenomenon by Ecker and Riemenschneider in 1951[1] and bolstered by the correlation of vasospasm with focal deficits by Fisher in 1977.[2] Vasospasm became the main focus of basic science and clinical investigations in this area. It has become apparent, however, that although vasospasm is an important component of DCI, it is not the entire story, and may even be an epiphenomenon. This alternative view had been suspected for many years and strongly advocated by some of us,[3,4] but the concept of arterial narrowing as the main—if not sole—etiology for DCI remained dominant. A paradigm shift occurred after the publication in 2008 and 2011 of the well-designed and well-executed CONSCIOUS 1 and 2 studies,[5,6] which showed conclusively that clazosentan (a highly specific endothelin receptor antagonist) significantly reduced angiographic vasospasm in a dose-dependent fashion, but had no significant effect on mortality or vasospasm-related morbidity. CONSCIOUS 1 and 2 thus proved that arterial narrowing is not the sole etiology of delayed injury after SAH. In addition, vasospasm has been shown to occur in other conditions such as meningitis[7] and traumatic brain injury,[3] and therefore it is not exclusively associated with aneurysmal SAH. These observations have encouraged exploration of alternative explanations for the delayed injury after SAH. We have focused on the role of leukocyte/endothelial cell interactions (ie, inflammation).[2,8,9] Others, as reviewed by the authors in this article, have explored the role of microcirculatory dysfunction, impaired vascular reactivity or dysautoregulation, thromboembolic events, and the poorly-understood phenomenon of cortical spreading depression.

The current study is another outstanding contribution by the group from Washington University in St. Louis in which they show that about one-third of infarcts after aneurysmal SAH are unrelated to angiographic arterial narrowing. In a prospectively-accrued cohort of 134 patients, all of whom were admitted within 48 hours of rupture, had screening catheter angiograms 6-8 days after rupture, and had CT scans both 24-48 hours after their procedure and again at least 7 days after rupture, 34% developed moderate-to-severe angiographic vasospasm and 15% developed delayed infarcts. (Procedure-related infarcts were excluded from the analysis.) Of the 29 delayed infarcts, 21 were associated with proximal arterial vasospasm, but 8 (28%) were not. The authors noted that 50% of vasospasm-unrelated infarcts were in "watershed" territories as compared to only 10% of vasospasm-related infarcts. Vasospasm-related infarcts were similar in size to those unrelated to vasospasm and were also evenly divided between cortical and subcortical regions. This study is an important contribution to the growing literature on the complex etiology of delayed injury and deterioration after aneurysmal SAH, of which arterial narrowing or vasospasm is only one component.

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