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Inflammation, Cerebral Vasospasm and Brain Injury in Subarachnoid Hemorrhage – a Shifting Paradigm and a New Beginning

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Critical care management of subarachnoid hemorrhage (SAH) patients remains a daily challenge for intensivists. SAH comes on suddenly and unpredictably, primarily afflicts relatively young and healthy people, requires prolonged critical care support and leaves over 50% of survivors in protracted severe disability.[1, 2] Surviving the initial hemorrhage and surgical or endovascular obliteration of the bleeding aneurysm only marks the beginning of a 14-21 day long complex disease course where over 50% patients would develop cerebral vasoconstriction and ~30% develop new neurological deficits while others may accrue injuries silently because the severity of their neurological deficit precludes adequate clinical detection of ongoing injury.[3, 4] To date, there are no bedside monitors or biomarkers that can timely detect onset or reflect severity of SAH-associated brain injury,[5] and intensivists often find ourselves “shooting in the dark” with fluid resuscitation, vasopressors and ionotropic support. There is a dire need to develop biomarkers – such as lactate in sepsis – to guide goal-directed therapy in this prolonged course of brain resuscitation after SAH.

Cerebral vasospasm and delayed cerebral ischemia (DCI) are important sequelae of SAH. The definition of these two entities have varied widely in the literature, leading to much confusion over these terminologies and difficulty comparing results from different SAH clinical studies. Cerebral vasospasm often refers to narrowing of cerebral arteries seen on radiographic imaging modalities but many studies also defined vasospasm using transcranial doppler ultrasound criteria. DCI is typically defined as the delayed onset of neurological deterioration not explained by other causes but have also been used to refer to the presence of cerebral infarction on imaging studies.[6] Historical data showed DCI is the single most important cause of morbidity and mortality in SAH patients who survived definitive aneurysm treatment.[4]

Why have we still not found a biomarker or an effective therapy for SAH after decades of investigation? At the heart of this issue is cerebral vasospasm and its complex relationship with DCI and SAH outcome. The traditional paradigm in SAH is that patients, even after definitive aneurysm treatment, can develop cerebral vasoconstriction around 4-9 days after initial hemorrhage, and this can lead to delayed cerebral infarction and ultimately to morbidity or death. Under this paradigm, cerebral vasoconstriction is the key pathologic process in SAH-associated brain injury. While the association between poor outcome and DCI is strong and consistent across studies,[7, 8] the connection between cerebral vasoconstriction and SAH-associated brain injury is ambiguous[9]: The incidence of cerebral vasoconstriction far exceeds that of DCI. Cerebral infarctions can occur in vascular distributions without cerebral vasoconstriction. The effect of cerebral infarction on SAH outcome appears independent of vasoconstriction status,[10] and reversal of cerebral vasospasm may not improve clinical outcome.[11] Nimodipine, the only drug shown to reduce DCI and improve SAH outcome, has no effect on cerebral vasospasm.[12] In 2011, the CONSCIOUS-2 trial results provided definitive evidence for this dissociation between cerebral vasospasm and SAH outcome. In this large randomized trial, clazosentan, an endothelin-1 receptor inhibitor, successfully reduced angiographic cerebral vasospasm and yet had no effect on 90-day global functional outcome after SAH.[13] With this, the need for a complete paradigm shift in the understanding of SAH brain injury pathophysiology became undeniable. Scientific evidence to date clearly suggest that SAH-associated brain injury is a complex, multifactorial process that extends far beyond cerebral vasoconstriction, and in fact vasospasm-independent mechanisms such as early brain injury, inflammation, and cerebral spreading depolarization may have significantly larger effects on DCI and SAH outcome. [9, 14]

There is a robust body of pre-clinical evidence suggesting that neutrophils in the central nervous system contribute to cerebral vasoconstriction and subsequent neurological deterioration after SAH, and interruption of neutrophil signaling or depletion of myeloid cell lines ameliorate vasospasm and neurological deterioration.[15–17] High mobility group box-1 (HMGB1) is a damage-associated molecular patterns (DAMPs) mediator which can trigger neutrophil signaling and mediate inflammation in experimental models of brain injury. Elevated HMGB1 levels in blood and CSF has been associated with disease severity and poor outcome in traumatic brain injury, traumatic spinal cord injury, ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and even sepsis. [18–23]

In this issue of *Critical Care Medicine*, Chaudhry *et al* [24] examined HMGB1 concentrations in serially-collected blood samples from 53 SAH patients presenting within 24 hours from hemorrhage onset and found that SAH patients have elevated serum HMGB1 levels throughout post hemorrhage days 1 – 13 compared to non-SAH control patients, and amongst SAH patients, those who develop cerebral vasospasm had significantly higher HMGB1 levels. Interestingly, they found no association between serum HMGB1 levels and DCI or SAH outcome at discharge. As leukocytes may be an important source for HMGB1 in systemic circulation, the authors examined their correlation and found that while leukocyte count correlated with HMGB1, it only explained 8.4% of the variabilites in serum HMGB1 levels. Furthermore, since HMGB1 may induce downstream IL-6 release, the authors examined association of serum HMGB1 and IL-6 concentrations and found that

while HMGB1 correlated with IL-6 levels, the effect size was exceedingly small – it accounted for only 0.2% of overall variabilities in serum IL-6 levels.

There are several unique strengths to this study. This is one of few SAH biomarker studies where high frequency, repeated sampling enabled a thorough understanding of the target biomarker's trajectory over time throughout the peak risk period for cerebral vasospasm and DCI. It elegantly demonstrates the dynamic changes in a target biomarker and the importance of studying a potential biomarker's trajectory over an entire disease course.

The fact that serum HMGB1 showed strong association with vasospasm but not with DCI or SAH outcome is important. One of the common explanations for this apparent discrepancy is that macroscopic vasospasm defined by cerebral angiography inadequately represents the underlying tissue perfusion at a microcirculatory level, and that the neurologic decline in SAH is a result of symptomatic brain ischemia not visible on cerebral angiogram. This study, however, defined cerebral vasospasm by CT perfusion - a modality that is presumably better at studying microcirculation and local tissue perfusion though it has not been validated for ischemia detection in SAH.[25] Despite this novel definition of vasospasm, HMGB1 still showed association only with vasospasm but not DCI or SAH outcome. This is consistent with prior SAH biomarker studies and clinical trial where the target molecule or therapeutic intervention showed association with either vasospasm or DCI and SAH outcome, but not both.[5, 11–13, 26, 27] It should be noted that the definitions for cerebral vasospasm and the timing for outcome assessment use in this study differed significantly from recent large randomized SAH clinical trials and prior SAH biomarker studies.[13, 28, 29] A possible explanation for HMGB1's lack of association with DCI and SAH outcome suggested by the authors is that critical care interventions may have completely overcome the deleterious effects of cerebral vasospasm and thereby uncoupled its association with DCI or SAH outcome. If such is the case, then a biomarker for cerebral vasospasm like HMGB1 may not add much clinical value. Another alternative is that the tools used to determine DCI and SAH outcome in this study are too crude to reflect the impact of cerebral hypoperfusion from vasospasm, and perhaps brain MRI or detailed neurocognitive outcome may be more sensitive endpoints. In the end, serum HMGB1 now joins a growing list of candidate clinical biomarkers for SAH that awaits further validation before it can be considered for adaptation in clinical use.[5]

What are the scientific implications of this study? DCI and brain injury in SAH are undeniably more complex and potential mechanisms extend far beyond cerebral vasospasm. Does this mean cerebral vasospasm is unimportant and that molecules like HMGB1 which only associates with vasospasm but not DCI or SAH outcome are irrelevant? Our bedside clinical observations continue to argue the contrary. A subset of SAH patients still develop acute and clinically significant neurological deficits with arterial vasoconstrictions, and these deficits can be reversed by rescue endovascular vasodilatation therapy or critical care resuscitation to improve cerebral perfusion. How then does this study add to this conflicting story of vasospasm, DCI, and SAH outcome? What we learned from this study is that circulating HMGB1 levels increase early in SAH – well before the onset of vasospasm and DCI. Those who go on to develop vasospasm present with elevated HMGB1 levels and their levels stays elevated throughout acute SAH course. We have seen other systemic

inflammatory biomarkers behave similarly – some are associated with vasospasm and others with SAH outcome.[5, 26, 27] A picture is beginning to emerge where different combinations of inflammatory mediators may separate SAH patients into distinct subgroups - one that is likely to develop vasospasm while another likely to develop brain injury despite the absence of cerebral vasospasm. These subgroups are likely biologically distinct and may respond very differently to different therapies. Future clinical trials likely need to distinguish between these important patient phenotypes using panels of biomarkers such as HMGB1. These biomarker panels may inform study design and enable enrichment future trial by selecting patient subgroups likely to respond to the intervention.

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References

1. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, Rosenwasser RH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009; 40(3):994–1025. [PubMed: 19164800]
2. Fernando SM, Reardon PM, Dowlathshahi D, English SW, Thavorn K, Tanuseputro P, Perry JJ, Rosenberg E, Wijdicks EF, Heyland DK, et al. Outcomes and Costs of Patients Admitted to the ICU Due to Spontaneous Intracranial Hemorrhage. *Crit Care Med*. 2018; 46(5):e395–e403. [PubMed: 29406421]
3. Weir B, Grace M, Hansen J, Rothberg C. Time course of vasospasm in man. *J Neurosurg*. 1978; 48(2):173–178. [PubMed: 624965]
4. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. *J Neurosurg*. 1990; 73(1):18–36. [PubMed: 2191090]
5. Chou SH, Robertson CS, Participants in the International Multi-disciplinary Consensus Conference on the Multimodality M. Monitoring biomarkers of cellular injury and death in acute brain injury. *Neurocrit Care*. 2014; 21(Suppl 2):S187–214. [PubMed: 25208676]
6. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, 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]
7. Ferguson S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2007; 60(4):658–667. discussion 667. [PubMed: 17415202]
8. Vergouwen MD, Etminan N, Ilodigwe D, Macdonald RL. Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2011; 31(7):1545–1553. [PubMed: 21505477]
9. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. *Br J Anaesth*. 2012; 109(3):315–329. [PubMed: 22879655]

10. Vergouwen MD, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke*. 2011; 42(4):924–929. [PubMed: 21311062]
11. Haley EC Jr, Kassell NF, Torner JC, Truskowski LL, Germanson TP. A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg*. 1994; 80(5):788–796. [PubMed: 8169616]
12. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, Disney LB, Khan MI, Grace M, Holness RO, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg*. 1988; 68(4):505–517. [PubMed: 3280746]
13. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, Vajkoczy P, Wanke I, Bach D, Frey A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011; 10(7):618–625. [PubMed: 21640651]
14. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, Kasuya H, Wellman G, Keller E, Zauner A, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. *Neurol Res*. 2009; 31(2):151–158. [PubMed: 19298755]
15. Provencio JJ, Vora N. Subarachnoid hemorrhage and inflammation: bench to bedside and back. *Semin Neurol*. 2005; 25(4):435–444. [PubMed: 16341999]
16. Provencio JJ. Inflammation in subarachnoid hemorrhage and delayed deterioration associated with vasospasm: a review. *Acta Neurochir Suppl*. 2013; 115:233–238. [PubMed: 22890674]
17. Dumont AS, Dumont RJ, Chow MM, Lin CL, Calisaneller T, Ley KF, Kassell NF, Lee KS. Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. *Neurosurgery*. 2003; 53(1):123–133. discussion 133–125. [PubMed: 12823881]
18. Wang KY, Yu GF, Zhang ZY, Huang Q, Dong XQ. Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. *Clin Chim Acta*. 2012; 413(21–22):1737–1741. [PubMed: 22789964]
19. Tsukagawa T, Katsumata R, Fujita M, Yasui K, Akhoon C, Ono K, Dohi K, Aruga T. Elevated Serum High-Mobility Group Box-1 Protein Level Is Associated with Poor Functional Outcome in Ischemic Stroke. *J Stroke Cerebrovasc Dis*. 2017; 26(10):2404–2411. [PubMed: 28645523]
20. Zhou Y, Xiong KL, Lin S, Zhong Q, Lu FL, Liang H, Li JC, Wang JZ, Yang QW. Elevation of high-mobility group protein box-1 in serum correlates with severity of acute intracerebral hemorrhage. *Mediators Inflamm*. 2010; 2010
21. Nakahara T, Tsuruta R, Kaneko T, Yamashita S, Fujita M, Kasaoka S, Hashiguchi T, Suzuki M, Maruyama I, Maekawa T. High-mobility group box 1 protein in CSF of patients with subarachnoid hemorrhage. *Neurocrit Care*. 2009; 11(3):362–368. [PubMed: 19777384]
22. Papatheodorou A, Stein A, Bank M, Sison CP, Gibbs K, Davies P, Bloom O. High-Mobility Group Box 1 (HMGB1) Is Elevated Systemically in Persons with Acute or Chronic Traumatic Spinal Cord Injury. *J Neurotrauma*. 2017; 34(3):746–754. [PubMed: 27673428]
23. Stevens NE, Chapman MJ, Fraser CK, Kuchel TR, Hayball JD, Diener KR. Therapeutic targeting of HMGB1 during experimental sepsis modulates the inflammatory cytokine profile to one associated with improved clinical outcomes. *Sci Rep*. 2017; 7(1):5850. [PubMed: 28724977]
24. Chaudhry SR, Güresir A, Stoffel-Wagner B, et al. Systemic HMGB1, a novel predictive biomarker for cerebral vasospasm in aneurysmal Subarachnoid Hemorrhage. *Crit Care Med*. 2018 in press.
25. Greenberg ED, Gobin YP, Riina H, Johnson CE, Tsiouris AJ, Comunale J, Sanelli PC. Role of CT perfusion imaging in the diagnosis and treatment of vasospasm. *Imaging Med*. 2011; 3(3):287–297. [PubMed: 22773929]
26. Chou SH, Feske SK, Atherton J, Konigsberg RG, De Jager PL, Du R, Ogilvy CS, Lo EH, Ning M. Early elevation of serum tumor necrosis factor- α is associated with poor outcome in subarachnoid hemorrhage. *J Investig Med*. 2012; 60(7):1054–1058.
27. Chou SH, Feske SK, Simmons SL, Konigsberg RG, Orzell SC, Marckmann A, Bourget G, Bauer DJ, De Jager PL, Du R, et al. Elevated peripheral neutrophils and matrix metalloproteinase 9 as biomarkers of functional outcome following subarachnoid hemorrhage. *Transl Stroke Res*. 2011; 2(4):600–607. [PubMed: 22207885]

28. Dorhout Mees SM, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J, van Oostenbrugge RJ, Al-Shahi Salman R, Lavados PM, Rinkel GJ, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*. 2012; 380(9836):44–49. [PubMed: 22633825]
29. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD, Collaborators S. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurol*. 2014; 13(7):666–675. [PubMed: 24837690]