

## Review Article

# Potential Biomarkers for Vasospasm and Clinical Outcome after Aneurysmal Subarachnoid Hemorrhage

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## Abstract

Aneurysmal subarachnoid hemorrhage (SAH) and its sequela is a devastating disease process often leading to poor clinical outcome. The development of cerebral vasospasm (CV) and other delayed ischemic neurologic deficits (DINDs) determine the prognosis of patients after SAH. As a result, several studies have investigated the etiology of CV and DINDs in order to establish biological biomarkers that are clinically relevant for diagnostic and/or monitoring purposes. Despite our knowledge of the disease progression and our understanding of the role of inflammation, endothelial and vascular smooth muscle cell dysfunction, brain injury, and genetics, no candidate biomarker is routinely being used in the clinic. We review the current literature pertaining to biomarkers of CV and their clinical utility in the management of SAH patients.

**Keywords:** Biomarkers; Delayed ischemic neurological deficits; Cerebral vasospasm; Subarachnoid hemorrhage; Genetic markers

## Introduction

Aneurysmal subarachnoid hemorrhage (SAH) remains a devastating disease, with a majority of patients suffering a poor outcome. Despite advances in microsurgical and endovascular therapies, patients are frequently left with disabling neurologic deficits, resulting in a diminished quality of life and a loss of independence. For those that survive the initial aneurysm rupture, a significant percentage of persistent focal and/or cognitive deficits are the result of cerebral vasospasm (CV) and delayed ischemic neurologic deficits (DINDs) [1]. CV, which occurs in 70% of all SAH patients, is clinically significant in approximately 30% of the population and is the most serious complication in those surviving the first 24 hours following aneurysm rupture [2]. Importantly, CV accounts for a disproportionately high morbidity and mortality among young persons. Although the etiology of CV remains unclear, several studies have suggested that inflammation, endothelial dysfunction, response to brain injury, and genetic markers all play a role in CV pathogenesis. Despite our knowledge of the disease progression, there are no established biological biomarkers currently being used in the clinic for diagnostic or monitoring purposes. We review the current literature pertaining to biomarkers of CV and their clinical utility in the management of SAH patients.

## Inflammation

Aneurysm rupture results in the forceful entry of arterial blood into the subarachnoid space, leading to the circulation of erythrocytes and plasma throughout the cerebrospinal fluid (CSF). With time, these red blood cells are lysed, thereby creating a cytotoxic environment rich in free hemoglobin (Hgb) and the products of heme breakdown [3]. Through a series of complex cellular and molecular events, these byproducts of erythrocyte lysis trigger an immune response [4]. This inflammation cascade involves accumulation of immune cells through the expression of specific intercellular adhesion molecules (ICAMs), cytokine production, immunoglobulin and complement

activation, and various signaling pathways [5]. As a result, the post-SAH inflammatory response has become a target of interest in identifying the molecular and cellular biomarkers of CV.

## Intercellular Adhesion Molecules

ICAMs play a critical role in the inflammatory response to injury, thereby making them potentially attractive markers for the prediction of CV in the setting of post-SAH inflammation [6]. Multiple animal models have identified leukocyte-endothelial cell interactions to play a role in the pathogenesis of CV [7, 8]. Three families of ICAMs in particular, the selectins, integrins, and the immunoglobulin super family, may serve as potential clinically relevant biomarkers.

Although ICAMs have been shown to be upregulated following SAH [9-14], conflicting studies on its role in CV and DINDs have been reported. Polin et al. found significantly elevated CSF levels of ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin after SAH compared with control patients [9]. Interestingly, in the same study, E-selectin was the only adhesion molecule significantly elevated in the CSF of patients who later developed CV compared with those patients with uncomplicated SAH [9]. Kaynar et al. reported that ICAM-1 and VCAM-1 levels in the CSF and serum of patients with SAH were significantly elevated compared with control patients with hydrocephalus [10]. Nissen et al. reported no significant difference in serum concentration in several adhesion molecules including ICAM-1, VCAM-1, platelet endothelial cell adhesion molecule (PECAM-1), and E-selectin in patients who developed DINDs after SAH compared with those who did not [14]. However, the authors were able to show significant levels of serum P-selectin concentrations and lower levels of L-selectin concentrations in patients with DINDs [14]. Furthermore, investigating ICAM-1 levels, Mocco et al. and Mack et al. were both able to demonstrate increased soluble ICAM-1 levels in patients with SAH compared with control patients. In their studies, patients who later developed CV showed significant levels of ICAM-1 during the perivasospasm period (e.g., first 2 weeks) [11, 12], with

delayed ICAM-1 elevation (e.g., peak levels 8-12 days after SAH) correlating with poor clinical outcome [11].

The clinical utility of the two major integrins facilitating cell-cell adhesion and interaction, lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1), has yet to be evaluated in humans. However, monoclonal antibodies against these integrin family members using various SAH animal models have demonstrated a decrease in inflammatory response and CV and suggest potential candidate biomarkers. By blocking leukocyte migration into the subarachnoid space, CV was prevented in rats [7], rabbits [15], and cynomolgus monkeys [16]. Remarkably, these studies suggest that leukocytes play an important role in the pathogenesis of CV, since CV was prevented in the primate model despite the unaltered presence of hemoglobin in the subarachnoid space [16].

## Cytokines

In response to SAH, activation of microglia and astrocytes result in the proliferation and the secretion of three important cytokines: tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1-beta (IL-1 $\beta$ ), and interleukin-6 (IL-6) [17]. Multiple authors have reported the detection of these cytokines in the CSF of SAH patients [18-24]. Using cerebral microdialysis to measure CSF TNF- $\alpha$  levels, Hanafy et al. demonstrated a progressive rise in brain interstitial TNF- $\alpha$  levels 4 – 6 days after SAH [25]. Mathiesen et al. reported that patients with poor outcome after SAH had elevated TNF- $\alpha$  levels in their CSF on post-SAH days 4 – 10 [19]. In addition, studies by Fassbender et al. [23] and Chou et al. [24] also linked TNF- $\alpha$  levels with poor clinical outcome. Specifically, Chou et al. determined that elevated serum TNF- $\alpha$  levels 2-3 days after SAH were associated with a poor clinical outcome three months post-hemorrhage. Interestingly, in the same study, TNF- $\alpha$  levels were not associated with vasospasm [24].

Several studies have shown increased IL-6 levels in CSF following SAH [18, 21, 22, 26]. Patients with CV had significantly elevated IL-6 levels compared to patients without CV [20, 26, 27]. In addition, numerous studies have identified significantly elevated CSF levels of IL-6 in the acute phase (days 0-6) following SAH [18, 20-22, 26, 27]. As a result, CSF IL-6 concentration early in the disease progression, may predict CV development following SAH [26]. High concentrations of CSF IL-6 have also been observed in patients who developed DINDs, suggesting IL-6 CSF concentration as a potential predictor of clinically significant CV [28].

Studies investigating levels of IL-1 $\beta$  in SAH patients are inconsistent. Whereas, several studies found no detectable IL-1 $\beta$  in serum or CSF of SAH patients [21, 29], Hendryk et al. reported a significant increase in CSF IL-1 $\beta$  in SAH patients who developed CV and DINDs [22]. IL-1 receptor antagonist (IL-1ra), a potent inhibitor of IL-1, has been shown to be elevated in the CSF of patients after SAH [30] and may be associated with delayed ischemic events and poor clinical outcome [19].

The elevation of additional cytokines following SAH has been observed, however, the significance of these molecules as they relate to CV has yet to be determined. Interleukin-8 (IL-8) has been shown to be elevated in the CSF of patients with SAH [20, 21, 29], although Gaetani et al. found no association with CV [20]. The levels of monocyte chemoattractant protein-1 (MCP-1) were

found to be significantly higher in patients with SAH than in those with unruptured aneurysms [20, 31]. Although both studies found higher MCP-1 levels in CSF following SAH, the two studies conflict in determining an association with CV. Kim et al. found a significant elevation of MCP-1 levels in patients with angiographically confirmed vasospasm [31]. Conversely, Gaetani et al. found no significant difference in MCP-1 levels between patients with or without CV [20]. Finally, in a small study conducted by Mathiesen et al., the authors identified increased neopterin concentrations in both the serum and CSF of patients suffering from DINDs compared to uncomplicated SAH cases [32].

## C-reactive Protein

C-reactive protein (CRP) is a sensitive inflammatory marker that has been studied in relation to cardiovascular diseases [33, 34]. CRP is synthesized by hepatocytes in response to several cytokines including IL-1, IL-6, and TNF- $\alpha$  [35]. As mentioned above, these cytokines have been shown to be associated with CV pathogenesis and are currently being evaluated as candidate biomarkers. Romero et al. demonstrated higher CRP serum levels following SAH to be associated with worse clinical outcomes and neurologic deficits [36]. CRP levels were significantly elevated in the early stages (days 3-7) of disease progression, making CRP a potentially attractive clinically relevant marker for the early identification of those at risk for CV and DINDs [36].

## Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is a liposomal enzyme released by leukocytes, particularly by activated neutrophils, in response to a stimulus. Several studies have demonstrated a correlation between serum MPO and risk of myocardial infarction in patients with coronary artery disease [37-39]. Furthermore, serum MPO has been shown to have predictive power in evaluating prognosis in patients following an acute myocardial infarction [40-42].

Given the association between MPO levels and myocardial ischemic events, Lim and colleagues evaluated MPO as a potential biomarker of CV [43]. Serum MPO levels were elevated in SAH patients, compared to patients with unruptured aneurysms. In the same study, elevated serum MPO correlated with clinically significant CV in SAH patients. Furthermore, elevated MPO levels preceded or occurred on the day of symptomatic CV onset in the majority of patients. Based on these results, Lim and colleagues concluded that inflammation played an important role in CV. They also concluded that many of the SAH patients who did not show clinically evident CV had a subclinical level of vasospasm occurring, which in turn caused their MPO levels to rise compared to those patients with unruptured aneurysms [43]. As a result, this early rise in serum MPO may be a viable marker for detecting CV prior to the onset of symptomatology [43].

## Complement and Circulating Immune Complexes

There is strong clinical evidence to support complement and circulating immune complexes (CIC) as potential biomarkers for CV. Pellettieri et al. observed that patients with radiographic and/or clinical CV had a significantly higher frequency (52%) of CIC compared to SAH patients without CV (9%) [44]. Follow-up data

confirmed this association and determined that CIC levels during the first week after SAH correlated with CV [45]. Another study also determined that CIC levels were associated with CV and poor clinical outcome [46]. In addition, complement component C3d has been shown to be associated with CV [46] and C3a and C4a have been reported to be associated with DINDs [47]. In contrast, Kawano et al. reported a decrease in levels of CH50, C3, and C4 in patients who developed CV and DINDs [48]. Finally, the lectin complement pathway (LCP) has recently been shown to be activated in patients after SAH and has been linked to SAH severity and development of CV [49].

## Endothelial and Vascular Smooth Muscle Cell Dysfunction

### Endothelin

The inflammatory response also results in the release of multiple factors responsible for vascular smooth muscle cell (VSMC) contraction [50]. Endothelin (ET) is one of the most potent vasoconstrictors known [51] and has been investigated in relation to SAH and CV. ET has been measured in the CSF and plasma of patients with SAH using a variety of methods. There are conflicting studies on ET levels in CSF and plasma of SAH patients and their relationship to the development of CV and DINDs [52-61]. Kessler et al. reported a significant rise in ET levels in the CSF, but not in the plasma of patients with SAH who developed CV [53]. Additional studies have also found elevated ET CSF levels to correlate with poor clinical outcome [54, 55, 58]. Interestingly, Mascia et al. found high CSF ET levels in patients with a poor neurological condition unrelated to CV. In fact, the authors demonstrated low ET levels in patients with clinically significant vasospasm. The authors of the study concluded that the rise in CSF ET levels may be the result of severe neuronal damage regardless of mechanism (e.g., vasospasm or primary hemorrhagic event) [54]. Another study also determined that the rise in CSF ET levels appear to be the result of cerebral ischemia rather than the result of CV [59].

### Oxidative stress

Nitric oxide (NO) is a signaling molecule involved in numerous cellular functions including regulating vascular tone. As a potent vasodilator, NO and NO-containing compounds counteract the vasoconstricting effects of ET [62]. During the first 24 hours following SAH, NO levels fall resulting in constriction of the cerebral vasculature [63]. Temporal changes in CSF nitrite/nitrate (NOx) levels in patients after SAH have been studied with variable results [64, 65]. For instance, Jung et al. and Ramesh et al. found lower NOx levels in patients who developed CV compared to those patients who did not develop CV [66, 67], while Petzold et al. reported higher NOx levels in patients with SAH compared to controls [68]. There is also inconsistency regarding NOx levels and neurologic outcome. Whereas Rejdak et al. found that patients with good clinical outcome had significantly lower CSF NOx levels compared with those with worse clinical outcome [69], Lin et al. reported no correlation between CSF NOx levels and poor clinical outcome in SAH patients [70]. Measuring plasma NOx levels, Ramesh et al. demonstrated that patients with worse clinical outcome had significantly lower NOx levels compared to controls [67]. Adding to the discrepancy is the report by Staalso et al. in which the authors found that temporal

changes in NOx levels were dependent on the World Federation of Neurological Societies SAH grade. Initially, the NOx levels were 45% higher in the first 5 days in poor grade patients compared to grade 1 patients, however, on day 11 to 16, the NOx level in poor grade patients declined to below grade 1 patients [71].

Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of several nitric oxide synthase (NOS) family members. CSF ADMA levels seem to correlate with development of CV in both animal [72] and human studies [66, 73]. While CSF ADMA levels remained unchanged in patients with SAH who did not develop CV, Jung et al. reported an increase in CSF ADMA levels in those patients who developed CV 3 – 9 days after SAH. These levels then decreased gradually between days 12 – 21 [66]. Similar to ADMA levels in the CSF, plasma ADMA levels were found to increase over the first week after SAH [74]. In addition to studying NOx levels, Staalso et al. also reported that low plasma arginine/ADMA ratios predict mortality after SAH [71].

Additional mediators of the oxidative stress response have been investigated as potential biomarkers of SAH and CV. The superoxide dismutase family (SOD), is downregulated following SAH [75] while malondialdehyde (MDA), which is increased following SAH, has been demonstrated to be higher in SAH patients with poor clinical outcome [75, 76]. Another antioxidant system that utilizes glutathione peroxidase, which is involved in reducing lipid and hydrogen peroxide, appears to increase in activity but not concentration following SAH [77, 78]. Increased evidence of oxidative stress was observed in the CSF of patients with CV despite the increased activity of glutathione peroxidase, suggesting high reactive oxygen species or the antioxidant pathways may be involved in the pathogenesis of vasospasm [78].

### Neuropeptides

Neuropeptides have been evaluated in SAH and CV pathogenesis due to their vascular tone properties. However, inconsistent results in the levels of neuropeptides detected in patients with SAH have led to controversy surrounding this topic. Varying levels of calcitonin gene related peptide (CGRP), substance P, vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) have all been reported by various investigators with no clear consensus on an association [50]. Juul et al. reported high levels of CGRP in SAH patients compared to controls and concluded that this increase may be a compensatory mechanism to avoid CV by dilating the cerebral vessels [79]. However, Edvinsson et al. evaluated CGRP levels in SAH patients and demonstrated in two separate studies that lower levels of CGRP levels were found in SAH patients compared to controls [80, 81]. Similar to these results, investigators studying VIP and substance P using human studies and animal experiments have also demonstrated a gradual reduction in these neuropeptides [79, 82]. Although Hara et al. demonstrated a clear reduction in VIP and substance P in rats, the reduction of these neuropeptides in monkeys with SAH was not as clear, since there was also a reduction observed in the sham monkeys [82]. Based on these animal results, there is no consistent evidence for the reduction in these neuropeptides. Furthermore, in the aforementioned studies evaluating CGRP, Juul et al. and Edvinsson et al. also investigated levels of VIP and substance P and found no significant differences in levels between SAH patients and controls [79, 81]. Finally, although



there are conflicting reports on levels of NPY in SAH patients [83, 84], two recent studies demonstrated higher levels of NPY in SAH patients compared to controls [85] with higher levels found in patients with CV than in those patients without CV [86].

Another neuropeptide, adrenomedullin, has been shown to be elevated in SAH patients and is predictive of neurological outcome [87-90]. However, there are inconclusive results for adrenomedullin levels and development of CV with Kikumoto et al. and Fujioka et al. reporting no association of plasma adrenomedullin levels with CV, while Wijdicks et al. reporting elevated plasma adrenomedullin levels 5 days after SAH in patients who developed CV [87, 88, 91]. Interestingly, Fujioka et al. demonstrated that CSF adrenomedullin levels may be associated with CV [91].

Although secreted by the heart in response to excessive stretching of cardiomyocytes, Brain natriuretic peptide (BNP) has been shown to be elevated in SAH patients and correlate with clinical course including developing CV and DINDs [92-95]. Interestingly, Taub et al. reported high BNP levels associated with cerebral infarction, and in fact, levels were more prominent in patients without angiographic vasospasm [96].

## Brain Injury

Cellular damage occurs as a consequence of SAH and its sequela, whereby various factors are released into the subarachnoid space, many of which may serve as potential candidate biomarkers. Under normal physiological conditions, concentrations of these factors are typically negligible in both the CSF and serum. Two of these brain injury factors that have been investigated for their association with SAH pathogenesis are S100B, a protein synthesized by astrocytes and Schwann cells, and neuron-specific enolase (NSE), an enzyme synthesized by neurons. Similar to other candidate biomarkers mentioned previously, there are inconclusive results regarding S100B and NSE as biomarkers for CV. While several studies have validated S100B levels as a predictor of bad clinical outcome [97-101], the predictive power of S100B for development of CV is inconsistent, as Mortiz et al. and Amiri et al. reported no association [97, 102], whereas Oertel et al. reported lower S100B levels in SAH patients who developed CV [98]. An increase in NSE levels follows SAH; however, there appears to be no association with CV [97, 98, 101].

Other brain injury markers investigated for their link to SAH and CV include glial fibrillary acidic protein (GFAP), neurosin or kallikrein-related peptidase 6 (KLK-6), neurofilaments (NF), and ubiquitin C hydrolase 1 (UCHL1). Temporal changes are vital in using GFAP as a potential biomarker with several studies reporting increased levels within 1-6 hours after onset of SAH but decreasing later in disease progression [103]. Decreased serum levels of KLK-6 were found in patients with SAH, especially in those patients who succumbed to the disease [104]. Neurofilaments and phosphorylated forms of NF are increased in SAH patients and seem to correlate with poor clinical outcome [68, 105-107]. Finally, Lewis et al. reported that UCHL1 levels measured 10 days after a SAH were predictive of neuronal loss and poor clinical outcome [108].

## Genetic Biomarkers

Several genetic markers have been reported to be associated with

SAH and CV. Polymorphisms within the endothelial nitric oxide synthase (eNOS) gene (e.g., intron 4 27-base pair variable-number-tandem-repeat (27 VNTR) and the promoter single-nucleotide-polymorphism (-786T>C SNP)) have been shown to be associated with SAH and CV. The role of the T and C alleles and their association with CV remains unclear. Starke et al. reported that patients with the T allele of eNOS were more likely to develop severe CV [109]. However, Ko et al. and Khurana et al. reported that the C allele of eNOS was associated more with developing CV [110, 111]. The eNOS 27 VNTR polymorphism predicts susceptibility to intracranial aneurysm rupture [110] but is not associated with CV [111]. Another polymorphism that has been implicated as a risk factor for SAH is (-308 G<A SNP) in the TNF- $\alpha$  gene [112]. Finally, patients with the haptoglobin 2-2 phenotype had a significantly greater risk for developing CV than those with other haptoglobin phenotypes. Further, the haptoglobin 2-2 phenotype may predict clinical outcome [113, 114].

## Miscellaneous Markers

Several additional molecules have been investigated as potential biomarkers for predicting risk for SAH or developing CV. Glucose cerebral metabolism and a calculated metabolic ratio (MR) were evaluated which demonstrated that the MR is a reliable indicator for risk of poor neurological outcome after SAH [115]. Apolipoprotein E (ApoE) has been reported to be lower in the CSF of patients with SAH compared with controls. In addition, CSF ApoE levels appear to correlate with neurological outcome [116]. Adiponectin levels were found to be lower in SAH patients [117, 118] and lower adiponectin levels may be associated with the development of delayed cerebral ischemia [118]. Zanier et al. studied the relationship between heart-fatty acid-binding protein (H-FABP) and tau protein levels with severity and clinical outcome in SAH patients. They concluded that both H-FABP and tau protein levels correlated with the extent of brain ischemia, occurrence of CV, and neurological outcome [119]. Investigating alpha-II-spectrin breakdown products (SBDP), Lewis et al. found an increase in CSF SBDP concentration up to 12 hours before the onset of CV [120]. YKL-40 levels in both the CSF and serum of SAH patients were elevated compared to controls [121, 122], although there was no correlation found between YKL-40 levels and development of CV [121]. Although Isman et al. reported observing elevated CSF chitotriosidase levels on days 5 and 7 after SAH; the authors did not find any correlation with chitotriosidase levels and CV or neurological outcome [123]. Serum magnesium levels were investigated in relationship to CV and clinical outcome after SAH with studies identifying no relationship [124, 125]. Finally, matrix metalloproteinases (MMPs) have the potential to offer an early diagnostic biomarker in the setting of CV after SAH [126].

## Conclusion

While numerous biomarkers have been investigated for their predictive value in SAH and CV, there is no biomarker that is routinely used in the clinic. Until then, a better understanding of disease pathogenesis is needed before concise and robust biomarkers are identified and translated into clinical practice. With the current candidate biomarkers outlined in this review, additional studies evaluating the utility and effectiveness of these biological biomarkers in a prospective clinical trial is warranted.

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