Review Article

Inflammation, Cerebral Vasospasm, and Evolving Theories of Delayed Cerebral Ischemia

Kevin R. Carr, 1 Scott L. Zuckerman, 2 and J Mocco 2

1 Department of Neurological Surgery, University of Texas Health Sciences Center at San Antonio, San Antonio, TX 78229, USA
2 Department of Neurological Surgery, Vanderbilt University School of Medicine, Nashville, TN 37212, USA

Correspondence should be addressed to J Mocco; j.mocco@vanderbilt.edu

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Cerebral vasospasm (CVS) is a potentially lethal complication of aneurysmal subarachnoid hemorrhage (aSAH). Recently, the symptomatic presentation of CVS has been termed delayed cerebral ischemia (DCI), occurring as early as 3–4 days after the sentinel bleed. For the past 5–6 decades, scientific research has promulgated the theory that cerebral vasospasm plays a primary role in the pathology of DCI and subsequently delayed ischemic neurological decline (DIND). Approximately 70% of patients develop CVS after aSAH with 50% long-term morbidity rates. The exact etiology of CVS is unknown; however, a well-described theory involves an antecedent inflammatory cascade with alterations of intracellular calcium dynamics and nitric oxide fluxes, though the intricacies of this inflammatory theory are currently unknown. Consequently, there have been few advances in the clinical treatment of this patient cohort, and morbidity remains high. Identification of intermediaries in the inflammatory cascade can provide insight into new clinical interventions in the prevention and management of cerebral vasospasm and will hopefully prevent neurological decline. In this review, we discuss current theories implicating the inflammatory cascade in the development of CVS and potential treatment targets.

1. Introduction

Subarachnoid hemorrhage (SAH) is a devastating neurological insult that causes significant morbidity and mortality [1]. One of the greatest sources of this morbidity and mortality is cerebral vasospasm (CVS), leading to delayed cerebral ischemia (DCI) [2]. While angiographic vasospasm is thought to occur in approximately 70% of patients after aSAH, only 25% develop symptomatic CVS [3, 4]. Morbidity remains high despite years of clinical and basic science research done on the topic, with approximately 50% infarction rates in affected patients [5, 6].

An antecedent inflammatory cascade is one of the many etiologies thought to be responsible for the development of CVS. Experimental studies have shown involvement of cytokines, cell adhesion molecules, and leukocytes, and early clinical studies have attempted to inhibit components of the inflammatory cascade to mitigate CVS [7–19]. Additionally, endothelin receptor activation, nitric oxide inhibition, thromboxane receptor modification, and many cell signaling cascades are thought to play an integral role in the development of this pathology [20–27]. Currently, the primary treatment for this patient population involves hemodynamic augmentation and medically or surgically mediated intra-arterial vasodilation. These treatments, while providing amelioration in the short term, have proved relatively ineffective in staving off neurological decline, in part due to lack of large scale analyses [1, 28]. In our review, we hope to summarize past and current research in the area of inflammation and the development of CVS. An appreciation of these key inflammatory intermediaries will allow for the development of clinically significant interventions in this patient population.

2. Clinical Diagnosis of CVS

In patients with aSAH, neurological dysfunction presents within several hours after the injury. This decline was initially attributed to the progression of mass effect secondary to acute SAH; however, current evidence suggests that an acute brain injury with subsequent cerebral ischemia plays a primary
role. It is thought that the introduction of blood products, specifically hemoglobin, into the extravascular space initiates narrowing of the arterial vasculature within several hours [29], starting at approximately three days after-injury and lasting up to several weeks [30]. The arterial vasculature demonstrates diffuse or focal stenosis with significant restriction of blood flow visualized via angiography. CVS presents with focal neurological dysfunction and can precipitate the development of permanent ischemia in approximately 50% of patients with CVS [2].

The gold standard for the diagnosis of CVS is angiography, specifically with digital subtraction angiography (DSA) [31]. As an improvement to the technique described by Ecker and colleagues in 1951 [32], DSA allows for high quality angiographic images via the digital subtraction of extraneous artifact [33]. In its use as a diagnostic tool, mild vasospasm is defined by less than 25% reduction in vessel patency. A greater than 50% reduction is termed severe vasospasm [34]. Many authors have since espoused the utility of CTA and MRA as alternatives to the invasive techniques used in DSA [35–37]. In addition to being less invasive and severalfold faster than conventional angiography, CTA and MRA produce images of higher resolution than their predecessor [38, 39]. These techniques however rely heavily on digital reconstruction, and their accuracies vary depending on the vascular territory assessed and operator experience [31, 35, 39, 40].

Transcranial Doppler sonography (TCD) is currently the primary tool used in the noninvasive diagnosis of cerebral vasospasm. Its use was first described in 1981 when Dalessandri et al. demonstrated efficacy in the visualization of cerebral blood flow in cerebral arteries [41]. It is currently the single most important noninvasive measure of cerebral vasospasm [42, 43]. When vasospasm induces a decrease in arterial diameter, cerebral blood flow (CBF) velocity concomitantly increases. CVS is most times described when CBF velocity exceeds 120 cm/s [44, 45]. An increased ratio of CBF velocity between intracranial vessels, the middle cerebral artery (MCA) or anterior cerebral artery (ACA), and an extracranial ICA can be used to indicate CVS. This value is known as the Lindegaard index and is widely used today [46]. Most institutions identify clinical vasospasm as a ratio above 3:1. The diagnostic reliability of TCD has historically been called into question since factors such as the arterial window analyzed, patient movement, and operator experience affect the reliability of the test [31, 43, 47]. Specifically, changes in systemic pressure, cardiac output, and other factors that affect hemodynamic homeostasis can adversely affect reliability of the tool due to its strong dependence on cerebral blood flow dynamics [48]. In a comparative study between TCD and DSA in the assessment of aneurysmal vasospasm, Okada and colleagues highlighted the poor sensitivity of TCD for detecting vasospasm and noted that DSA was distinctly superior as a diagnostic tool [47]. Other studies have underscored the incongruences in the diagnostic sensitivity of this tool [49, 50]. Tools such as jugular venous oxygen saturation monitoring, Xe-enhanced CT, positron emission tomography (PET), single photon emission CT (SPECT), and magnetic resonance imaging have also been used to diagnose CVS with varying sensitivities [51].

3. CVS and Inflammation

3.1. History. The earliest correlation between CVS and inflammation was established over 60 years ago. Walton in 1955 demonstrated that febrile patients who presented with SAHs fared worse than their afebrile counterparts [52]. Several decades later, studies by Rousseaux et al. confirmed a definitive relationship between the occurrence of symptomatic CVS and fever in affected patients (Table 1) [53]. It was in the late 1980's however that Spallone and colleagues demonstrated that leukocytosis, the sentinel indicator of systemic inflammation, was significantly higher in patients with aSAH [54]. These discoveries spurred interest in the role of the inflammatory response as a causative factor in the development of the pathology. Later studies substantiated these earlier findings, and additional inflammatory markers and cytokines were identified to play a pivotal role in the inflammatory process (Table 1).

3.2. The Inflammatory Cascade and CVS. As a result of decades of research into the inflammatory mediators of CVS, several theories explaining the pathophysiology have been proposed. One such theory states that the extravasation of erythrocytes into the cerebral parenchyma acts as the nidus for the vasospasms that characterize acute and chronic CVS [II, 18, 55, 56]. Extracpuscular hemoglobin (Hb) is a proinflammatory moiety as opposed to its intravascular homolog [57–60]. The presence of Hb in the extravascular space liberates reactive oxygen species (ROS) that result in the peroxidation of membrane lipids of endothelial cells and proliferation of smooth muscle [61, 62]. It is also thought that these oxidative stressors inhibit bradykinin mediated vascular relaxation after aSAH [63]. Additionally, it has been hypothesized that the presence of subarachnoid blood is a potent stimulant for nuclear factor-kappa B (NF-κB) mediated cytokine release augmenting the inflammatory reaction [II, 64]. Normally, once erythrocytes have entered the extravascular space, exposed Hb is rapidly bound to a heptically produced haptoglobin (HP). HP exists in two isoforms, HP 1-1 and HP 2-2 of which HP 2-2 is thought to bind with less affinity and as such is relatively pro-inflammatory in comparison to its analog [23, 27, 56, 65]. Macrophages phagocytize Hb bound moieties and remove them from the extravascular space. The initial pro-inflammatory effect elicited by Hb and Hb bound moieties initiates an inflammatory cascade involving an increase of cytokines, leukocytes, and cell adhesion molecules (CAMs) characterizing the inflammatory process [7, 13, 18, 56, 66, 67].

The elevation in inflammatory cytokines and cell adhesion markers promotes the initial margination of leukocytes by CAMs on the endothelial surface. Of these cell adhesion markers, selectins (L-, P-) are most important in the initial capture [9, 20, 68–71]. Secondly, leukocyte rolling is facilitated by P- and E-selectins in which captured leukocytes are sequentially bound and released by adjacent CAMs. The end result is a sequential transmigration of leukocytes down a chemoattractant concentration gradient to the site of inflammation. Finally, firm adhesion to the endothelium effectively halts leukocyte rolling and promotes leukocyte diapedesis.
### Table 1: Landmark discoveries of the relationship between vasospasm and inflammation in the last half century.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Inflammatory parameter assessed</th>
<th>Model</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walton (1955) [52]</td>
<td>Fever</td>
<td>Human</td>
<td>SAH patients with fever have decreased survival</td>
</tr>
<tr>
<td>Rousseaux et al. (1980) [53]</td>
<td>Fever</td>
<td>Human</td>
<td>SAH patients with fever have decreased survival</td>
</tr>
<tr>
<td>Spallone et al. (1987) [54]</td>
<td>Leukocytosis</td>
<td>Human</td>
<td>SAH is accompanied by leukocytosis</td>
</tr>
<tr>
<td>Mathiesen et al. (1990) [137]</td>
<td>Neopterin</td>
<td>Human</td>
<td>CSF neopterin levels rise with SAH</td>
</tr>
<tr>
<td>Minami et al. (1991) [103]</td>
<td>LTC4</td>
<td>Canine</td>
<td>Subarachnoid foreign bodies induce angiographic BA vasospasm</td>
</tr>
<tr>
<td>Peterson et al. (1990) [138]</td>
<td>Cell free blood components</td>
<td>Canine</td>
<td>Subarachnoid foreign bodies induce angiographic BA vasospasm</td>
</tr>
<tr>
<td>Edwards et al. (1992) [57]</td>
<td>EDRF</td>
<td>Porcine</td>
<td>Adventitial hemoglobin reduces EDRF concentrations</td>
</tr>
<tr>
<td>Onda et al. (1999) [139]</td>
<td>MCP-1, cystatin B, inter-alpha-trypsin inhibitor, serum amyloid A protein, and GPI30</td>
<td>Canine</td>
<td>SAH increases expression of inflammatory markers genes</td>
</tr>
<tr>
<td>Fabender et al., (2000) [9]</td>
<td>ET1, IL-6, and TNFα</td>
<td>In vitro</td>
<td>Leukocytes activated by incubation with blood release inflammatory markers</td>
</tr>
<tr>
<td>Aihara et al. (2001) [140]</td>
<td>IL-1A, IL-6, IL-6, II10, VCAM-1, TGF-ss, and bFGF</td>
<td>Canine</td>
<td>SAH increases expression of markers with BA vasospasm</td>
</tr>
<tr>
<td>McGirt et al. (2002) [141]</td>
<td>MM-9, VEGF, and vWF</td>
<td>Human</td>
<td>Increases in VEGF, MMP-9, and VEGF precede angiographic vasospasm</td>
</tr>
<tr>
<td>Sasaki et al. (2004) [142]</td>
<td>IL-1a, IL-1b, and IL-8</td>
<td>Canine</td>
<td>Hemolysate increased inflammatory marker expression by MAPK mediated pathways</td>
</tr>
<tr>
<td>Recinos et al. (2006) [19]</td>
<td>LPS</td>
<td>Leporine</td>
<td>LPS induces BA narrowing and clinical CVS</td>
</tr>
<tr>
<td>Zhou et al. (2007) [143]</td>
<td>TNFα, ICAM-1, and MPO</td>
<td>Leporine</td>
<td>Hemolysate increases NF-Kb DNA binding activity with increase in inflammatory markers and angiographic BA vasospasm</td>
</tr>
<tr>
<td>Jędrzejowska-Szypulka et al. (2009) [68]</td>
<td>IL-1B</td>
<td>Murine</td>
<td>IL-1B activity increased with hemolysate and reversed with IL-1B antibodies</td>
</tr>
<tr>
<td>Wang et al. (2010) [144]</td>
<td>CD34</td>
<td>Murine</td>
<td>CD34 expression increases with SAH at the peak of vasospasm</td>
</tr>
<tr>
<td>Wirrig et al. (2011) [145]</td>
<td>SPC</td>
<td>Murine</td>
<td>SPC increases MCP-1 and acts as inflammatory mediator in CVS</td>
</tr>
</tbody>
</table>


This process is mediated by another class of CAMs, the integrins of which CAM-1, LFA-1 and other moieties play vital roles. Immunoglobulins ICAM-1, and VCAM-1 are also required for adhesion [73–75]. Experimental models have successfully demonstrated the temporal relationship between the initial inciting injury and increases in cytokine concentrations [76–78]. Of particular interest are IL-1β, IL-6, TL-8, and TNF-α. In various studies, increases in the intraventricular concentrations of these moieties have been demonstrated to occur after injury [79–81]. Though the CSF concentrations of these inflammatory intermediaries increase after-hemorrhage, the change in serum concentrations is not as reliable. In fact, studies have demonstrated both elevations [82] and no relevant changes [76] in the analysis of systemic concentration of these cytokines. It is irrefutable, however, that leukocytosis and changes in C-reactive protein levels (CRP) correlate strongly with clinical outcomes after-injury [83, 84].

Transendothelial migration, or diapedesis, is the final step in the recruitment of inflammatory leukocytes and encompasses a multitude of cell adhesion molecules and intracellular cell signaling pathways [72]. Macrophages, monocytes and neutrophils are the primary cells implicated in the initial stages of injury and have been found in postinjury histological analysis to be a highly represented cell type in adjacent tissue [85, 86]. These inflammatory cells mediate macrocytosis of free erythrocytes as part of their natural function; however, after aSAH there is a disruption of normal cerebral blood flow preventing the re-entry of macrophages and leukocytes into circulation. This results in the degradation and degranulation of these cells in the parenchymal space. Ultimately, a release of inflammatory cytokines and...
other vasoactive compounds, which characterize the chronic vasospasm of CVS, is thought to occur approximately four days after injury [18].

In the final analysis, the upregulation of ET-1, destructive free radicals, NO dysregulation, and spasmodic cytokines are all thought to play a substantial role in the onset of vasospasm [1, 87–89]. ET-1 itself is a potent vasoconstrictor whose upregulation peaks 3-4 days after injury [90]. It is thought to be increased due to cerebral ischemia and other stressors with possible augmentation by the aforementioned antecedent inflammatory cascade. Its effect on vasoconstriction is multifaceted [91, 92]. Through a negative feedback loop, its activation of endothelial nitric oxide synthetase (NOS) depletes NO concentrations [93]. NO plays a significant role in vascular tone through the inhibition of calcium production and subsequent reduction in contractile forces; thus, its inhibition leads to vessel narrowing [94]. Additionally, ET-1 is also integral to fibrosis, tissue growth, and inflammation [26, 92, 95]. In summary, through several distinct mechanisms, the inflammatory changes surrounding SAH lead to global stenosis of cerebral vasculature [26, 96–99].

3.3. Research Findings Relating Inflammation to CVS. Research has focused on modifying several inflammatory markers (Table 2). Several clinical trials have either corroborated or refuted the clinical efficacy of the suggested treatments [1]. Anti-inflammatory agents such as dexamethasone and cyclosporine A (Cys-A) have shown favorable improvements in experimental models [100, 101]. However, other known agents, such as tacrolimus, an inhibitor of T-cell maturation similar to Cys-A, have not shown similar results [102]. There are also studies implicating the complement system, the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase pathway, and multiple other systems; however, results even in the experimental stages have been varied [103–106].

There have been experimental reports documenting improvement in CVS using various pharmaceutical agents, however, the variety of these treatments is sparse (Table 3). In 2011, Velat and colleagues reviewed 44 randomized control trials (RCT) and 9 meta-analyses on vasospasm after SAH [1]. Their studies suggested that only oral nimodipine was statistically significant dose dependent reduction in vasospasm after administration of a polyclonal antibody targeted against IL-6 (P < 0.05) [107]. Such findings indicate that cytokine upregulation is antecedent to radiographic vasospasm, and their attenuation may minimize vessel narrowing. The propensity for magnesium supplementation to mitigate CVS has also been widely studied [108–113]. In fact, a small Swiss study in 2012 suggested that high dose magnesium administration compared to low dosage suppressed post-SAH increases in IL-6 (P = 0.021) and IL-1β (P < 0.001), respectively [78].

Agents such as organic stress reducers including trehalose modulate the effect of the cyclooxygenase-2 (COX-2) catalytic pathway [20]. In experimental murine models, the polysaccharide reduced concentrations of pro-inflammatory markers leading to a reversal of SAH induced vasospasm. Of the multiple markers that trehalose modulates is endothelin-1, which modulates vasoconstriction [91, 92], via its effects on nitric oxide, fibrosis, tissue growth, and inflammation [92]. Consequently, it has been the target of major studies on the treatment of vasospasm [114]. The reduction in plasma arachidonic acid is also thought to mediate these experimental findings. Molecular hydrogen has been found to be useful experimentally to decrease vasospasm and peroxidation [115]. These evidences along with other recent experimental findings suggest a multifactorial process that precedes CVS and clinical neurological dysfunction, which may or may not be directly related.

Myeloperoxidase (MPO), a marker of inflammation in coronary artery disease, is thought to be implicated in the inflammatory process of CVS [116]. MPO is a lysosomal enzyme that is a component of the respiratory burst in leukocyte antibacterial function. The enzyme catalyzes the production of hypohalous acids like hypochlorous acid (HOCl), which modify cellular membranes [117]. In reports by Lim and colleagues, the biomarker demonstrated elevations in CSF concentrations that mirror the onset of CBF abnormalities in CVS, supporting MPO as a surrogate predictor of CVS after SAH. Because of to its role in inflammation, its upregulation is most likely related to antecedent leukocyte recruitment [116].

3.4. DCI Has an Evolving Pathophysiology. The mortality that ensues after CVS is often due to delayed cerebral ischemia (DCI). DCI is defined as new focal neurological deficits (symptomatic vasospasm) or ischemic focus in the setting of radiographic vasospasm [118]. While the relationship between inflammation and CVS is irrefutable, it is unlikely to be the single perpetrator behind delayed cerebral ischemia (DCI) and subsequent neurologic decline. Results from the CONSCIOUS trials assessed the effects of the endothelin-1 receptor antagonist Clazosentan after SAH, and while there was significant improvement in angiographic CVS, neurological dysfunction was only minimally affected [119]. Hansen-Schwartz and colleagues concluded that these results point to a more extensive implication of inflammation in the pathophysiology of post-SAH neurological dysfunction. Hansen-Schwartz also argued that the lack of temporal alignment between angiographic CVS and DCI symptoms suggest the need for further studies [120].

Cortical spreading depolarization (CSD), intravascular microthrombosis, and early brain injury have all received traction in the field as alternate theories of CVS [120–124]. In the immediate posthemorrhage period, rapid increases in cerebral edema [125], ICP [126, 127], and changes in cerebral autoregulation [128] are all thought to disrupt the homeostatic milieu resulting in early brain injury. This injury fosters an environment for cerebral ischemia with altered perfusion and hypoxia. Transient and sporadic neuroelectrical
Table 2: Early studies report improvement in experimental proxies of CVS in various models.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Parameter assessed</th>
<th>Model</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokiyoshi et al. (1991) [146]</td>
<td>Symptomatic vasospasm</td>
<td>Human</td>
<td>TXA2 synthetase inhibition decreased symptomatic vasospasm</td>
</tr>
<tr>
<td>Lin et al. (2005) [67]</td>
<td>ACA diameter</td>
<td>Murine</td>
<td>Anti-E selectin mAb prevents SAH induced angiographic vasospasm</td>
</tr>
<tr>
<td>Fei and Gobwa (2007) [101]</td>
<td>MCA velocity</td>
<td>Human</td>
<td>Topical dexamethasone prevents angiographic vasospasm</td>
</tr>
<tr>
<td>Iseda et al. (2007) [147]</td>
<td>BA diameter, IL-1B</td>
<td>Leporine</td>
<td>Caspase inhibitor (Z-VAD-FMK) decreased angiographic BA vasospasm and IL-1B levels</td>
</tr>
<tr>
<td>Lin et al. (2007) [66]</td>
<td>ICAM-1, BA diameter</td>
<td>Leporine</td>
<td>Endothelin converting enzyme inhibitor (CGS 26303) decreases ICAM-1 levels and BA vasospasm</td>
</tr>
<tr>
<td>Chen et al. (2008) [69]</td>
<td>JAK2</td>
<td>Leporine</td>
<td>JAK2 inhibitor (AG490) decreases JAK2 activation and angiographic BA vasospasm</td>
</tr>
<tr>
<td>Yoshimoto et al. (2009) [148]</td>
<td>Angiography</td>
<td>Human</td>
<td>Cilostazole prevents angiographic vasospasm after SAH</td>
</tr>
<tr>
<td>Wu et al. (2010) [149]</td>
<td>TLR4, TNF1</td>
<td>In vitro</td>
<td>PPAR gamma agonist decreases TLR4 expression and cytokine release</td>
</tr>
<tr>
<td>Chang et al. (2010) [150]</td>
<td>ICAM-1, VCAM-1, E-Selectin, and BA diameter</td>
<td>Murine</td>
<td>6-MP decreases ICAM-1 and E-Selectin and increases angiographic BA vasospasm after SAH</td>
</tr>
</tbody>
</table>


Table 3: Recent studies have shown improvements in clinical and experimental vasospasm with the use of other various pharmacological additives.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Parameter altered/assessed</th>
<th>Model</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyers and Connolly (2011) [119]</td>
<td>Endothelial receptor antagonist</td>
<td>Delayed ischemic neurological decline</td>
<td>Human</td>
<td>Endothelial receptor antagonists (Clazosentan) have no effect on vasospasm related morbidity and mortality</td>
</tr>
<tr>
<td>Fathi et al. (2011) [89]</td>
<td>Sodium nitrate</td>
<td>Arterial diameter</td>
<td>Primates</td>
<td>IV sodium nitrite reverses CVS after SAH</td>
</tr>
<tr>
<td>Muehlschlegel et al. (2011) [151]</td>
<td>Dantrolene</td>
<td>TCD</td>
<td>Human</td>
<td>IV dantrolene decreases CBF after SAH</td>
</tr>
<tr>
<td>Echigo et al. (2012) [20]</td>
<td>Trehalose</td>
<td>NF-Kb, ET-1, COX-2, and NOx</td>
<td>Leporine</td>
<td>Trehalose decreases lipid peroxidation, arachidonic acid release, vasospasm, and inflammatory markers after SAH</td>
</tr>
<tr>
<td>Hong et al. (2012) [115]</td>
<td>Hydrogen rich saline</td>
<td>SOD, GPx, and malondialdehyde</td>
<td>Murine</td>
<td>Molecular hydrogen reduces peroxidation and vasospasm after SAH</td>
</tr>
<tr>
<td>Pradilla et al. (2012) [23]</td>
<td>L-Citrulline</td>
<td>BA diameter, neurobehaviour, and NOS expression</td>
<td>Murine</td>
<td>Systemic L-citrulline prevents angiographic BA vasospasm and improves neurobehaviour and NOS expression after SAH</td>
</tr>
<tr>
<td>Zhang et al. (2012) [152]</td>
<td>mTOR inhibition</td>
<td>BA diameter, appetite, and activity scores</td>
<td>Canine</td>
<td>mTOR inhibitor (rapamycin) reduced CVS after SAH</td>
</tr>
</tbody>
</table>

disruptions also occur in the injured brain after acute injury [129]. Through experimental murine models, researchers have demonstrated that these brief episodes of electrical dampening differentially affect cerebral perfusion resulting in either hyperperfusion or hypoperfusion. This hemodynamic imbalance propagates damage created during early brain injury [130]. Finally, correlations between elevated procoagulant factors and DCI occurrence have strongly suggested a role for microthrombosis in the pathophysiology [131]. The detection of microthrombi in postmortem analysis [132] and a 70% prevalence of microthrombi in SAH patients [133] also point to the involvement of the coagulation cascade in the development of DCI. It is now more likely that CVS is one of many factors that play some part in the neurological decline consistent with DCI.

3.5. New Research. Current clinical trials are investigating possible contributing factors antecedent to DCI and DIND. Most notably, the EARLYDRAIN and LUMAS trials evaluate early evacuation of CSF through a lumbar drain [134, 135]. The LUMAS trial evaluated 210 patients with aSAH and randomized 105 to receive standard therapy and a lumbar drain, with the remaining 105 randomized to the control group receiving only standard management. The authors found that lumbar drainage of CSF after aSAH was associated with reduced DIND and improved early clinical outcome but had no difference in outcomes at 6 months. Preliminary studies have also shown efficacy using a kinetic treatment, intrathecal thrombolytic therapy in conjunction with head shaking. In this small study, 9 patients were selected to receive multimodal treatment while 11 received standard therapy. After 14 days of observation, there was decreased DIND and vasospasm related infarct in the intrathecal thrombolytic therapy group compared to the control [136]. Lastly, the depolarizations in ischaemia after aneurysmal subarachnoid haemorrhage (DISCHARGE-1) trial are an ongoing multicenter diagnostic phase III study that assesses electrical depression of the cerebral cortex after aSAH. The aim is to calculate the sensitivity and specificity of the duration of cortical spreading depression as a proxy for DCI after aSAH. As we look to future research, it is hoped that these theories may become incorporated in to standard therapies for the treatment of CVS.

4. Conclusion

From all indications, one of the major limiting factors in the management of CVS is an understanding of the extent of early brain injury secondary to SAH. Various studies have proven the relationship between vasospasm and accompanying neurologica decline. We are currently limited by the difficulty in consistently and accurately diagnosing and treating affected patients. It is unlikely that there will be a “silver bullet” treatment for CVS and DCI. The role of inflammation in CVS represents a possible mechanism behind the development of DCI after SAH, and targeting the inflammatory process has potential to significantly reduce CVS, though further studies are necessary. Cerebral vasospasm continues to be regarded as an important factor in the progression to DCI in patients following SAH. It cannot be however regarded as the single factor behind the neurological decline in this patient cohort.

**Abbreviations**

CVS: Cerebral vasospasm  
DCI: Delayed cerebral ischemia  
DIND: Delayed ischemic neurological decline  
aSAH: Aneurysmal subarachnoid hemorrhage  
TBI: Traumatic brain injury  
CTA: Computed tomography angiography  
PET: Positron emission tomography  
SPECT: Single photon emission computed tomography  
LTC4: Leukotriene C4  
MCPI: Monocyte chemotactic protein 1  
ET1: Endothelin 1  
TNFα: Tumor necrosis factor alpha  
MMP9: Matrix metalloproteinase  
bFGF: Basic fibroblast growth factor  
EDRF: Endothelium derived relaxing factor  
IL1: Interleukin 1  
LPS: Lipopolysaccharide  
ICAM-1: Intercellular adhesion molecule 1  
MPO: Myeloperoxidase  
vWF: Von Willebrand’s factor  
CD34: Cluster of differentiation 34  
SPC: Sphingosylphosphorylcholine  
BA: Basilar artery  
GP130: Glycoprotein 130  
TXA2: Thromboxane A2  
PAF: Platelet activating factor  
LFA-1: Lymphocyte function associated antigen  
NO: Nitrous oxide  
JNK: c-Jun N terminal kinase  
mAb: Monoclonal antibody  
HMG-CoA: 3-Hydroxy-3-methylglutaryl-coenzyme A  
JAK2: Janus kinase 2  
PDE: Phosphodiesterase  
6-MP: 6-Mercaptopurine,  
PPAR gamma: Peroxisome proliferator activated receptor gamma  
SOD: Superoxide dismutase  
CBF: Cerebral blood flow  
GPx: Glutathione peroxidase  
NOS: Nitric oxide synthase  
BA: Basilar artery  
mTOR: Mammalian target of rapamycin.

**Conflict of Interests**

There were no external sources of financial support for this paper.
Disclosure

The authors report no conflict of interests concerning the materials or methods used in this study or the findings specified in this paper.

References


