High Wall Shear Incites Cerebral Aneurysm Formation and Low Wall Shear Stress Propagates Cerebral Aneurysm Growth

Vivig Shantha Kumar, Vignarth Shantha Kumar

Abstract

This review discusses mechanisms for the development of cerebral aneurysms. Endothelial cells exhibit a variety of structural and functional changes when they come into contact with normal laminar flow. In response to laminar shear stress, endothelial cells modify their potassium ion channels, go through cytoskeletal rearrangements and shape modifications and create prostacyclin. In cerebral arteries, aneurysmal dilatation most frequently starts at locations with substantial wall shear stress, which include arterial bifurcations and vascular branch sites, where blood flow abruptly switches to turbulent flow. At this point, high shear stress frequently arises, placing increased strain on the vasculature. As the vascular branch points and arterial bifurcations are the initial sites of cerebral aneurysm genesis, this helps confirm the role of high wall shear stress in the development of cerebral aneurysms. Low wall shear stress increases the initial proinflammatory effect already present in the vasculature, which furthers the formation of cerebral aneurysms. In fact, regions of aneurysmal regions with low wall shear stress grow more quickly and are more prone to rupture compared to regions with high wall shear stress. Therefore, it seems plausible to assume that turbulent blood flow inside a dilated cerebral aneurysm causes low wall shear stress, thereby encouraging aneurysmal growth.

Keywords: Cerebral aneurysm; Hemodynamic disturbances; Wall shear stress; Aneurysmal growth; Aneurysmal rupture

Introduction

A confined, outward pathological dilatation of the artery wall, cerebral aneurysm (CA) is thought to affect 1-3% of people in the general population [1]. CA development and growth follows an amalgamation of multiple insults with individual contributions from hemodynamic stress and inflammatory pathways [2, 3]. Substantial clinical and experimental experiences demonstrate a role of hemodynamic influences in CA pathogenesis, suggesting that altered hemodynamics modulate a biphasic response defined by early initial CA formation and later cerebral growth [4-8]. A series of actions connected to stages of arterial wall remodeling in response to hemodynamic stresses are represented by the initiation, growth, and rupture of CAs [9, 10]. Hemodynamic-induced endothelial dysfunction is a starting point for the development of CAs. Varying patterns of blood flow exert mechanical stresses on vascular endothelial cells, altering the functions of these cells and predisposing to vessel wall changes [11-14]. The primary hemodynamic cause of CA growth, formation, and rupture is wall shear stress (WSS). High shear stress in arterial branch points and bifurcations coincides with histological markers of nascent CA formation [15, 16]. Cerebral vessels at these locations commonly demonstrate early destructive vessel wall changes such as, most commonly, damage to endothelial cells with signs of either altered protective endothelial cell phenotype or endothelial cell loss and fragmentation of the internal elastic lamina (IEL). Low WSS, on the other hand, is commonly observed at the growing end of CAs such as the neck and dome regions of CAs [17, 18]. These regions are observed to demonstrate marked inflammatory vessel wall remodeling demonstrated by increased macrophage tissue trafficking, release of macrophage derived products (matrix metalloproteinases (MMPs)), and loss of smooth muscle cells (SMCs). Therefore, our main objective in this study is to understand the contributions of varying hemodynamic perturbations toward the development and growth of CAs.

Vasculoprotective Effect of Normal Laminar Shear Stress

Under physiological states, cerebral blood vessels display a laminar flow pattern. Laminar flow refers to a unidirectional, orderly pattern characterized by parallel vectors. In order to control a number of vascular processes, endothelial cells’ reactions to normal fluid shear stress are crucial. Endothelial cells that are subjected to a typical laminar flow and typical WSS
show a number of structural and functional modifications. Under normal physiological laminar shear stress, endothelial cells adopt an anti-inflammatory and nonproliferative surface expression characterized by increased resistance to inflammation, growth, and apoptosis [19]. Laminar shear stress modulates vascular tone through its influence on the production of nitric oxide (NO) [20, 21]. Endothelial nitric oxide synthase (eNOS) modulates local production of NO and is activated through phosphorylation of protein kinase B in response to laminar stress, leading to upregulation of eNOS activity [22, 23]. Besides upregulating eNOS activity, protein kinase B phosphorylation, laminar WSS induces continuous eNOS mRNA transcription through the c-Src-dependent pathways [24]. Additionally, in endothelial cell cultures, laminar shear stress induces Kruppel-like factor 2 (KLF2), which contributes to NO-dependent vasodilation [25, 26]. Endothelial cell overexpression of KLF2 abundantly induces eNOS expression [27, 28]. Laminar fluid shear stress mediates an antithrombotic and anti-inflammatory effect through the upregulation of KLF2 [29, 30]. Induced by laminar shear stress, KLF2 reduced the expression of the pro-inflammatory adhesion molecules vascular cell adhesion molecule (VCAM)-1 and E-selectin in endothelial cells [31]. Further, endothelial cells introduced with KLF2 were found to display decreased attachment of white blood cells in vitro flow assay studies [31]. Likewise, expression of the nuclear factor kappa B (NF-κB) ligand is downregulated [32, 33]. Decreased expression of NF-κB, a proinflammatory transcription factor, minimizes the development of a proinflammatory extracellular environment within the vascular wall. Also, laminar shear stress mediates antithrombotic responses through KLF2. Endothelial cells in normal vessels adapt an anticoagulant response to laminar shear stress by upregulating thrombomodulin, heparin sulfate, and tissue factor inhibitor [34]. The expression of thrombomodulin is also continuously increased by laminar shear stress, but it increases by a factor of two more than it does in normal cells [35]. Furthermore, shear stress increases endothelial expression of tissue plasminogen activators while suppressing plasminogen activator inhibitor type 1 release [36].

Laminar shear stress also promotes cell cycle arrest in the G1 or G0 phase, which keeps endothelial cells in a quiescent condition [33]. Endothelial cell intracellular processes such as gene transcription, protein synthesis, cell proliferation, and ultimately cytoskeletal rearrangement and morphological changes are also regulated by normal physiological shear stress [37, 38]. The mitogen-activated protein kinase (MAPK) family of proteins is one of the most significant signaling pathways mediating endothelial cell proliferative response to laminar WSS [39, 40]. MAPK proteins (ERK ½, p38 and JNK) activated in response to shear stress facilitate conduct of extracellular signals into the cell nucleus, where they influence gene transcription [22, 41, 42]. The net effect of MAPK activation is the ultimate activation of ERK ½ leading to protein synthesis, cell proliferation and an inhibition of apoptosis [43-45]. Additionally, cyclin dependent-kinase, responsible for vascular endothelial cell proliferation, is suppressed [22]. Repression of endothelial cyclin dependent kinase prevents aberrant cell proliferation resulting in a healthy balance between proliferation and apoptosis.

Endothelial cell structural changes in response to high shear stress

The frequent occurrence of CAs in vascular branch points and bifurcation points emphasizes the significance of hemodynamic stresses in the beginning of CA formation [47-51]. Indeed, there is a higher prevalence of CAs in association with morphological abnormalities of the cerebral vasculature, such as hypoplasia/occlusion of a section of the circle of Willis or arteriovenous malformations that provide elevated flow patterns and high WSS locally [47, 52-55]. Aneurysmal dilation of cerebral vessels most commonly begins at sites of high WSS. High WSS commonly develops at arterial vascular branch points and arterial bifurcations, where blood flow suddenly changes from the steady uniform laminar pattern into a more chaotic turbulent pattern exerting greater tension on the vascular wall. Several pieces of animal studies highlight a central role of altered hemodynamics in the initiation of CA formation. Elevation of the WSS beyond threshold conditions, from observations in several animal models, documents histopathological vascular wall changes suggestive of early CA formation: fragmentation of the IEL and endothelial cell phenotype modulation [48, 56]. From histopathological examination of affected cerebral blood vessels, Steiger et al deduced that experimentally induced sustained elevations of WSS is attended by a fragmentation of the IEL of blood vessels [56]. Similarly, Steinlens et al noted that, in addition, endothelial cells show an alteration in their normal phenotype as well as endothelial damage [48]. Gao et al using a rabbit model, demonstrated a drastic nine-fold increase in basilar artery flow following ligation of the common carotid artery. Additionally, newly formed CAs were noted at the basilar artery bifurcation, characterized histologically by a loss of the internal elastic media and an outward bulged and thinned tunica media [57]. Dogs’ carotid arteries were ligated experimentally to create new branch points, and Meng et al observed remodulative changes at these bifurcations that resembled the beginning of an intracranial aneurysm, including disruption of the IEL, loss of medial SMCs, and a decreased proliferation of SMCs [58]. Further, Jamous et al studied CA occurring at high flow bifurcation sites and documented endothelial cell morphological alterations during the early phase of aneurysm development. In the early phase of CA development, endothelial cells were observed to have an abnormal endothelial cell morphology ranging from...
segmental detachment of the endothelial cell plasma membrane to endothelial cell deformation with a vacuolated cytoplasm and/or nucleus depending on the degree of destructive remodeling [59]. Fukuda et al [60] similarly observed that high wall shear incites CA formation and endothelial cell injury at sites of nascent CA formation, similarly, corresponding to endothelial cell structural modifications as described by Jamous et al [59]. One such study performed by Fukuda et al correlated aneurysmal degenerative changes in endothelial cells with the magnitude of WSS in variable areas of the cerebral blood vessel. Herein, it was discovered that in the region of the vessel bifurcation, the intimal endothelial cells showed characteristic initial changes suggestive of early progression to aneurysm dilation. Given the bifurcation of the vessels at this site, it was noted that the intima of these vessels experienced the highest magnitude of WSS [60]. Along the same lines, observations from animal studies still further strengthen the positive correlation between a high WSS and early aneurysmal changes. Moreover, in experimental models of CA formation in rats and primates, increased cerebral blood flow and hypertension were necessary prerequisites for aneurysmal dilation [50, 61-63]. In general, these studies conclude that aneurysm initiation starts with deranged initial endothelial cell responses leading to structural and functional modifications of the endothelium.

**Activation of Endothelial Cell Proinflammatory Response by High WSS**

Flow acceleration at bifurcation points produces a hemodynamic environment characterized by high WSS which triggers initiation of aneurysmal dilation. In experimental models of CAs [4, 15-17], increased cerebral blood flow and systemic hypertension are necessary prerequisites for the initiation of CA formation (Table 1) [48, 56, 58, 60, 64-73]. Likewise, Kulcsar et al analyzed the hemodynamics of a cerebral vasculature in three patients before and after the development of an intracranial aneurysm and observed that intracranial aneurysm consistently formed at locations characterized by high WSS [74]. Further, Metaaxa et al using rabbit models noted the occurrence of nascent aneurysm formation at the basilar terminus region following basilar artery flow increase, a region of elevated WSS [75]. High WSS is exceedingly implicated in destructive vessel remodeling and endothelial cells at arterial bifurcations, suggested by the fact that vascular branch points and apices become progressively dysfunctional following prolonged abnormal hemodynamic stresses [19]. Increased wall shear and excessive hemodynamic stresses activate endothelial cell mechanoreceptors leading to increased signal transduction and activation of inflammatory pathways, leading to destructive inflammatory vessel wall remodeling. High WSS, however, evokes a proinflammatory, procoagulant and proliferative phenotype predisposing to vascular remodeling. Activation of NF-κB, a proinflammatory transcription factor, in endothelial cells challenged with hemodynamic stress activates inflammatory signaling pathways leading to CA initiation [76] NF-κB, a proinflammatory transcription factor, is activated by increased shear stress on endothelial cells, regulating the expression of various proinflammatory genes [77-81]. In vivo experimental models of CAs observed that increased flow and hypertension are necessary prerequisites for NF-kB activation in rat models of aortic aneurysms [82]. In response to turbulent flow, NF-kB activation occurs predominantly in the endothelial cells and macrophages. In quiescent unstimulated cells, NF-kB is tucked away in the cytoplasm in combination with inhibitor IκB proteins, preventing its translocation into the nucleus. Appropriate activating signals phosphorylate IκB, acting to abrogate the inhibitory anti-migratory influence of IκB. NF-kB subsequently translocates to the nucleus to evoke the transcription of proinflammatory genes [76]. Cultured endothelial cells demonstrate increased nuclear translocation of NF-kB in response to fluid shear stress by activating IκB kinase through phosphorylation [83]. Further, use of antibody directed against the p65 nuclear localization signal subunit of NF-kB demonstrated increased localization and activation of NF-kB in the arterial walls with the use of immunohistochemical studies [84]. Likewise, use of immunostaining and western-blot analysis techniques confirmed that NF-kB was significantly phosphorylated and activated in the vascular endothelial cells and macrophages during the initiation of CAs in murine rat models of CA [85-87]. Animal models clearly advocate that NF-kB activation at the site of vascular injury is necessary for the formation of intracranial aneurysms. Mice devoid of NF-kB expression were observed to have a significant blockade of aneurysm formation. NF-kB plays a critical developmental role in the genesis of nascent CAs by regulating the transcription of downstream pro-inflammatory genes leading to phenotypic alterations of the vascular endothelium [64, 88]. The major downstream target of NF-kB following activation is the upregulation of proinflammatory adhesion molecules, VCAM-1 and monocyte chemotactic protein (MCP)-1, on the vascular endothelium leading to increased neutrophil and macrophage tissue trafficking. Macrophage infiltration results in the release of MMPs (MMP-2 and MMP-9), capable of proteolytically degrading the extracellular matrix, as well as the induction of inducible nitric oxide synthase (iNOS) leading to the pathological formation of NO mediating vascular SMC apoptosis.

**Growing and Thin End of CAs Demonstrate Low WSS**

Evidence implicating low WSS in the growth of CA development is suggested by several studies. Cebal et al [89] initially inferred that local propagation and growth of CAs is driven by interactions between regional blood flow and the vascular wall. Several experimental in vitro studies, subsequently, collectively agree on low blood flow velocity as a critical driving force [17, 89, 90]. Watton et al observed continuous enlargement of the growing end of CAs due to a low WSS following an initial aneurysmal bulge enlargement [91]. Tateshima et al using middle CAs with the development of an enlarged bleb measured local WSS patterns and observed that the enlarged bleb end of a growing aneurysm displayed low WSS.
Likewise, Kadasi et al, using computational fluid dynamic models of 16 CAs identified during surgery noted that the occurrence of low WSS coincided with the thinner growing regions of the aneurysmal wall [93]. Shojma et al in his computational analysis of 20 CAs affecting human middle cerebral arteries consistently observed that low WSS was noted at the apex of the CA, a region of the aneurysm corresponding to the height of aneurysmal growth [4]. Similar conclusions regarding the relationship between WSS and aneurysmal growth was explored by Boussel et al, who suggested that regions of the CA with low WSS experienced higher rates of aneurysmal growth compared to regions of the CA with high WSS, which experienced lower rates of aneurysmal growth [94]. Further observations highlighting the contribution of low WSS in the propagation and increase in size of CAs comes from the study of Skodvin et al [95], which studied the relationship between low WSS and the risk of rupture. Here, it was observed that CAs that displayed larger areas of low WSS were more likely to rupture, indirectly suggesting a positive correlation between low wall stress and aneurysmal size [95].

Further examination of the molecular cross-talk between low blood flow velocity and CA growth is linked to structural changes of vascular endothelial cells. Endothelial cells, exposed to patterns of low WSS, are characterized by decreased...

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CA: cerebral aneurysms; SMC: smooth muscle cell; MMP: matrix metalloproteinase; PDGF: platelet-derived growth factor; FGF: fibroblast growth factor; tPA: tissue plasminogen activator; NF-κB: nuclear factor kappa B; COX: cyclooxygenase.
cell-cell adhesion, endothelial cell loss, and thrombus formation, which are necessary prerequisites for the structural weakening of the aneurysmal wall [94, 96, 97]. After initiation of CA formation, the region of blood vessels exposed to high WSS demonstrates fragmentation and loss of the IEL mediated by MMPs [56, 58]. Given the fact that the IEL contributes significantly to the structural integrity of the vessel wall, destruction of the IEL leads to an initial outward bulge creating local flow patterns of stagnant flow and low WSS. Aneurysmal bulge development exposes the growing end of the aneurysmal sac to low WSS, accelerating the previously initiated proinflammatory response by the vascular endothelium in response to high WSS. The predominance of low WSS in high growth regions of CAs defines a dominant function of low WSS in the continued growth and expansion of CAs; however, studies highlighting plausible molecular mechanisms governing this growth are relatively sparse [4, 91-94]. Endothelial cells exposed to sustained periods of low WSS respond by increasing proliferation of endothelial cells, triggering apoptosis of endothelial cells, upregulating proinflammatory and procoagulant mediators, increasing production of vasoconstrictive agents and decreasing production of vasodilatory mediators and antioxidative agents [98]. The ensuing endothelial dysfunction triggers the upregulation of adhesion molecules (VCAM-1 and intercellular adhesion molecule (ICAM)-1) and proinflammatory cytokines (tissue necrosis factor (TNF)-α, interleukin (IL)-1) and reactive oxygen species on the luminal cell surface [94, 99]. Further, low WSS increases endothelial expression of NF-κB ligand, a proinflammatory transcription factor. Increased transcription of the NF-κB pathway provides for increased adhesion and infiltration of leukocytes to the vascular endothelium. Leukocyte trafficking into the arterial wall allows for the release of proteases and proinflammatory cytokines that degrade the structural matrix and induce vascular smooth muscle apoptosis [100]. The weakened media in the arterial wall subsequently facilitates aneurysmal dilation under low WSS. Additionally, low WSS reduces mechanical stimulation and deformation of the vascular endothelium, resulting in an impaired synthesis and secretion of NO from the endothelium. Decreased expression of NO on the intimal surface promotes vasoconstriction and platelet aggregation [101, 102]. Consequently, increased inflammatory cell adhesion as well as aggregation of red blood cells and platelets damages the intima, resulting in intimal inflammation [103, 104]. As such, following injury inflammation of the intima, upregulation of inflammatory cell adhesion proteins is subsequently attended by increased leukocyte trafficking into the vascular wall. In contrast to a high WSS environment not favorable for tissue trafficking of leukocytes due to insufficient residence time in the vasculature, a low wall shear facilitates leukocyte transmigration due to the presence of a pro-adhesive endothelium in conjunction with increased residence time in the vasculature [105]. The resulting inflammatory cell infiltrates structurally degrades the extracellular matrix by releasing MMPs (MMP-2 and MMP-9). Additionally, following aneurysm initiation, the dome experiences low levels of WSS as a result of regional blood flow stagnation. Local stagnation of blood flow prevents shear stress-induced eNOS action leading to a dysfunction of flow induced NO synthesis. Decreased synthesis of endothelial derived NO triggers apoptosis of vascular SMCs setting into motion, the process of vessel wall remodeling [60, 106-108].

Collectively these studies suggest that areas of an CA displaying low WSS experience greater rates of growth and are more prone to rupture compared to areas of an aneurysm that display high WSS. So, it is safe to assume that low WSS generated by turbulent blood flow within a dilated CA functions to propagate aneurysmal growth.

**Low WSS Enhances Inflammatory Cell Accumulation and Endothelial Cell Loss Contributing to Vessel Wall Weakening and Rupture**

Low levels of WSS evoke a proinflammatory endothelial cell phenotype leading to aneurysmal growth, progression, and rupture. In response to a laminar, physiological level of shear stress, endothelial cells adopt a nonproliferative and noninflammatory phenotype. Following initiation of nascent CA formation, aneurysmal dilation creates turbulent flow patterns characterized by fewer organized parallel flow vectors, exposing the endothelium of the growing sac to lower WSS. Low wall shear inside the growing end of the aneurysmal sac evokes an atherogenic response by promoting expression of a proinflammatory endothelial cell phenotype [109-112]. Moreover, low wall shear modifies the secretory response of endothelial cells, characterized by decreased production of vasodilators (NO and prostacyclin) and antioxidants (superoxide dismutase) and increased production of vasoconstrictors (endothelin-1), reactive oxygen species and proinflammatory cytokines (TNF-α and IL-1B) [89]. Endothelial cells increase synthesis and release of reactive oxygen species and proinflammatory cytokines and upregulate proinflammatory cell surface adhesion molecules (VCAM-1, ICAM-1) on the luminal cell surface [105]. Further, low shear stress facilitates apoptosis of endothelial cells with a weakening of the aneurysmal wall. Indeed, in a comparative study between ruptured and unruptured CAs, ruptured CAs were observed to show increased rates of apoptosis [112, 113]. Moreover, areas of low WSS coincided with thin wall regions of the CA such as the dome. The net outcome achieved [58] is increased inflammatory cell infiltration, MMP production, SMC proliferation and migration leading to weakening of the vessel wall and aneurysmal rupture (Table 2) [4, 72, 92, 94-97, 114-119].

Building on this, lymphocytes play a vital role in the rupture of aneurysms [11]. T lymphocytes promote the destructive inflammatory process through the elaboration of proinflammatory cytokines (TNF and interferon (IFN)-γ) leading to activation of macrophages, B lymphocytes and upregulation of surface adhesion molecules. Sawyer et al observed that following initiation of intracranial aneurysms in experimental hypertension molecules, lymphocyte-depleted mice developed significantly fewer aneurysms compared to lymphocyte-rich mice [120]. In addition, lymphocyte release of IFN-γ, a potent inducer of macrophage activation, determines the course of aneurysmal growth and rupture [11, 121]. In a comparative study, macrophage infiltration was shown to be significantly
correlated with an increased risk of rupture in ruptured CAs compared to unruptured CAs [122-124]. Further, macrophage-derived proteases (MMPs 1, 2, and 9) are consistently overexpressed in aneurysmal walls and ruptured aneurysms show a higher expression of MMP-2 and MMP-9 compared to unruptured aneurysms [123]. Similarly, Sawyer et al demonstrated that lymphocyte-depleted mice had lower levels of MMP-2 and MMP-9 compared to lymphocyte-rich mice and consequently had lower risk of CA rupture [120]. Kurki et al in a comparative study between ruptured and unruptured cerebral aneurysm models using oligonucleotide microarrays to analyze endothelial cell gene expression in varying hemodynamic stress observed increased inflammatory cell chemotaxis and leukocyte trafficking, oxidative stress, extracellular matrix degradation and destructive vascular remodeling in ruptured aneurysms as opposed to unruptured aneurysms [125]. Apart from mediating proinflammatory changes on the vessel wall, low WSS exerts detrimental vascular wall remodeling changes by influencing endothelial cell expression of NO. In response to low WSS, endothelial cells suppress expression of endothelial-derived NO [126]. Given the vital role of NO in vascular physiology such as regulation of vascular tone, inhibition of SMC proliferation, decreased production of pro-inflammatory mediators, loss of NO has detrimental effects of aneurysmal growth [127]. Aneurysmal wall devoid of adequate NO production displays increased oxidative stress due to an increase in oxidase activity unbalanced by appropriate superoxide scavenger activity [128].

Ultimately, in regions of the vessel wall displaying atherosclerotic and hyperplastic changes as well in aneurysmal rupture, low WSS was demonstrated, highlighting a pivotal role of low WSS in inducing a proinflammatory atherogenic response culminating in vessel wall weakening and subsequent aneurysmal rupture.

### Conclusions

It has been discovered that CA regions with low WSS expand faster and are more likely to burst than those with high WSS. Consequently, it is plausible to infer that low WSS, which in turn promotes aneurysmal growth, is caused by turbulence in the blood flow within a dilated CA. The preponderance of low WSS in high growth regions of CAs suggests that low WSS plays a prominent role in the continuing growth and expansion of CAs; nevertheless, research showing probable molecular processes behind this growth are rare. Low WSS contributes to the formation and expansion of CAs, starting with its effects on vascular endothelial cells. In response to sustained low WSS, endothelial cells multiply more, cause death in endothelial cells, increase pro-inflammatory and procoagulant mediators, produce more vasoconstrictive agents, and decrease the production of antioxidative and vasodilatory mediators, culminating in a destructive cascade of vessel wall remodeling unable to tolerate hemodynamic stresses leading to aneurysmal growth and eventual rupture.
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Conflict of Interest

The authors declare that there is no conflict of interest.

Author Contributions

Vivig Shantha Kumar was responsible for writing the discussion, incorporating the tables and references and proofreading the article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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