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Review Article

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

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Abstract

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 site 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 aneurysms (CA) are thought to affect 1-3% of people in the general population [1]. Cerebral aneurysm development and growth follows an amalgamation of multiple insults with individual contributions from hemodynamic stress and inflammatory pathways [2,3]. Substantial clinical and experimental experience demonstrate a role of hemodynamic influences in cerebral aneurysm pathogenesis, suggesting that altered hemodynamics modulate a biphasic response defined by early initial cerebral aneurysm formation and later cerebral growth [4-8]. A series of actions connected to stages of arterial wall remodeling in response to hemodynamic stresses is represented by the initiation, growth, and rupture of cerebral aneurysms [9,10]. Hemodynamic induced endothelial dysfunction is a starting point for the development of cerebral aneurysms. 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 cerebral aneurysm growth, formation, and rupture is wall shear stress. High shear stress in arterial branch points and bifurcations coincides with histological markers of nascent cerebral aneurysm 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. Low wall shear stress, on the other hand, is commonly observed at the growing end of cerebral aneurysms such as the neck and dome regions of cerebral aneurysms [17,18]. These regions are observed to demonstrate marked inflammatory vessel wall remodeling demonstrated by increased macrophage tissue trafficking, release of macrophage derived products (MMPs), & loss of smooth muscle cells.

As such, our main objective in this study is to understand

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the contributions of varying hemodynamic perturbations toward the development and growth of cerebral aneurysms.

Review

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 [1]. 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].

Shear stress modulates vascular tone through its influence on the production of nitric oxide [20,21]. Endothelial nitric oxide synthase modulates local production of nitric oxide 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 through protein kinase B phosphorylation, laminar wall shear stress 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, which contributes to NO-dependent vasodilation [25,26]. Endothelial cell over expression of KLF2 abundantly induces endothelial nitric oxide synthase expression [27,28]. Laminar fluid shear stress mediates an antithrombotic and anti-inflammatory effect through the upregulation of Kruppel-like factor-2 [29,30]. Induced by laminar shear stress, KLF-2 reduced the expression of the pro-inflammatory adhesion molecules vascular cell adhesion molecule-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 beta ligand is downregulated [32,33]. Decreased expression of NF-KB, 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 family of proteins is one of the most significant signaling pathways mediating endothelial cell proliferative response to laminar wall shear stress [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 between maintenance. Moreover, the antimitotic pathway of AMPK and the proliferative pathway of AKT is simultaneously activated. Dual activation of both the AMPK/AKT pathway maintains a balanced expression of mTOR signaling, a molecular pathway governing vascular endothelial cell proliferation [46]. Ultimately, through these molecular signaling pathways, endothelial cells remain in a quiescent antiproliferative state secondary to an arrest of the cell cycle in either the G1 or G0 phase promoting indefinite endothelial cell survival.

Vascular Endothelial Cell Structural Changes in Response to High Shear Stress. The frequent occurrence of cerebral aneurysms in vascular branch points and bifurcation points emphasizes the significance of hemodynamic stresses in the beginning of cerebral aneurysm formation [47-51]. Indeed, there is a higher prevalence of cerebral aneurysms 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 wall shear stress locally [47,52-55]. Aneurysmal dilation of cerebral vessels most commonly begins at sites of high wall shear stress. High wall shear stress 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 cerebral aneurysm formation. Elevation of the wall shear stress beyond threshold conditions, from observations in several animal models, document histopathological vascular wall changes suggestive of early CA formation: Fragmentation of the internal elastic lamina 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 are attended by a fragmentation of the internal elastic lamina of blood vessels [56]. Similarly, Stehbens, 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 9 fold increase in basilar artery flow following ligation of the common carotid artery. Additionally, newly formed cerebral aneurysms 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]. Dog's carotid arteries were ligated experimentally to create new branch points, and Meng, et al., [58] observed remodulative changes at these bifurcations that resembled the beginning of an intracranial aneurysm, including disruption of the internal elastic lamina, loss of medial SMCs, and a decreased proliferation of SMCs [59]. Further, Jamous, et al., studied cerebral aneurysm occurring at high flow bifurcation sites and documented endothelial cell morphological alterations of during the early phase of aneurysm development. In the early phase of cerebral aneurysm 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 [60]. Fukada, et al., similarly observed that high wall shear incites CA formation and endothelial cell injury at sites of nascent CA formation similarly corresponds to endothelial cell structural modifications as described by Jamous. One such study performed by Fukada, et al., correlated aneurysmal degenerative changes in endothelial cells with the magnitude of wall shear stress 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 wall shear stress [61]. 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 cerebral aneurysm formation in rats and primates, increased cerebral blood flow and hypertension were necessary prerequisites for aneurysmal dilation [50,62-64]. 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 wall shear stress flow acceleration at bifurcation points produces a hemodynamic environment characterized by high wall shear stress which triggers initiation of aneurysmal dilation. In experimental models of cerebral aneurysms, increased cerebral blood flow and systemic hypertension are necessary prerequisites for the initiation of CA formation [4,15-17]. Likewise, Kulcsar, et al., analyzed the hemodynamics of a cerebral vasculature in 3 patients before and after the development of an intracranial aneurysm and observed that IA consistently formed at locations characterized by high WSS [65]. Further, Metaxa, 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 wall shear stress [66]. High wall shear stress 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 wall shear stress, however, evokes a proinflammatory, procoagulative and proliferative phenotype predisposing to vascular remodeling. Activation of nuclear factor KB, a proinflammatory transcription factor, in endothelial cells challenged with hemodynamic stress activates inflammatory signaling pathways leading to CA initiation [67] NF-Kb, a proinflammatory transcription factor, is activated by increased shear stress on endothelial cells, regulating the expression of various proinflammatory genes [68-72]. *In vivo* experimental models of cerebral aneurysms observed that increased flow and hypertension are necessary prerequisites for NF-KB activation in rat models of aortic aneurysms [73]. 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 IKB proteins, preventing its translocation into the nucleus. Appropriate activating signals phosphorylate IKB, acting to abborate the inhibitory anti-migratory influence of IKB. NF-kB subsequently translocates to the nucleus to evoke the transcription of proinflammatory genes [67]. Cultured endothelial cells demonstrate increased nuclear translocation of NF-KB in response to fluid shear stress by activating IKB kinase through phosphorylation [74]. 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 [Schneider A] [75]. 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 cerebral aneurysms in murine rat models of cerebral aneurysm [76-78]. 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 nuclear factor kB expression were observed to have a significant blockade of aneurysm formation. NF-KB plays a critical developmental role in the genesis of nascent cerebral aneurysms by regulating the transcription of downstream pro-inflammatory genes leading to phenotypic alterations of the vascular endothelium [79,80]. The major downstream target of NF-kB following activation is the upregulation of proinflammatory adhesion molecules, VCAM-1 and MCP-1, on the vascular endothelium leading to increased neutrophil and macrophage tissue trafficking. Macrophage infiltration results in the release of matrix metalloproteinases, MMP-2 and MMP-9, capable of proteolytically degrading the extracellular matrix as well as the induction of iNOS leading to the pathological formation of nitric oxide mediating vascular smooth muscle cell apoptosis (Table 1).

Growing & thin end of cerebral aneurysms demonstrate low wall shear stress

Evidence implicating low wall shear stress in the growth of cerebral aneurysm development is suggested by several studies. Cerebral, et al., initially inferred that local propagation

Table 1: High Wall Shear Stress: Summary of hemodynamic pattern, growth rate, and vascular wall changes.

References	Wall shear stress	Pattern of growth vessel wall changes	
Steiger [56]	High WSS	Initiation of CA Formation	Fragmentation of Internal Elastic Lamina
Stehbens [48]	High WSS	Initiation of CA Formation	Loss of normal phenotype of formation endothelial cells and endothelial damage
Meng [59]	High WSS	Initiation of CA Formation	Internal elastic lamina disruption Medial smooth muscle cells are lost Reduced vascular smooth muscle cell proliferation Decrease in fibronectin
Fukada [61,114]	High WSS	Initiation of CA Formation	Fragmentation of endothelial cell plasma membrane Endothelial cell vacuolization Endothelial cell damage with/without nuclear and cytoplasmic vacuolization
Jamous [115]	High WSS	Initiation of CA Formation	Fragmentation of endothelial cell plasma membrane Endothelial cell vacuolization Endothelial cell damage with/without nuclear and cytoplasmic vacuolization
Wang [116]	High WSS	Initiation of CA Formation	Endothelial Cell Loss
Kolega J [80]	High WSS	Initiation of CA Formation	Endothelial Cell Damage Endothelial Cell turnover MMP production by mural cells Mural Cell Apoptosis
Dolan JM [117]	High WSS	Initiation of CA Formation	Endothelial Cell Turnover
Meng H [59]	High WSS	Initiation of CA Formation	ECM degradation Medial Thinning
Hoi [118]	High WSS	Initiation of CA Formation	MMP production by ECs
Fukada & Aoki [114]	High WSS	Initiation of CA Formation	NF-κB & COX-2 increased
Pawlowska [119]	High WSS	Initiation of CA Formation	IL-1β increased
Taylor, et al., [120]	High WSS	Initiation of CA Formation	Migration of SMC from media to intima; change of SMC phenotype from contractile to secretory, w/ MMP production by SMC
Shi & Tarbell [121]	High WSS	Initiation of CA Formation	PDGF & FGF-2 released from SMCs
Papadaki [122]	High WSS	Initiation of CA Formation	Increased tPA production

and growth of cerebral aneurysms 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 [17,81,82]. Watton, et al., observed continuous enlargement of the growing end of cerebral aneurysms due to a low wall shear stress following an initial aneurysmal bulge enlargement [83]. Teteshima, et al., using middle cerebral aneurysms with the development of an enlarged bleb measured local wall shear stress patterns and observed that the enlarged bleb end of a growing aneurysm displayed low wall shear stress [84]. Likewise, Kadasi, et al., using computational fluid dynamic models of 16 cerebral aneurysms identified during surgery noted that the occurrence of low wall shear stress

coincided with the thinner growing regions of the aneurysmal wall [85]. Shojma, et al., in his computational analysis of 20 cerebral aneurysms affecting human middle cerebral arteries consistently observed that low wall shear stress was noted at the apex of the cerebral aneurysm, a region of the aneurysm corresponding to the height of aneurysmal growth [4]. Similar conclusions regarding the relationship between wall shear stress and aneurysmal growth was explored by Boussel, et al., who suggested that regions of the cerebral aneurysm with low wall shear stress experienced higher rates of aneurysmal growth compared to regions of the cerebral aneurysm with high wall shear stress, which experienced lower rates of aneurysmal growth [86]. Further observations highlighting the contribution of low wall shear stress in the propagation and increase in size of cerebral aneurysms comes from Skodvin, et al., study of the relationship between low wall shear stress and the risk of rupture. Here, it was observed that cerebral aneurysms that displayed larger areas of low wall shear stress were more likely to rupture, indirectly suggesting a positive correlation between low wall stress and aneurysmal size [87].

Further examination of the molecular cross-talk between low blood flow velocity and cerebral aneurysm growth is linked to structural changes of vascular endothelial cells. Endothelial cells, exposed to patterns of low wall shear stress, are characterized by decreased cell-cell adhesion, endothelial cell loss and thrombus formation, necessary prerequisites for the structural weakening of the aneurysmal wall [86,88,89]. After initiation of cerebral aneurysm formation, the region of blood vessels exposed to high wall shear stress demonstrates fragmentation and loss of the IEL mediated by matrix metalloproteinases [56,59]. Given the fact that the internal elastic lamina 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 wall shear stress. Aneurysmal bulge development exposes the growing end of the aneurysmal sac to low wall shear stress, accelerating the previously initiated proinflammatory response by the vascular endothelium in response to high WSS. The predominance of low wall shear stress in high growth regions of cerebral aneurysms defines a dominant function of low wall shear stress in the continued growth and expansion of cerebral aneurysms, however, studies highlighting plausible molecular mechanisms governing this growth are relatively sparse [4,83-86].

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 [81]. The ensuing endothelial dysfunction triggers the upregulation of adhesion molecules (VCAM-1 and ICAM-1) and proinflammatory cytokines (TNF-Alpha, Interleukin 1) and reactive oxygen species on the luminal cell surface [86,90]. Further, low wall shear stress increases endothelial expression of NF-KB ligand, a proinflammatory transcription factor. Increased transcription of the NF-KB 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 [91]. The weakened media in the arterial wall subsequently facilitates aneurysmal dilation under low wall shear stress. Additionally, low wall shear stress reduces mechanical stimulation and deformation of the vascular endothelium, resulting in a impaired synthesis and secretion of nitric oxide from the endothelium. Decreased expression of nitric oxide on the intimal surface promotes vasoconstriction and platelet aggregation [92,93]. Consequently, increased inflammatory cell adhesion as well as aggregation of red blood cells and platelets damages the intima, resulting in intimal inflammation [94,95]. 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 wall shear stress 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 [96] The resulting inflammatory cell infiltrates structurally degrades the extracellular matrix by releasing matrix metalloproteinases (MMP-2 and MMP-9). Additionally, following aneurysm initiation, the dome experiences low levels of wall shear stress 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 nitric oxide synthesis. Decreased synthesis of endothelial derived nitric oxide triggers apoptosis of vascular smooth muscle cells setting into motion, the process of vessel wall remodeling [61,97-99].

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

Low wall shear stress enhances inflammatory cell accumulation & endothelial cell loss contribute to vessel wall weakening and rupture

Low levels of wall shear stress 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 cerebral aneurysm formation, aneurysmal dilation creates turbulent flow patterns characterized by fewer organized parallel flow vectors, exposing the endothelium of the growing sac to lower wall shear stress. Low wall shear inside the growing end of the aneurysmal sac evokes a atherogenic response by promoting expression of a proinflammatory endothelial cell phenotype [100-102]. Moreover, low wall shear modifies the secretory response of endothelial cells, characterized by decreased

production of vasodilators (nitric oxide and prostacyclin) and antioxidants (superoxide dismutase) and increased production of vasoconstrictors (endothelin-1), reactive oxygen species and proinflammatory cytokines - TNF-alpha and IL-1B) [81]. 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 [96]. 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 cerebral aneurysms, ruptured cerebral aneurysms were observed to show increased rates of apoptosis [103,104]. Moreover, areas of low wall shear stress coincided with thin wall regions of the cerebral aneurysm such as the dome. The net outcome achieved is increased inflammatory cell infiltration, matrix metalloproteinase production, smooth muscle cell proliferation and migration leading to weakening of the vessel wall and aneurysmal rupture [59].

Building on this, lymphocytes play a vital role in the rupture of aneurysms [11]. T-lymphocytes propagate the destructive inflammatory process through the elaboration of proinflammatory cytokines (TNF and IFN-gamma) 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 fever aneurysms compared to lymphocyte rice mice [105]. In addition, lymphocyte release of IFN-gamma, a potent inducer of macrophage activation, determines the course of aneurysmal growth and rupture [11,106]. In a comparative study, macrophage infiltration was shown to be significantly correlated with an increased risk of rupture in ruptured cerebral aneurysms compared to unruptured cerebral aneurysms [107-109]. Further, macrophage derived proteases- matrix metalloproteinase 1,2 and 9- are consistently over expressed in aneurysmal walls and ruptured aneurysms show a higher expression of MMP-2 and MMP-2 compared to unruptured aneurysms [108]. 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 cerebral aneurysm rupture [105]. Kukri, 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 [110]. Apart from mediating proinflammatory changes on the vessel wall, low wall shear stress exerts detrimental vascular wall remodeling changes by influencing endothelial cell expression of nitric oxide. In response to low wall shear stress, endothelial cells suppress expression of endothelial-derived nitric oxide [111]. Given the vital role of nitric oxide in vascular physiology such as regulation of vascular tone, inhibition of smooth muscle cell proliferation, decreased production of proinflammatory mediators, loss of nitric oxide has detrimental effects of aneurysmal growth [112]. Aneurysmal wall devoid of adequate nitric oxide production displays increased oxidative stress due to an increase in oxidase activity unbalanced by appropriate superoxide scavenger activity [113].

Ultimately, in regions of the vessel wall displaying atherosclerotic and hyperplastic changes as well in aneurysmal rupture, low wall shear stress was demonstrated, highlighting a pivotal role of low wall shear stress in inducing a proinflammatory atherogenic response culminating in vessel wall weakening and subsequent aneurysmal rupture (Table 2).

Table 2: Low wall shear stress: Summary of hemodynamic pattern, growth rate, and vascular wall changes

References	Wall Shear Stress	Pattern of Growth Vessel Wall Changes	
Tateshima [84]	Low WSS	Growth and expansion of CA	Not Assessed
Shojma [4]	Los WSS	Growth and expansion of CA	Not Assessed
Boussel [86]	Low WSS	Growth and expansion of CA	Disorganization of endothelium, increased production of vasoconstrictive & inflammatory agents; increased apoptosis of ECs
Skodvin [87]	Low WSS	Growth and expansion of CA	Not Assessed
Malek [123]	Low WSS	Growth and expansion of CA	Endothelial Cell upregulation of ICAM, VCAM, Interleukin 1, Reactive Oxygen Species
Qiu T [124]	Low WSS	Growth and expansion of CA	Increased Inflammatory cell infiltration
Chiu JJ	Low WSS	Growth and expansion of CA	Increased reactive oxygen species formation
Galis [125]	Low WSS	Growth and expansion of CA	MMP production by macrophages
Ross R [99]	Low WSS	Growth and expansion of CA	SMC proliferation and migration Thrombus formation
Lu & Kassab [126]	Low WSS	Growth and expansion of CA	Decreased production of PGI2, leading to atherosclerotic changes; increased oxidative stress
Zhou [127]	Low WSS	Growth and expansion of CA	Increased selectin-mediated leukocyte rolling
Papadaki [122]	Low WSS	Growth and expansion of CA	Decreased tPA production
Turjman [96]	Low WSS	Growth and expansion of CA	Reorganized ECs w/ cuboidal shape; promoted thrombosis & leukocyte adhesion

Conclusion

It has been discovered that cerebral aneurysm regions with low wall shear stress expand faster and are more likely to burst than those with high wall shear stress. Consequently, it is plausible to infer that low wall shear stress, which in turn promotes aneurysmal growth, is caused by turbulence in the blood flow within a dilated cerebral aneurysm. The preponderance of low wall shear stress in high growth regions of cerebral aneurysms suggests that low wall shear stress plays a prominent role in the continuing growth and expansion of cerebral aneurysms; nevertheless, Research showing probable molecular processes behind this growth is rare. Low wall shear stress contributes to the formation and expansion of cerebral aneurysms, 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

None.

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