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Pavlos Texakalidis
Emory University School of Medicine

Ahmad Sweid
Thomas Jefferson University

Nikolaos Mouchtouris
Thomas Jefferson University

Eric C. Peterson
University of Miami School of Medicine

Chrissa Sioka
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University of Ioannina School of Medicine

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Authors

Pavlos Texakalidis, Ahmad Sweid, Nikolaos Mouchtouris, Eric C. Peterson, Chrissa Sioka, Leonardo Rangel-Castilla, John Reavey-Cantwell, and Pascal Jabbour

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Authors: Pavlos Texakalidis MD¹, Ahmad Sweid MD², Nikolaos Mouchtouris MD², Eric C Peterson MD³, Chrissa Sioka MD PhD⁴, Leonardo Rangel-Castilla MD⁵, John Reavey-Cantwell MD⁶, Pascal Jabbour MD²

Affiliations:

1. Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA
2. Department of Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA
3. Department of Neurosurgery, University of Miami School of Medicine, Miami, FL, USA
4. Department of Nuclear Medicine, University of Ioannina School of Medicine, Ioannina, Greece
5. Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA
6. Department of Neurosurgery, Virginia Commonwealth University, Richmond, VA, USA

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Corresponding Author

Pascal Jabbour MD

Division of Neurovascular Surgery and Endovascular Neurosurgery,
Department of Neurological Surgery, Thomas Jefferson University
Hospital 901 Walnut St, 3rd Floor, Philadelphia PA 19107, United States.
E-mail address: pascal.jabbour@jefferson.edu

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Short Title: Biology and Physics of Cerebral Aneurysms

Abstract

Cerebral Aneurysms (CAs) are characterized by a pathological wall structure with internal elastic lamina and media disruption which leads to focal weakened pouches of the arterial wall. The prevalence of unruptured CAs is estimated to be 2-5% in the general population. During the past few decades, the pathophysiological mechanisms behind the formation, growth and rupture of CAs have been the focus of numerous research studies. In this review, the inflammatory pathways, genetics and risk factors for the formation, growth and rupture of CAs are summarized. In addition, the concepts of geometrical indices, flow patterns and fluid dynamics that govern CA development are discussed.

Keywords: cerebral aneurysms; intracranial aneurysms; inflammation; wall shear stress; flow dynamics

Introduction

The prevalence of unruptured cerebral aneurysms (CA) is estimated to be 2-5% in the general population.¹ CAs are characterized by a pathological wall structure with internal elastic lamina and media disruption which leads to focal weakened pouches of the arterial wall.^{2,3} The majority of CAs remain clinically silent during the lifetime of patients who harbor them. However, aneurysmal rupture and subsequent subarachnoid hemorrhage (SAH), the most catastrophic sequelae, are associated with an approximately 50% mortality and 30-50% neurologic morbidity rate among the survivors.⁴ Despite the technological advances and use of novel devices to manage CAs, they continue to pose a significant risk of mortality and neurologic morbidity.⁴

During the past few decades, the pathophysiological mechanisms behind the formation, growth and rupture of CAs have been the focus of numerous research studies.^{5,6} Inflammatory pathways and mediators implicated in CA formation and growth along with extensive imaging studies have provided new insights into our understanding of CAs.^{7,8} Deciphering the biology and physics of CAs could potentially optimize patient management and result in novel treatment options. This review aims to summarize current scientific knowledge with regards to CA formation, growth and rupture.

Biology of CAs

1) Inflammatory Pathways

Several studies have demonstrated that inflammation has an impact on the formation and growth of CAs.⁸⁻¹¹ One hypothesis is that an initial hemodynamic insult leads to complex inflammatory processes which involve the matrix metalloproteinases (MMPs), vascular smooth muscle cells (VSMCs), macrophages and oxidative stress.

Endothelial dysfunction is considered the first step in the formation of CAs and this can be the result of smoking, hypertension, local flow dynamics dysregulation and non-modifiable factors including genetics. Oxidative stress is considered to be a major source of endothelial injury and entails the accumulation of free radicals due to increased production and/or decreased removal.⁵ The next step involves a coordinated inflammatory response implicating macrophages, mast cells, T cells and a number of cytokines and inflammatory mediators. This inflammatory response leads to the phenotypic modulation of VSMCs, which are the main matrix-synthesizing cells within the media of the arterial wall.¹² These VSMCs induce disruption of the internal elastic lamina, cause

dysregulated collagen synthesis and extracellular matrix remodeling.¹³ The late steps in the biology of CA growth involve VSMC apoptosis which results in further thinning of the media and increased rupture risk.¹¹

In addition, macrophages infiltrate the vascular wall as a result of the inflammatory mediators and cytokines. Macrophages express and release MMPs which cleave the extracellular matrix and collagen of the arterial wall.⁷ This, in turn, leads to the recruitment of other inflammatory cells, upregulates the expression of additional proteases and rapidly increases the degeneration and weakening of the arterial wall.¹⁴ These processes are often characterized by a positive feedback regulation and act together, ultimately culminating in aneurysm formation and growth. Further inflammation may severely impact the arterial wall and trigger aneurysmal rupture and SAH.¹¹

Several experimental studies have supported these inflammatory pathways. A number of studies have focused on the VSMCs' and macrophages' role in the biology of CAs. The study by Ali et al. suggested that tumor necrosis factor- α (TNF- α) is implicated in the phenotypic modulation of VSMCs towards a pro-inflammatory and matrix remodeling phenotype.¹³ Guo et al. showed that the density of VSMCs in the media of CAs was significantly lower compared to normal arterial walls (43.9 VSMC/HPF vs. 222.8 VSMCs/HPF; $p < 0.01$).¹⁵ Interestingly, a study of mice with elastase-induced CAs showed that macrophages were the predominant cells that infiltrated the aneurysm wall.¹⁶ They also demonstrated that mice with macrophage depletion had a statistically significant lower incidence of CAs when compared with the control group ($p < 0.05$). In addition, this study supported that monocyte chemoattractant protein-1 (MCP-1) depleted mice also had a statistically significant lower incidence of CAs when compared with wild-type mice ($p < 0.05$).¹⁶ Aoki et al. suggested that MCP-1 plays a critical role in CA formation; conversely, they demonstrated that its inhibition resulted in the cessation of CA growth in mice.¹⁷

Oxidative stress and reactive oxygen species were shown to induce VSMC phenotypic switching and apoptosis; this was postulated to play a role in CA formation growth and risk of rupture.^{18–20} A study of both human and mice intracranial aneurysms demonstrated that inducible nitric oxide synthase (iNOS) immunoreactivity was consistent with the development of early aneurysmal changes.²¹ This study also showed that aminoguanidine, an iNOS inhibitor, reduced the incidence of induced CAs.²¹ In addition, another study demonstrated an upregulated gene profile related to reactive oxygen species, MMPs, growth factors, apoptosis, chemokines, adhesion

molecules and complement in experimentally induced CAs.²² **(Figure 1)** Hasan et al. studied ten human CAs and introduced the concept of a macrophage subtype imbalance (M1: pro-inflammatory; M2: anti-inflammatory) in ruptured versus unruptured aneurysms.²³ Specifically, they showed that M1 and M2 were equally distributed within the aneurysm wall of unruptured aneurysms; in contrast, M1 pro-inflammatory macrophages were the predominant type of macrophages in ruptured aneurysms.²³

II) Genetics

The genetic predisposition to develop CAs and SAH has been well-established. There is an almost 2-fold and 4-fold or more increase in the incidence of CAs in patients with one and two affected first degree relatives, respectively, when compared to the general population.^{24,25} Familial CAs are more commonly multiple and found in the middle cerebral artery, may rupture at a younger age and may be larger than sporadic CAs.^{26–29} Genome-wide linkage studies have identified a number of susceptibility loci that may contain genes implicated in familial CAs.³⁰ For example, 1p34.3-p36.13, 19q13.3, Xp22 and 7q11 were found to have a strong association with familial CAs.^{30–32} The 7q11 region contains the collagen type 1A2 gene and is adjacent to the elastin gene, both of which contribute to the structural integrity of the arterial walls.^{33–35} A systematic literature review showed that the 9p21/CDKN2, a loci which is implicated in vessel wall remodeling, had the strongest association with aneurysm rupture (Odds ratio: 1.42; p=0.01).³⁶ Another large scale genome-wide association study with approximately 2,000 patients with CAs and 8,000 controls reported single nucleotide polymorphisms in the 2q33.1, 8q11.23 and 9p21.3 loci, which are thought to be associated with sporadic and familial CAs.³⁷ Candidate genes that have been studied are MMPs, angiotensin-converting enzyme, phospholipase C, NOS, transforming growth factor-beta receptor among others. However, the outcomes of genetic linkage studies are inconsistent in the literature.³³ Even though a large number of studies have implicated the effect of genetics on the development of CAs, it is more likely that CAs are the result of a multifactorial process where both genetics and environmental factors play a role.

On the other hand, several hereditary diseases with an established genetic profile are known to be associated with an increased risk of CA formation and rupture. The most common is autosomal dominant polycystic kidney disease (ADPKD), which has a mutation in the PKD1 and PKD2 genes. The prevalence of CAs in ADPKD is estimated within the range of 10-13% and up

to 25% in those with a positive family history of CA or SAH.³⁸ Other hereditary syndromes associated with CAs are fibromuscular dysplasia and Ehlers-Danlos type IV.²⁴

III) Risk Factors

Several modifiable and non-modifiable factors have been proposed to affect the risk of aneurysm formation, growth and rupture. The most studied and well-established modifiable factors are cigarette smoking and hypertension. Smoking and hypertension were independent risk factors for CA formation with an OR of 3.0 and 2.9, respectively.³⁹ The same study highlighted that the combined risk of individuals who smoke and are hypertensive increases synergistically to a statistically significant OR of 8.3.³⁹ Smoking and hypertension are both known to increase oxidative stress. Oxidative stress acts as the initial hemodynamic insult causing endothelial injury and subsequent inflammation, ultimately resulting in aneurysm formation.⁵ Smoking increases the production of reactive oxygen species through NADPH oxidase activation.⁴⁰ In contrast, there is currently no strong evidence pointing towards a direct unidirectional link between hypertension, free radical generation and aneurysm formation. There is inconsistent evidence regarding the effect of alcohol consumption and formation of CAs; in comparison, heavy alcohol consumption has been shown to increase the risk of SAH.^{5,41} Atherosclerosis is also consistently present in saccular CAs; however, whether atherosclerosis can cause CAs is still unknown.^{42,43}

As discussed above, family history of CAs and SAH is one of the non-modifiable risk factors which might be associated with specific genetic loci. Interestingly, the number of first-degree relatives with SAH affects the risk of SAH for an individual. Bor et al. evaluated approximately 135,000 patients and showed that individuals with 1 affected and 2 affected relatives had an OR of 2.15 and 51, respectively, for an increased risk of SAH.⁴⁴ Female gender and older age were also considered non-modifiable risk factors for CAs in a meta-analysis of 95,000 patients.⁴⁵ In addition, female patients had a three-fold increase in the risk of aneurysmal rupture compared to male patients.⁴⁶

Hereditary syndromes are also non-modifiable risk factors. ADPKD-associated CAs are commonly found in the MCA and tend to have a small diameter (mean 4.4 mm).^{47,48} CAs in the ADPKD population occur in approximately 10-13% whereas in the general population the incidence ranges from 3-5%.^{38,49} However, a 20-year follow-up study and a systematic literature review suggested that the risk of growth or rupture in ADPKD patients is not higher when

compared to the general population.^{47,50} These results, however, should be interpreted with caution as ADPKD patients usually receive more aggressive treatment after diagnosis. Ehlers-Danlos type IV is another hereditary syndrome with an associated increased risk of CAs; importantly, catheter angiography may be higher risk for these patients due to fragility of the arterial walls.⁵¹ Moreover, sickle cell anemia is considered a non-modifiable risk factor for CAs. Patients with sickle cell anemia might present with multiple aneurysms, including aneurysms in the posterior circulation. The presumed mechanism is endothelial injury due to the sickle cells.^{52,53} In addition, Loeys-Dietz syndrome is thought to be associated with a high risk of CA formation, with an estimated prevalence of CAs ranging from 10-28%; however, data is limited.^{54,55} A study of 376 hereditary hemorrhagic telangiectasia (HHT) patients reported that only 2.1% of patients harbored CAs.⁵⁶ Nevertheless, this study found that 12.8% of patients had arteriovenous malformations.⁵⁶ Whether Marfan disease, neurofibromatosis, multiple endocrine neoplasia type I and acromegaly are associated with an increased risk to harbor CAs is still controversial.^{24,57-60}

Physics of CAs

I) Geometry

A variety of geometrical factors have been utilized with the goal to determine CAs prone to rupture. One of the simplest factors that has been historically used is the *maximal aneurysm size*. Several suggestions have been made in the past with regards to maximal CA size. The critical threshold above which there is an increased risk of rupture varied between 5-10mm. Even though there is evidence that maximal size and CA rupture are correlated,^{61,62} data from studies comparing the diameter of ruptured vs unruptured CAs are inconclusive.⁶³⁻⁶⁵ A systematic literature review suggested that the mean difference of the diameter between ruptured and unruptured aneurysms was only 1.5mm.⁶⁶ Importantly, data from a number of studies showed that 70-85% of the unruptured aneurysms had a maximal diameter of less than 10mm which further questions the applicability and sensitivity of this factor.⁶⁷⁻⁶⁹

Aspect ratio, defined as aneurysm height divided by aneurysm neck is considered a useful geometrical parameter that can be used for risk stratification. Reports from several studies have suggested that ruptured aneurysms most commonly have an average aspect ratio of 2.4 whereas unruptured aneurysms have an average aspect ratio of 1.6 or lower.^{66,70-72} A study of 129 patients with ruptured and 72 patients with unruptured CAs reported that approximately 80% of the

ruptured aneurysms had an aspect ratio greater than 1.6, whereas almost 90% of the unruptured had aspect ratio less than 1.6.⁷³ Nevertheless, there is no consensus with regards to an optimal aspect ratio threshold value that could be used in routine clinical practice. Future studies with larger patient samples and prospective design would be more likely to provide accurate thresholds with the potential to predict rupture.

Size ratio, is the aneurysm-to-parent vessel size ratio and has been shown to be a promising geometric factor that can help predict aneurysm instability and risk of rupture.⁷⁴ Results from a prospective study underscored that size ratio was the only statistically significant predictor of aneurysm rupture (OR: 2.12; 95% CI: 1.09-4.13) and this was validated by larger studies.^{75,76} A virtual experimental study also reported that higher size ratio is associated with flow patterns typical for ruptured CAs, independent of aneurysm type and size.⁷⁷ It has been also suggested that size ratio might be a more efficient predictor for rupture of small aneurysms <5mm.⁷⁶

The *area ratio* defined as the ratio of the area of the aneurysm to the parent artery in the neck plane and may be a potential predictor of CA rupture. In a multicenter study of 2,674 CAs in Chinese population, area ratio ≥ 1.5 (adjusted OR, 4.089; 95% CI, 1.247–13.406), and irregular wall (adjusted OR, 10.443; 95% CI 3.394 –32.135) were significant predictive factors for aneurysm rupture after adjustment for aneurysm size.⁷⁸ Of note, additional morphological parameters have been used with various applicability.⁷⁹ In this era of technological advancements and development of novel imaging software, more sophisticated combinations of geometrical variables are emerging. This could lead to the development of an imaging-based predictive test which utilizes the morphological characteristics of an individual aneurysm and computes the adjusted risk of rupture with an acceptable area under the curve.

II) Flow Patterns

CA flow has been investigated by clinical and experimental studies in animals and in vitro. The aneurysmal flow patterns are based on the geometrical indices of the CA-parent vessel complex and the volumetric flow characteristics in the afferent and efferent arteries. Different intra-aneurysmal flow patterns have been described in sidewall CAs, bifurcation aneurysms with symmetric or asymmetrical outflow and asymmetric bifurcation aneurysms.⁸⁰ The typical flow pattern of a sidewall CA is characterized by flow that impinges on the distal CA neck, enters the aneurysm, travels along the wall and exits the CA at the proximal neck.^{66,81} This intra-aneurysmal

flow pattern is also associated with reduced flow velocity in the center in theoretical models and human imaging studies.^{82,83} Geometric indices that impact flow patterns in bifurcation CAs are the bifurcation angle, branch diameters and flow dynamics in these branches.⁸⁰ Flow in bifurcation CAs usually enters the side of the neck which is closer to the larger branch, creates a vortex in the aneurysmal sac and exits into the daughter branch closest to the exit.^{84,85} Of note, higher aspect ratios affect the flow by creating a much slower circulation near the dome and reduce the flow penetrance in the aneurysm.⁸⁵ Another important consideration when studying the flow patterns and flow dynamics of CAs is the cardiac cycle.⁸⁶ For example, pulsatile flow during systole can drive blood flow from the parent vessel into the aneurysm, contributing to vortex formation, while the flow can either exit the aneurysm or redistribute into stagnation zones or vortical regions during diastole.^{86,87} There is also a temporal component in the flow patterns of the parent vessel at the aneurysm neck due to the cardiac cycle. More specifically, portions of the aneurysmal vortex or secondary flow structures (e.g. recirculation zones, helical flow patterns) may be generated at this location.^{88,89} However, individual aneurysms generally develop unique flow patterns which are affected by a number of geometrical indices, flow dynamics in the parent vessel and anatomy of the parent vessel-aneurysm complex.

III) Flow Dynamics and *Wall Shear Stress (WSS)*

A detailed and accurate hemodynamic description of a CA would require the evaluation of blood velocities within the flow pattern, density and viscosity as well as the geometry and mechanical properties of the arterial wall. This would allow the description of WSS distribution in the parent artery and CA flow. WSS is defined as the force per unit area which is exerted by a solid boundary (i.e. arterial wall) on a fluid in motion (i.e. blood) and vice-versa, in a direction on the local tangent plane. The impact of WSS on cerebral arterial walls has been a subject of recent study. WSS has been found to affect endothelial homeostasis and induce aneurysm formation and atherosclerotic lesions.⁹⁰⁻⁹² Meng et al. suggested that the combination of high WSS and high WSS gradient increases the risk for aneurysm formation at arterial bifurcations.⁹² However, there is conflicting evidence with regards to the mechanism through which WSS facilitates CA growth and rupture.⁹³⁻⁹⁶ Shojima et al. studied 20 middle cerebral artery aneurysms and proposed that a high WSS may contribute to the initial phase of hemodynamic stress, but that a low WSS may promote aneurysmal growth and increase the risk of rupture due to degenerative wall changes.⁹⁴ Similarly,

Miura et al. compared the morphologic and hemodynamic parameters between ruptured and unruptured CAs and showed that low WSS was the only independent predictor of aneurysm rupture in multivariate analyses.⁹⁵ In contrast, a study of 210 patient-specific CA geometries performed 1,050 image-based computational flow dynamics simulations and reported that elevated maximum WSS is associated with a positive history of CA rupture.⁹³ Interestingly, the authors also highlighted that low WSS levels did not show any association with rupture.⁹³ However, it should be noted that growing CAs tend to have complex flow patterns which induce variable WSS distributions along the CA wall.⁹⁷ There is also evidence that low WSS with high oscillations may induce focal CA growth (i.e. bleb or blister) while high WSS may be associated with global enlargement of the CA.⁹⁸ Future studies are needed to better characterize the effect of WSS on aneurysm formation, growth and rupture.

The mechanism through which WSS exerts its effects on the vascular wall and endothelium has been investigated by a number of studies. WSS is known to trigger several kinase pathways which lead to the activation of multiple transcription factors and result in the translation of vasoactivators, monocyte chemoattractants and endothelial growth factor genes that dysregulate vascular homeostasis and function.⁹⁰ A study of elastase-induced CAs in rabbits demonstrated that low WSS was associated with upregulation of MMPs or pro-MMPs and downregulation of their inhibitors, as compared to the control group.⁹⁹ Importantly, Wang et al. suggested that high WSS decreased endothelial NOS expression and increased inflammatory markers in the CA as compared to adjacent arterial segments and controls.¹⁰⁰ In conclusion, despite the complex interactions of hemodynamics with CA formation, growth and rupture, it is likely that both increased and decreased WSS contribute to the initial hemodynamic stress insult to the cerebrovascular tree, albeit with different mechanisms.¹⁰¹

Imaging Techniques and Risk Stratification

Investigating the pathophysiological mechanisms implicated in CA formation and growth is as important as developing novel tools that will provide new insights in the risk stratification of CAs. Advances in imaging techniques that utilize the established knowledge of inflammatory pathways associated with CA formation are already showing promising results. The use of high resolution magnetic resonance imaging has been used for a variety of cerebrovascular diseases including CA evaluation.¹⁰² It has been hypothesized that aneurysmal wall enhancement may be a

surrogate marker of wall inflammation. A meta-analysis by Texakalidis et al. showed that CAs with wall enhancement had statistically significant higher odds of being unstable (OR: 20; 95% CI: 6.4-62.1) with a sensitivity of 95% (90.4-97.8) and a negative predictive value of 96.2% (92.8-98).¹⁰³ Another imaging technique targeting inflammatory cells is Ferumoxytol-Enhanced MRI. Ferumoxytol is a nanoparticle that can be used as a contrast agent and marker of inflammation because it is cleared by macrophages.¹⁰⁴ A number of studies has also suggested that Ferumoxytol-Enhanced MRI may also help individualize risk stratification for rupture in CAs.^{105,106} Hasan et al showed that uptake of Ferumoxytol in the CA wall within the first 24 hours may predict aneurysm instability and rupture in the next six months.¹⁰⁵ Future studies are anticipated to validate these results.

In addition, risk stratification with the use of the Unruptured Intracranial Aneurysm Treatment Score (UIATS) or PHASES, based on easily available characteristics of the patient and the CA, may prove to be accurate and guide clinical decision making.^{107,108}

Conclusions

The pathophysiology of CAs has been extensively studied. The inflammatory pathways and physics behind the formation, growth and rupture of CAs have been described by a number of experimental and clinical studies. The combination of current scientific knowledge has allowed for the development of novel imaging techniques with the potential to optimize risk stratification of aneurysms prone to rupture. Future studies are anticipated to expand our understanding of this disease and develop innovative treatments.

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Figure Legends

Figure 1. Cerebral aneurysm (CA) formation and rupture. Aneurysm formation is initiated by hemodynamically triggered endothelial dysfunction. An inflammatory response implicating several cytokines and inflammatory mediators as well as macrophages, T cells, and mast cells ensues. Concurrently, smooth muscle cells (SMCs) undergo phenotypic modulation to a pro-inflammatory phenotype. The inflammatory response in vessel wall leads to disruption of internal elastic lamina, extracellular matrix digestion, and aneurysm formation. Loss of mural cells and further inflammation and vessel wall degeneration ultimately lead to CA rupture. bFGF indicates basic fibroblast growth factor; COX2, cyclooxygenase-2; ECM, extracellular matrix; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NK, natural killer; NO, nitric oxide; PGD, prostaglandin D; PGE, prostaglandin E; ROS, reactive oxygen species; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; and VSMC, vascular smooth muscle cell. (Copyright 2019 Wiley. Used with permission from Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. *Stroke*. 2013;44(12):3613-3622. doi:10.1161/STROKEAHA.113.002390)