Avens Publishing Group
J Surgery
July 2022 Vol:10, Issue:1


Open Access Review Article

Journal of Surgery

# Role of Wall Shear Stress in an Intracranial Aneurysm Formation: A Systematic Review

**Neupane D[1]*, Lageju N[1], Dahal A[2], Jaiswal LS[3], Manandhar S[1], Chhetri S[1], Acharya R[1], Pokhrel N[1] and Panthi S[1]**

[1]*Department of Surgery, B. P. Koirala Institute of Health Sciences, Dharan, Nepal.*

[2]*Division of Neurosurgery, B. P. Koirala Institute of Health Sciences, Dharan, Nepal.*

[3]*Division of CTVS, B. P. Koirala Institute of Health Sciences, Dharan, Nepal*

***Address for Correspondence**
Neupane D, Department of Surgery, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; E-mail: neupanedurga26@gmail.com

**Submission:** 06 June, 2022
**Accepted:** 25 July, 2022
**Published:** 29 July, 2022



**Keywords:** Intracranial; Aneurysm; Cerebral; Hemodynamics; Wall Shear Stress; Computational Fluid Dynamics

## Abstract

**Background:** Recent evidence suggests a link between hemodynamic factors and intracranial aneurysm inception. However, the role of wall shear stress is not clearly understood.

**Aim:** To elucidate the role of wall shear stress in intracranial aneurysm formation.

**Methods:** We performed areview of literature by recruiting articles from 2000 through 2019. 2134 unique articles were identified, of which 32 were retrieved for more detailed evaluation. 17 articles met the inclusion criteria and were involved in the qualitative analysis. Standard guidelines were followed.

**Results:** Wall shear stress showed to have a significant role in intracranial aneurysm inception. Other hemodynamic factors also played role in the inception of cerebral aneurysms. The geometry and optimality principle along with social factors like smoking is also responsible for the formation of cerebral aneurysms.

**Conclusion:** Wall shear stress plays a major role in intracranial aneurysm formation. Gradient oscillatory number is the emerging hemodynamic factor for the inception of cerebral aneurysms. However, limited experiments in humans have resulted in inconclusive results.

## Abbreviations

CA-Cerebral Aneurysm; IA-Intracranial Aneurysm; WSS-Wall Shear Stress; AComA-Anterior Communicating Artery; PComA-Posterior Communicating Artery; ACA- Anterior Cerebral Artery; ICA- Internal Carotid Artery; MCA- Middle Cerebral Artery; OA- Ophthalmic Artery; AChA- Anterior Choroidal Artery GON-Gradient Oscillatory Number; CFD-Computational Fluid Dynamics; WSSG-Wall Shear Stress Gradient; SWSS-Spatial Wall Shear Stress; SW- Side wall; BF- Bifurcation; IEL- Internal Elastic Lamina

## Background

Aneurysm formation is a continuous remodelling process that involves the breakdown of the extracellular matrix and is described by the loss of the internal elastic lamina, media layer thinning, and bulge formation [1,2]. Cerebral aneurysms (CAs) are distinguished by a pathological wall structure characterized by rupture of the internal elastic lamina and media, resulting in focally weakened arterial wall pouches [3,4]. The incidence of unruptured CAs in the general population has been approximated to be 2% to 5% [5]. Hemodynamics has been found to play a significant role in the genesis, progression, and rupture of intracranial aneurysms (IA) [6-8]. Specific elements, such as site, blood pressure, boundary condition, and vascular shape, do, nevertheless, influence hemodynamic factors [9-11]. Recent fluid dynamics research has highlighted the close connections between hemodynamics and IAs [12]. Among numerous hemodynamic characteristics, high wall shear stress placed on artery bifurcation points, where IAs originates, is related to IA formation and growth [12]. As a result, high wall shear stress (WSS) can be identified as a cause of IA development. WSS is flow-induced stress that acts on the endothelium surface and is analogous to the frictional force of viscous blood [13,14]. WSS is regarded as a crucial factor of artery diameter and is involved in vascular remodeling [15]. An growing number of research in recent years have shown that WSS is intimately associated with determining aneurysm development, growth, and rupture [16-20].

Previously, reviews on the involvement of hemodynamics in the development of IAs were examined, with the role of WSS being recognized as the most essential element. The purpose of this review is to shed light on the involvement of WSS in the formation state of intracranial aneurysms.

## Methods

### Literature Search

PubMed and Google Scholar were used as sources for searching published studies from 2000 through December 2019. Searches were conducted using the keywords “intracranial aneurysm” in combination with “computational fluid dynamics”, “hemodynamics” and “wall shear stress”. Titles, abstracts, and full text were screened for study and report characteristics that matched eligibility criteria. References within studies were perused and incorporated if they met our inclusion criteria. Two independent reviewers screened and retrieved reports, and a third reviewer settled any confusion if any between the two. Others were involved in manuscript preparation. The final version of the paper was approved by all the authors.

### Eligibility Criteria

The following criteria were designed for the selection of eligible studies.

**Study design:** Observational studies measuring the influence of WSS on intracranial aneurysm inception using methods of computational fluid dynamics were eligible.

ISSN: 2332-4139

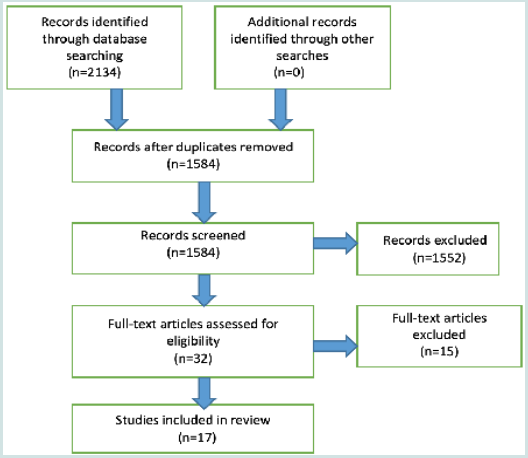


**Figure 1:** Literature search strategy..

**Language of study:** Only English language studies were reviewed.

**Objective outcomes:** Included studies were to objectively assess the role of WSS in intracranial aneurysm formation.

**Data abstraction:** Data were manually extracted by investigators from eligible studies. First author, type of study design, year of publication, number of subjects, number of aneurysms, location of aneurysms, type of aneurysms, sex of participants, mean age of participants were extracted.

### Exclusion Criteria

Articles published in any other languages except English, animal studies, case reports, review articles, viewpoints, study without computational fluid dynamics (CFD) analysis were excluded.

## Results

### Literature search and data extraction

2134 unique articles were identified, of which 32 were retrieved for more detailed evaluation. 17 articles met the inclusion criteria and were involved in the qualitative analysis. Figure 1 shows the results of our literature search and selection. Table 1 shows the summary of study data for the risk of aneurysm formation.

### Study design

All eligible studies were observational studies measuring the influence of WSS in intracranial inception.

### Risk of formation

In a study conducted by Castro et al, three individuals were chosen for Model A (without aneurysms) and Model B (with aneurysms). A comparison of the two models for Patient 1 reveals that the aneurysm began to develop in the high WSS region. The aneurysm impacted two unconnected high WSS areas in patient 2. In the case of patient 3, the aneurysm developed across an area with both high and moderate WSS values. In a study of Anterior Communicating Artery (AComA) aneurysms, Castro et al discovered a probable link between areas of high WSS prior to aneurysm development and aneurysm location [21].

Le et al performed a retrospective hemodynamic analysis before and after aneurysm development in a ruptured aneurysm of the posterior communicating artery and an unruptured aneurysm of the posterior communicating artery using a vessel surface repair approach [22]. The first patient was a 62-year-old male who had a ruptured aneurysm, and the second was a 48-year-old man who had an unruptured aneurysm. Their early findings revealed that the artery wall was exposed to higher WSS, WSSG, and blood-flow velocity before the formation of an aneurysm [22]. Utami et al. achieved consistent findings [23].

Sasaki and colleagues investigated twenty-one bifurcation models with varied in-branch angles and branch sizes. The highest WSS value was studied in all models using a steady-flow simulation using computational fluid dynamics. The amplitude of WSS was shown to be substantially linked with bifurcation geometry and aneurysm development [24].

The role of the optimality principle was discussed by Zhang et al [25]. They demonstrated that normal anterior cerebral artery bifurcations followed the optimality principle, but AComA bifurcations did not, Disobeying the optimality principle results in dramatically increased hemodynamic stress, which may damage the bifurcation wall and lead to aneurysm formation. IA developed in locations other than the bifurcation apex [25]. In support of this, Geers et al investigated the involvement of WSS in aneurysm formation at locations other than the bifurcation apex and the exterior wall of the arterial bed [26].

Sunderland et al created 3D computational vasculatures using angiographic pictures of 18 patients who had several closely spaced IAs in the internal carotid artery. Two models were created: one with all IAs computationally eliminated and one with one IA retained. They discovered that a combination of hemodynamic parameters was more important in the onset of an aneurysm than individual indices [27]. Kulcsar et al and Watanabe et al obtained similar findings [28,29].

Kono et al described a patient who had a freshly developed aneurysm with proximal stenosis, which was validated by serial imaging. They created two pre-aneurysm models, one with stenosis and one without, and ran computational fluid dynamics simulations on both. Because of the stenosis-induced jet flow, the maximal WSS and WSSG at the aneurysm start site were roughly doubled and tripled, respectively. As a result, they underlined the importance of proximal stenosis in aneurysm formation [30]. Lauric et al, on the other hand, investigated the curvature effects on hemodynamic circumstances [31]. Many additional elements had an important part in the development of IAs. Singh et al investigated the effects of smoking and hypertension on the establishment of aneurysms [32].

Shimogonya et al, on the other hand, discovered no significant correlation between WSS and aneurysm inception [33]. They also developed a novel hemodynamic measure termed Gradient Oscillatory Number (GON), which may impact aneurysm development. Chen et colleagues found that regionally higher WSS and GON were strongly linked with locations vulnerable to sidewall IA development in the hypothesized pre-diseased geometries of 22 clinical sidewalls IAs [34]. Ford et al discovered similar findings [35].

ISSN: 2332-4139

**Table 1**: The summary of study data for the risk of aneurysm formation.

| Author, year | Female:Male | Mean age, yrs | Location of aneurysm | Type | Positive correlation of WSS |
|---|---|---|---|---|---|
| Castro 2011 [21] | | | 2AcomA | BF | 3/3 |
| Le 2013 [22] | 1:1 | 55 | 2PcomA | | 2/2 |
| Utami 2011 [23] | | | 4 geometry | | 4/4 |
| Sasaki 2018 [24] | | | 21 aneurysms | BF | |
| Zhang 2019 [25] | | | 122 AComA, 21non-AComA | | |
| Geers 2016 [26] | | | 10 ACA | BF | |
| Sunderland 2019 [27] | | | Multiple ICA | SW | |
| Kulcsar 2011 [28] | All female | | 1Basilar tip, 1ICA, 1PcomA | 2SW, 1BF | 3/3 |
| Watanabe 2018 [29] | 12:3 | 54.8 | 15 Paraclinoid ICA | | 13/15 |
| Kono 2014 [30] | All male | 63 | 1AChA | | 1/1 |
| Lauric 2014 [31] | All female | 57.1 (22.6) | 10 inner bend of carotid siphon | SW | |
| Singh 2009 [32] | 1:1 | 45 | 2ICA bif | BF | 2/2 |
| Shimogonya 2008 [33] | | | 1ICA | SW | 0/1 |
| Chen 2013 [34] | 14:8 | 58 | 1ICAbif, 10PCoA, 3OA, 1AChA, 2ACA, 2ACoA, 1MCA, 2BA | SW | 20/22 |
| Ford 2009 [35] | | | 3ICA,1BA,1MCA | SW | 0/5 |
| Tanaka 2018 [36] | | | 2MCA, 1ICA | 2BF, 1SW | 0/3 |
| Zhang 2018 [37] | | | 81AComA | | |

Tanaka et al discovered no obvious connections between hemodynamic parameters and aneurysm initiation, contradicting all of the preceding studies [36]. The magnitude of WSS in ruptured and unruptured aneurysms has been determined in certain studies. Nonetheless, the degree of WSS observed varies, and the threshold of high or low WSS has been documented very infrequently. WSS values ranging from 7.8 to 12.3 dyne/cm$^2$ were shown to independently describe aneurysm development by Zhang et al. There was a one-fold increase in the likelihood of AComA aneurysm development with each additional unit of WSS [37].

## Discussion

The analysis of cerebral arteries from autopsies and IA animal models has been critical in understanding the early alterations in the emerging aneurysm. The aneurysm wall frequently has a disturbed internal elastic lamina (IEL), media thinning, and bulge development.

For the etiology of IAs, several theories have been proposed. The first theory claimed a congenital etiology, but the second theory proposed that IAs are acquired lesions that develop over time, with hemodynamic conditions having a role in their onset. Indeed, the preferred position of the aneurysm at artery bifurcations with a certain flow pattern suggested a role for hemodynamics in aneurysm development. Meng et al. investigated how "a hemodynamic insult" may result in maladaptive remodelling of the vessel wall. They identified three regions at arterial bifurcations with different blood patterns using CFD, the first one being the impingement zone, where blood from the parent artery hits the apex of the bifurcation and creates a stagnation point before accelerating into the branches (WSS ≤ 20 dynes/cm$^2$; velocity < 0.05 m/s; positive Wall Shear Stress gradient(WSSG);the second one being the acceleration region, where blood flow continues to accelerate until the maximum velocity (WSS > 20 dynes/cm$^2$, high positive WSSG); and the third one being recovery region where the velocity of blood reaches the maximum and starts to decelerate until the physiological level of WSS ~20 dynes/cm$^2$(negative WSSG). They discovered early alterations mimicking IA initiation in places subjected to SWSS and positive WSSG by mapping CFD with histological analysis of the arterial bifurcation. Further research found that aneurysmal remodeling occurs only when hemodynamic forces exceed a particular threshold (WSS > 1.22 x 103 dynes/cm$^2$ and WSSG > 530 Pa/mm) in their rabbit model.

Although these findings assist to clarify the function of hemodynamic pressures in the onset of IA, Meng et al investigations were conducted on an artificial extracranial bifurcation in a small number of animals and require additional validation in other, preferably intracranial, animal models. Furthermore, the stated hemodynamic threshold values are only for rabbits and may change in humans where vessel diameter is varied and several confounding variables, such as genetic risk factors and habits such as smoking, might impact IA development.

The idea of the WSS threshold, on the other hand, explains why IAs occur more frequently at particular bifurcations and individuals than others. Each arterial bifurcation has a unique flow pattern based on its location, bifurcation angle, and parent and daughter artery sizes, making some more likely to reach the threshold. Singh et al33 investigated the effects of smoking and hypertension on aneurysm development. As a result, a weaker wall caused by age, smoking, hypertension, and genetic disorders would be more susceptible to hemodynamic disturbances. A meta-analysis of patients' hemodynamic forces and the development of IAs supports the notion that IAs are caused by spatial WSS (SWSS) and positive WSSG [38,39].

There are some limitations to this study. Firstly, only CFD-related studies are examined. The current IA CFD models produce poor results due to improper simplifications, reliance on physically meaningless parameters, and a sloppy computational representation of physiologic blood flow. As a result, new generation IA CFD models should be explored in order to understand the function of various hemodynamic variables in the onset of IA. Secondly, only items published in English were considered.

## Conclusion

Intracranial aneurysm formation is thought to have a complex

ISSN: 2332-4139

origin, with hemodynamics playing a crucial part in the process. A rise in local WSS, as well as other hemodynamic indicators such as GON, comes into play. The geometry and curvature effects, as well as hemodynamic and therapeutically important variables like smoking and hypertension, all influence the development of IA.

**Eligibility Criteria**

The following criteria were designed for the selection of eligible studies.

**Study design:** Observational studies measuring the influence of WSS on intracranial aneurysm inception using methods of computational fluid dynamics were eligible.

**Language of study:** Only English language studies were reviewed.

**Objective outcomes:** Included studies were to objectively assess the role of WSS in intracranial aneurysm formation.

**Data abstraction:** Data were manually extracted by investigators from eligible studies. First author, type of study design, year of publication, number of subjects, number of aneurysms, location of aneurysms, type of aneurysms, sex of participants, mean age of participants were extracted.

**Exclusion criteria**

Articles published in any other languages except English, animal studies, case reports, review articles, viewpoints, study without computational fluid dynamics (CFD) analysis were excluded.

**Results**

**Literature search and data extraction:** 2134 unique articles were identified, of which 32 were retrieved for more detailed evaluation. 17 articles met the inclusion criteria and were involved in the qualitative analysis.Figure 1 shows the results of our literature search and selection. Table 1 shows the summary of study data for the risk of aneurysm formation.

**Study design:** All eligible studies were observational studies measuring the influence of WSS in intracranial inception.

## References

1. Krex D, Schackert HK, Schackert G (2001) Genesis of cerebral aneurysms-an update. Acta Neurochir (Wien) 143: 429 -448.
2. Stehbens WE (1963) Histopathology of cerebral aneurysms. Arch Neurol 8: 272-285.
3. Texakalidis P, Bekelis K, Atallah E, Tjoumakaris S, Rosenwasser RH, et al. (2017) Flow diversion with the pipeline embolization device for patients with intracranial aneurysms and antiplatelet therapy: a systematic literature review. Clin Neurol Neurosurg 161: 78-87.
4. Chalouhi N, Starke RM, Yang S, Bovenzi CD, Tjoumakaris S, et al. (2014) Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. Stroke 45: 54-58.
5. Brisman JL, Song JK, Newell DW (2006) Cerebral aneurysms. N Engl J Med 355: 928-939.
6. Xiang J, Tutino VM, Snyder KV, Meng H (2014) CFD: computational fluid dynamics or confounding factor dissemination? The role of hemodynamics in intracranial aneurysm rupture risk assessment. AJNR Am J Neuroradiol 35:1849-1857.
7. Chalouhi N, Hoh BL, Hasan D (2013) Review of cerebral aneurysm formation, growth, and rupture. Stroke 44: 3613-3622.
8. Cebral JR, Mut F, Weir J, Putman cm (2011) Association of hemodynamic characteristics and cerebral aneurysm rupture. AJNR Am J Neuroradiol 32: 264-270.
9. Shojima M, Oshima M, Takagi K, Torii r, Nagata K, et al. (2005) Role of the bloodstream impacting force and the local pressure elevation in the rupture of cerebral aneurysms. Stroke 36:1933-1938.
10. Chien A, Castro MA, Tateshima S, Sayre J, Cebral J, et al. (2009) Quantitative hemodynamic analysis of brain aneurysms at different locations. AJNR Am J Neuroradiol 30:1507-1512.
11. Meng H, Tutino VM, Xiang J, Siddiqui A (2014) High WSS or low WSS? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis. Am J Neuroradiol 35: 1254-1262.
12. Qui T, Jin G, Xing H, Lu H (2017) Association between hemodynamics, morphology, and rupture risk of intracranial aneurysms: a computational fluid modeling study. Neuro Sci 38:1009-1018.
13. Malek AM, Alper SL, Izumo S (1999) Hemodynamic shear stress and its role in atherosclerosis. JAMA 282: 2035-2042.
14. Meng H, Wang Z, Hoi Y, Gao L, Metaxa E, et al. (2007) Complex hemodynamics at the apex of an arterial bifurcation induces vascular remodeling resembling cerebral aneurysm initiation. Stroke 38: 1924-1931.
15. Karmonik C, Yen C, Grossman RG, Klucznik R, Benndorf G (2009) Intra-aneurysmal flow patterns and wall shear stresses calculated with computational flow dynamics in an anterior communicating artery aneurysm depend on knowledge of patient-specific inflow rates. Acta Neurochir (Wien) 151: 479-485.
16. Can A, Du R (2016) Association of hemodynamic factors with intracranial aneurysm formation and rupture: systematic review and meta-analysis. Neurosurgery 78: 510-520.
17. Skodvin TO, Evju O, Helland CA, Isaksen JG 92018) Rupture prediction of intracranial aneurysms: a nationwide matched case-control study of hemodynamics at the time of diagnosis. J Neurosurg: 129: 854-860.
18. Fukazawa K, Ishida F, Umeda Y, Miura Y, Shimosaka S, et al. (2015) Using computational fluid dynamics analysis to characterize local hemodynamic features of middle cerebral artery aneurysm rupture points. World Neurosurg 83:80-86.
19. Castro MA, Putman CM, Cebral JR (2011) Computational analysis of anterior communicating artery aneurysm shear stress before and after aneurysm formation. J Phys Conf Ser 332: 012001.
20. Le WJ, Zhu Y-Q, Li M-H, Yan L, Tan H-Q, et al. (2013) New method for retrospective study of hemodynamic changes before and after aneurysm formation in patients with ruptured or unruptured aneurysms. BMC Neurology 13: 166.
21. Utami N, Zakaria H, Mengko TL, Santoso OS (2011) Role of pressure and wall shear stress in initiation and development of cerebral aneurysms. 2nd international conference on instrumentation, communications, information technology, and biomedical engineering (ICICI-BME). IEEE, Bandung: 310-314.
22. Sasaki T, Kakizawa Y, Yoshino M, Fujii Y, Yoroi I, et al. (2019) Numerical analysis of bifurcation angles and branch patterns in intracranial aneurysm formation. Neurosurgery 85: E31-E39.
23. Zhang X-J, Li C-H, Hao W-L, Zhang D-H, Gao B-L (2019) The Optimality Principle Decreases Hemodynamic Stresses for Aneurysm Initiation at Anterior Cerebral Artery Bifurcations. World Neurosurg 121: e379-e388.
24. Geers AJ, Morales HG, Larrabide I, Butakoff C, Bijlenga P, et al. (2017) Wall shear stress at the initiation site of cerebral aneurysms. Biomech Model Mechanobiol 16: 97-115.
25. Sunderland K, Jiang J (2019) Multivariate analysis of hemodynamic parameters on intracranial aneurysm initiation of the internal carotid artery. Med Eng Phys 74: 129-136.
26. Kulcsar Z, Ugron A, Marosfoi M, Paál G, Szikora I (2011) Hemodynamics of

ISSN: 2332-4139

Cerebral Aneurysm Initiation: The Role of Wall Shear Stress and Spatial Wall Shear Stress Gradient. AJNR Am J Neuroradiol 32: 587-594.

27. Watanabe T, Isoda H, Takehara y, Terada M, Naito T, et al. (2018) Hemodynamic vascular biomarkers for initiation of paraclinoid internal carotid artery aneurysms using patient-specific computational fluid dynamic simulation based on magnetic resonance imaging. Neuroradiology 60: 545-555.
28. Kono K, Fujimoto T, Terada T (2014) Proximal stenosis may induce initiation of cerebral aneurysm by increasing wall shear stress and wall shear stress gradient. Int J Numer Meth Biomed Eng 30: 942-950.
29. Lauric A, Hippelheuser J, Safain MG, Malek MA (2014) Curvature effect on hemodynamic conditions at the inner bend of the carotid siphon and its relation to aneurysm formation. J Biomech 47: 3018-3027.
30. Singh PK, Marzo Alberto, Howard Bethany, Rufenacht DA, Bijlenga P, et al. (2010) Effects of smoking and hypertension on wall shear stress and oscillatory shear index at the site of intracranial aneurysm formation. Clinical Neurol Neurosurg 112: 306-313.
31. Shimogonya Y, Ishikawa T, Imai Y, Matsuki N, Yamaguchi T (2009) Can temporal fluctuation in spatial wall shear stress gradient initiate a cerebral aneurysm? A proposed novel hemodynamic index, the gradient oscillatory number (GON). J Biomech 42: 550-554.
32. Chen H, Selimovic A, Thompson H, Chiarini A, Penrose J, et al. (2013) Investigating the influence of haemodynamic stimuli on intracranial aneurysm inception. Ann Biomed Eng 41: 1492-1504.
33. Ford MD, Hoi Y, Piccinelli M, Antiga L, Steinman DA (2009) An objective approach to digital removal of saccular aneurysms: technique and applications. Br J Radiol 82: S55-S61.
34. Tanaka K, Takao H, Suzuki T, Fujimura S, Uchiyama Y, et al. Relationship between hemodynamic parameters and cerebral aneurysm initiation. Conf Proc IEEE Eng Med Biol Soc 2018: 1347-1350.
35. Zhang X, Yao ZQ, Karuna T, He X-Y, Wang X-M, et al. (2019) The role of wall shear stress in the parent artery as an independent variable in the formation status of anterior communicating aneurysms. Eur Radiol 29: 689-698.
36. Metaxa E, Tremmel M, Natarajan SK, Xiang J, Paluch RA, et al. (2010) Characterization of critical hemodynamics contributing to aneurysmal remodeling at the basilar terminus in a rabbit model. Stroke 41: 1774-1782.
37. Alfano JM, Kolega J, Natarajan SK, Xiang J, Paluch RA, et al. (2013) Intracranial aneurysms occur more frequently at bifurcation sites that typically experience higher hemodynamic stresses. Neurosurgery 73: 497-505.
38. Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, et al. (2017) Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. Neurology 89: 1408-1415.
39. Saqr KM, Rashad S, Tupin S, Niizuma K, Hassan T, et al. (2020) What does computational fluid dynamics tell us about intracranial aneurysms? A meta-analysis and critical review. J Cereb Blood Flow Metab 40: 1021-1039.