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RESEARCH ARTICLE

# Peri-Aneurysmal Contact as a Risk Factor for Aneurysmal Rupture in Unruptured Intracranial Aneurysms: An Overview

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## ABSTRACT

The occurrence and growth of unruptured intracranial aneurysms are believed to be influenced by intraluminal factors of blood flow dynamics and pathological factors of the aneurysm wall. In addition to these, the deformation and rupture of aneurysms require consideration of physical extra-luminal factors due to contact between the aneurysm and surrounding structures including brain parenchyma, cranial nerves, arteries, veins, cranial base bone and dura mater. The extra-luminal factors of aneurysms were evaluated based on the presence of peri-aneurysmal contact. Peri-aneurysmal contact, depending on the type, location, and size of aneurysms, influenced the growth pattern of the aneurysm. Recently, with the imaging of magnetic resonance cisternography, it had become possible to non-invasively assess the anatomical relationship between the outer wall of aneurysms and the surrounding structures. Fusion images overlaying 3D magnetic resonance cisternography with 3D computed tomography angiography or 3D magnetic resonance angiography detailed the anatomical relationship of peri-aneurysmal contact, position of contact sites, and depth. We depicted the anatomical construction of peri-aneurysmal contact and bleb in unruptured intracranial aneurysms using fusion images and studied the intraluminal blood flow dynamics using computational fluid dynamics. As a result, peri-aneurysmal contact was observed to be involved as an independent variable in the process of bleb formation. It was suggested that factors extra-luminal to the aneurysm, such as peri-aneurysmal contact, might have a greater impact on bleb formation than intraluminal factors like blood flow dynamics. Peri-aneurysmal contact emerged as a noteworthy extra-luminal factor, particularly associated with bleb formation, presenting a substantial risk of rupture in unruptured intracranial aneurysms. These findings underscore the importance of considering the presence and extent of peri-aneurysmal contact alongside intraluminal and wall-related factors in future evaluations. The implications of this overview extend to the development of risk assessment protocols, providing valuable insights for guiding early intervention strategies and ultimately contributing to improved patient outcomes.

**Keywords:** Bleb formation, Computational fluid dynamics, Hemodynamics, Peri-aneurysmal contact, Unruptured intracranial aneurysm.

## Abbrevations:

bTFE=balanced turbo field echo images
CFD=computational fluid dynamics;
CISS= constructive interference in steady state images;
CTA= computed tomography angiography;
FIESTA=fast imaging employing steady state images;
MRC=magnetic resonance cisternography;
MRA=magnetic resonance angiography;
PAC=peri-aneurysmal contact;
WSS=wall shear stress;
UIA=unruptured intracranial aneurysm.

## Introduction

The unruptured intracranial aneurysms (UIAs) represent a cerebral arterial pathology characterized initially by a rounded, strawberry-like outpouching appearance, originating at the branching point of cerebral arteries within the cisternal spaces[1]. The prevalence of UIAs stands at 3-5% in the adult population[2, 3]. The annual rupture rate of an aneurysm is approximately 1%, leading to subarachnoid hemorrhage with a high mortality rate (45%) [4,5]. Aneurysms at a heightened risk of rupture are often managed through surgical or endovascular interventions. The risk of rupture is frequently associated with morphological factors such as size, aspect ratio (aneurysm depth/neck width), and the formation of blebs[6-9]. Blebs, secondary bulges on the aneurysm wall, signify an increased localized vulnerability of the wall and pose a significant risk of rupture[10,11]; however, the mechanism behind bleb formation remains elusive.

The genesis and progression of UIAs are primarily believed to be influenced by blood flow dynamics and wall strength. As the aneurysm expands, exceeding the tolerable size within the subarachnoid space, it readily interfaces with surrounding brain parenchyma, cranial nerves, arteries, veins, cranial base bone and dura mater[12-19]. Contact between the aneurysm and surrounding structures (peri-aneurysmal contact, PAC) is hypothesized to induce constraints on the aneurysm's expansion, deformation due to pressure, weakening of the wall and bleb formation, leading to rupture and subsequent subarachnoid hemorrhage, or the development of neurological symptoms such as oculomotor nerve palsy due to contact or adhesion with cranial nerves[13-15].

Fluid dynamics-related intraluminal factors within the aneurysm, such as blood flow patterns and wall shear stress (WSS), alongside pathological factors of the aneurysm wall's elasticity and vulnerability, are considered primary contributors to the rupture of UIAs[20-24]. Alongside these intraluminal and wall-related factors, there exists a possibility that physical extra-luminal factors due to PAC may play a role in the deformation and rupture risk of aneurysms[13-16]. The insights from this overview have significant implications for the development of risk assessment protocols. They provide valuable guidance for shaping early intervention strategies, ultimately contributing to improved patient outcomes.

### 1. The Impact of Extra-luminal Factors on the Natural History of Intracranial Aneurysms

The peri-aneurysmal environment has been proposed as an extra-luminal factor in UIAs[13-16], where PAC has been subjected to imaging assessments. PAC is considered a useful extra-luminal factor not only in tracking the natural progression of aneurysms but also in considering the onset mechanism of neurological symptoms and planning surgical or endovascular interventions. However, several research questions in this regard remain unresolved.

The investigation of PAC in ruptured and UIAs was initially undertaken at the Department of Neuroradiology, University of Geneva (Prof. Daniel A Rüfenacht)[12-14,16]. Sugiu et al.[12] examined the presence of PAC in 101 cases of aneurysms (42 unruptured and 59 ruptured) and demonstrated that PAC influences the growth pattern of the aneurysm depending on the type, location, and size of the aneurysm. They further reported that regardless of the size of the aneurysm, the shape and contact status of PAC significantly contributed to aneurysm rupture.

Ruiz et al.[14] reported a higher incidence of PAC in ruptured intracranial aneurysms compared to unruptured ones, observing that PAC often displayed an asymmetric contact area concerning the long axis of the aneurysm. Additionally, Kakinuma et al.[25], based on intraoperative findings of ruptured cerebral aneurysms, noted that the rupture points were not located in the free space of the subarachnoid space but at contact or adhesion points with brain parenchyma, cranial nerves, and arachnoid. This suggested the possibility of aneurysm rupture occurring at the highest stress point between the aneurysm wall and surrounding tissues. Furthermore, in their pathological examination of symptomatic unruptured internal carotid posterior communicating artery aneurysms causing oculomotor nerve palsy, Kataoka et al.[26] identified PAC induced by acute adhesions and chronic scarring between the aneurysm wall and oculomotor nerves and surrounding tissues. They reported that even in UIAs, the aneurysm walls were generally thinner, exhibited similar vulnerability to rupture as seen in ruptured aneurysms, and displayed infiltrations of inflammatory cells within the walls.

## 2. MR Cisternography for Depicting Extra-luminal Factors

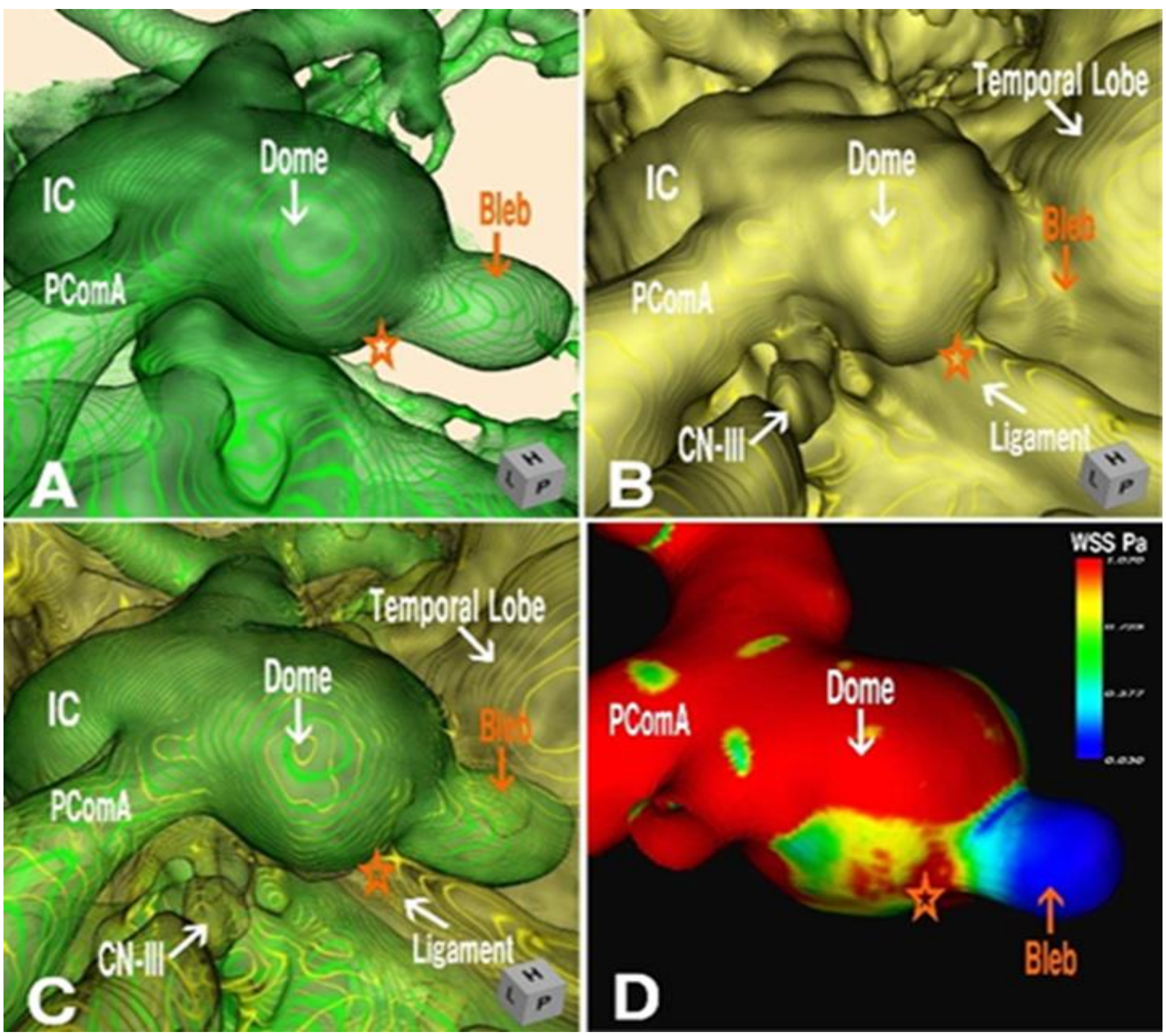
The cerebral aneurysm and its surrounding structures can be reasonably understood by interpreting original images from computed tomography angiography (CTA) or magnetic resonance angiography (MRA). However, for detailed visualization of the anatomical relationship between the aneurysm and surrounding structures (extra-luminal factors) and to delineate PAC, magnetic resonance cisternography (MRC), a contrast-enhanced hydrography within the subarachnoid space is more suitable[15, 27]. MRC is obtained using T2-weighted 3D fast spin-echo sequences (heavy T2-weighted images), fast imaging employing steady state images (FIESTA, GE Co), three-dimensional constructive interference in steady state images (CISS, Siemens Co), balanced turbo field echo images (bTFE, Philips Co), among others. These MRC techniques provide excellent signal-to-noise ratios, offering fine sectional information (volume data) of the aneurysm and its surrounding structures.

By using MRC, cerebrospinal fluid appears with high signal intensity and nearly homogeneous depiction, while structures within the cistern, such as aneurysms, parent vessels, bridging veins, brain parenchyma, cranial nerves, dura mater, and cranial base bony structures, are displayed as low signal intensity shadow defects. Consequently, non-invasive imaging evaluation of the anatomical relationship between the outer wall morphology of aneurysms and surrounding structures became feasible[15,27]. Additionally, through image reconstruction of MRC into a three-dimensional display (3D MRC), aneurysms are depicted three-dimensionally within the cistern along with surrounding structures, facilitating the evaluation of the morphological information of extra-luminal factors such as PAC from various directions.

## 3. Depiction of Intra- and Extra-luminal Factors via MRC-CTA Fusion Images

By aligning the X, Y, Z coordinate axes of the sectional information from MRC and CTA/MRA, an equi-coordinated 3D CTA/MRA can be obtained alongside MRC. Reference to the equi-coordinated 3D CTA/MRA aids in the straightforward identification of luminal structures like aneurysms and parent vessels depicted in 3D MRC. Additionally, by reconstructing the 3D images of both 3D MRC and equi-coordinated 3D CTA/MRA and overlaying them, fusion images of 3D MRC-CTA/MRA are generated[15,27]. As a result, the position and depth of PAC between the vascular structures of aneurysms and surrounding structures are detailed, enabling the examination of the morphological relationship between intraluminal and extra-luminal factors influencing the extension and deformation of cerebral aneurysms (Figure 1).

**Figure 1:** A case of an unruptured internal carotid-posterior communicating artery aneurysm.



**A:** 3D CTA reveals the aneurysm and bleb.
**B:** 3D MRC displays an external image of the aneurysm and peri-aneurysmal structures, including the temporal lobe and petroclinoid ligament of the tentorium.
**C:** 3D MRC-CTA fusion image clearly illustrates the aneurysm and its peri-aneurysmal structures. Note the deformation of the dome at the contact point due to the hard structure of petroclinoidal ligament.
**D:** CFD analysis depicts the distribution of WSS. The area corresponding to the bleb exhibits lower values of WSS.

## 4. Hemodynamics of Intra-luminal Factors

The development, growth, and rupture of unruptured intracranial aneurysms are significantly influenced by intraluminal hemodynamics, and numerous reports have highlighted this using fluid dynamics methods [28-36]. The rupture risk of an aneurysm has been evaluated based on its size, aspect ratio, and bleb formation. Ujiie et al.[6] suggested that cerebral aneurysms were more likely to develop and grow in asymmetrical vessel bifurcations with a ratio of 2.0 or more, and in large aneurysms with an aspect ratio exceeding 1.6, secondary swirling or stagnant blood flow regions occur on the distal side of the dome, inducing localized weakness in the aneurysm wall, eventually leading to rupture. Additionally, Tateshima et al.[28] measured wall shear stress (WSS) using a model of unruptured intracranial aneurysms with blebs and found that WSS was stronger on the dome side than at the inflow region of the neck, with the strongest WSS observed at the bleb. They suggest that exposure of the aneurysm wall to strong WSS leads to localized expansion and accelerated degeneration of the wall, resulting in bleb formation, and ultimately, the rupture of the aneurysm at that site.

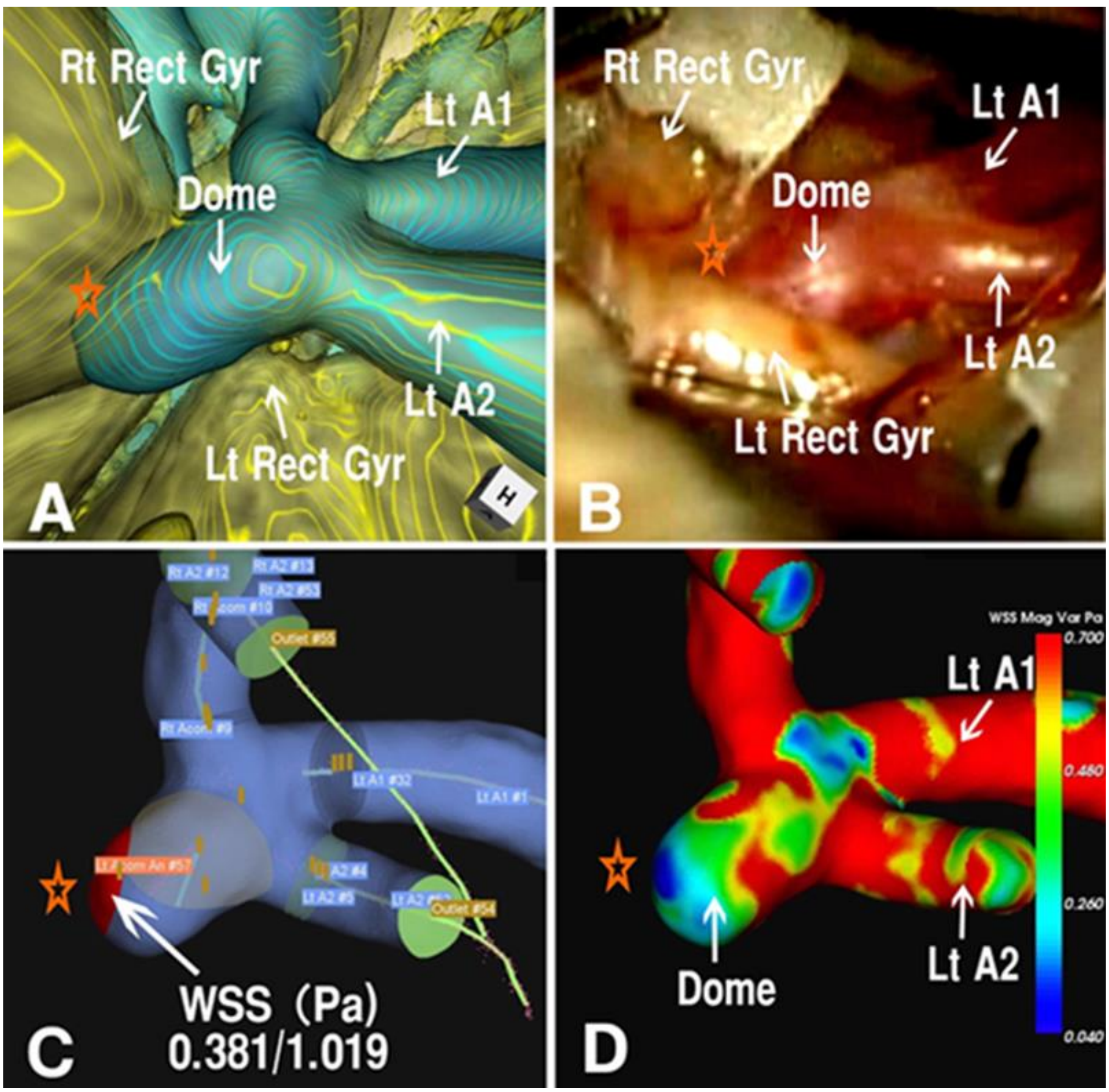
## 5. Influence of Extra-luminal Factors on Bleb Formation as Intra-luminal Factors

Deformation and morphological changes like blebs in unruptured intracranial aneurysms are considered crucial observations in assessing their susceptibility to rupture[28-36]. Regarding bleb formation, Cebral et al.[30], Russel et al.[33], and Salimi et al.[34] analyzed the hemodynamics of intraluminal blood flow using computational fluid dynamics (CFD) analysis and reported the involvement of strong inflow jets and high WSS. Conversely, Shojima et al.[35] and Machi et al.[36] reported the involvement of low WSS and high shear stress gradients. Whether bleb formation results from intraluminal factors such as intraluminal blood flow dynamics or is influenced by extra-luminal factors causing constraints in aneurysm extension, leading to changes in intraluminal blood flow dynamics, remains unclear. We measured the WSS at both the neck of the bleb and the entire dome, discovering that the WSS at the bleb constituted an average of only 17% of the total WSS across the entire dome[31]. The increase in WSS due to intraluminal blood flow does not directly correlate with bleb formation, suggesting potential involvement of intraluminal and extra-luminal factors like PAC.

We examined the relationship between PAC and bleb formation in UIAs from both morphological and hemodynamics perspectives[31]. The evaluation of PAC morphology was conducted using MRC-CTA/MRA fusion images. The aneurysm's hemodynamics were evaluated using CFD. Independent variables related to bleb formation were statistically analyzed.

Among 45 unruptured intracranial aneurysms, blebs were observed in 14 aneurysms (31.1%), all formed at the position of PAC (Group A). 31 aneurysms (68.9%) had no Blebs, with 13 of them showing PAC (Group B), and 18 had no PAC (Group C). According to statistical analysis, the sole independent variable associated with bleb formation was PAC ($p < 0.05$). The volume of aneurysms in Group A was the largest, followed by Groups B and C. WSS in aneurysms was lowest in Group A, followed by Groups B and C. The maximum WSS of blebs accounted for 17% of the maximum WSS in the aneurysm dome (Figures 2, 3). This indicates that bleb formation in UIAs is related to the establishment of PAC during their growth process, potentially exerting a more adverse effect on bleb formation than intraluminal blood flow dynamics[31].

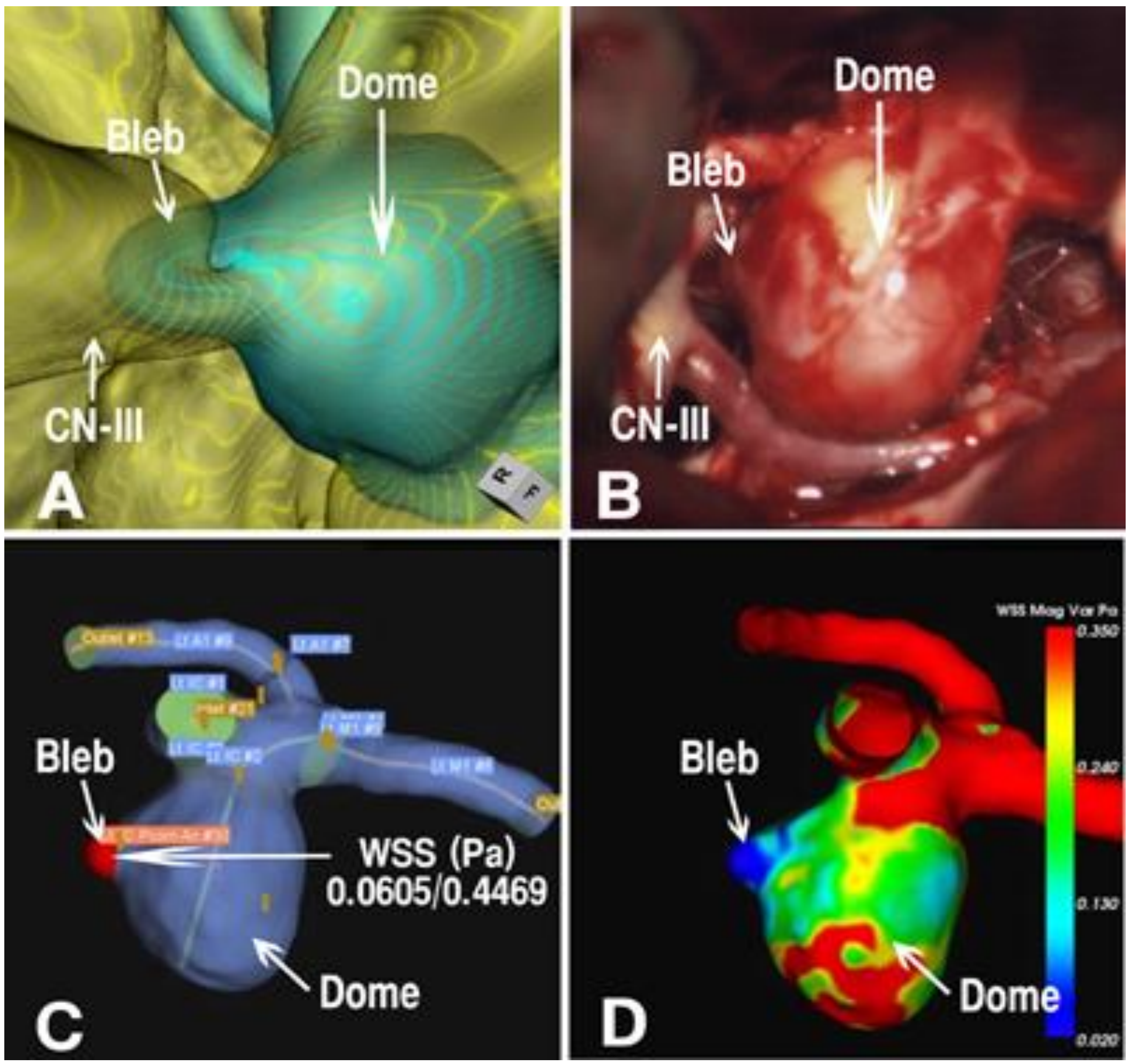
**Figure 2:** A case of an unruptured anterior communicating artery aneurysm.




**A:** The fusion image from 3D MRC-CTA vividly illustrates the aneurysm and its surrounding structures. Particularly noteworthy is the contact of the aneurysmal dome's tip with the right rectal gyrus of the frontal lobe.

B: Surgical photograph showing the interaction between the dome's tip and the peri-aneurysmal rectal gyrus.
C: CFD analysis revealed an average WSS value of 0.381 at the contact point of the dome's tip, out of the entire dome's value of 1.019 (37.4%).
D: CFD analysis displays the distribution of WSS. The area where the dome's tip contacts exhibited lower values of WSS.

Figure 3: A case of an unruptured left internal carotid-posterior communicating artery aneurysm, presenting left oculomotor nerve palsy.




A: The fusion image from 3D MRC-CTA vividly depicts the aneurysm and the impaired left oculomotor nerve. Particularly notable is the connection of the bleb on the aneurysm's dome, specifically in contact with and adhering to the oculomotor nerve.
B: Surgical photograph showing the interaction between the bleb and the surrounding oculomotor nerve.
C: CFD analysis revealed an average WSS value of 0.0605 at the bleb, out of the entire dome's value of 0.4469 (13.5%).
D: CFD analysis illustrates the distribution of WSS. The area where the bleb adheres exhibits lower values of WSS.

## Conclusions:

The development and growth of UICAs are influenced by intraluminal factors related to blood flow dynamics and pathological characteristics of the aneurysm wall. Additionally, the deformation and rupture of cerebral aneurysms involve physical extra-luminal factors resulting from PAC between the aneurysm and surrounding structures such as the brain parenchyma, cranial nerves, arteries, veins, cranial base bone and dura mater. These extra-luminal factors concerning aneurysms were evaluated based on the presence or absence of PAC. Imaging through MRC, along with the creation of fused images overlaying 3D MRC and 3D CTA or 3D MRA, enabled a detailed assessment of the anatomical construction of PAC, its contact locations, and depths. Bleb formation in aneurysms was an independent variable associated with the establishment of PAC during the aneurysm's growth process, suggesting that bleb formation might have a greater impact than intraluminal blood flow dynamics. The formation of blebs in UIAs represented a significant risk of rupture, highlighting the importance of evaluating the presence or absence of PAC as an extra-luminal factor alongside intraluminal and wall-related factors.

## Conflict of Interest Statement:

None

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## Author contributions:

T.S. (1) designed and organized the study. T.S, (1) wrote the manuscript. Y.S. (1) and YS (2), participated to discussion and review the manuscript.

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