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## Case Report

# A Case Report of Cerebral Vasospasm Following Elective Clipping of Unruptured Aneurysm: Pathogenetic Theories and Clinical Features of a Dangerous Underestimated Event

Ceraudo Marco<sup>1</sup>, Truffelli Monica<sup>1</sup>, Anania Pasquale<sup>1</sup>, Prior Alessandro<sup>1</sup>, D'Andrea Alessandro<sup>1</sup>, Zona Gianluigi<sup>1,2</sup> and Fiaschi Pietro<sup>1,2\*</sup>

<sup>1</sup>Division of Neurosurgery, IRCCS Ospedale Policlinico San Martino, Genova

<sup>2</sup>Università di Genova, Dipartimento di Neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili (DINOEMI)

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## ABSTRACT

**Background and Importance:** Angiographic-proven and clinically-evident cerebral vasospasm (CVS) after uneventful elective clipping of unruptured intracranial aneurysm (UIA) is a very rare and often underestimated event. To date, the knowledge of risk factors, pathophysiology, and demographic characteristics of these conditions are solely relegated to few case reports. With the aim of better characterize shared features and mechanism that could be involved in such event we also performed a review of the present literature and analyzed aneurysm's features, surgical factors, treatments, recovery and of all reported cases of CVS after elective clipping.

**Clinical Presentation:** We report a case of a cerebral vasospasm following elective clipping of a middle cerebral artery (MCA) bifurcation aneurysm in a 59-year-old woman who smoked next days after treatment, despite medical advice. We found ten cases comparable to ours with angiographic-proven and clinically evident cerebral vasospasm after uneventful elective clipping.

**Conclusion:** Classic mechanisms of CVS following SAH have been widely studied. In all the cases we analyzed, no subarachnoid bleeding occurred, as demonstrated in pre and postoperative CT scans and intraoperatively. Various theories on the possible mechanism have been advanced. It seems reasonable that CVS following elective clipping of unruptured aneurysm is a multifactorial phenomenon. Although its pathogenesis is unclear, clinicians should keep in mind the existence of this event, that is rare, but it could be seen in the clinical practice of every neurosurgery ward. In our opinion, it's worth to know this possible post-operative complication because, when suspected clinical signs and symptoms of delayed ischemic neurological deficit (DIND) arise after elective clipping, it's important to make an early diagnosis of CVS owing to early treatments are critical to improve clinical outcome.

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## Introduction

CVS is defined as narrowing of one, or more, large or medium-sized intracranial artery caused by a persistent contraction of its muscular wall, with consequent endoluminal diameter reduction [1, 2]. This event occurs in two-thirds of patients affected by subarachnoid hemorrhage (SAH) and it usually develops around the 4th day and gradually recedes

within the 21st day after SAH. Besides subarachnoid hemorrhage, CVS has been described after traumatic events: skull base surgery; meningitis; eclampsia and even in the presence of unruptured aneurysm [3-7]. In addition, CVS has been reported after elective clipping of unruptured aneurysm. The latter is a rare and often underestimated event that can develop after an apparently uncomplicated surgery. To date, the knowledge of risk factors, pathophysiology, and demographic

\*Correspondence to: Pietro Fiaschi, Division of Neurosurgery, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Largo Rosanna Benzi 10, 16132 Genoa, Italy, Tel: 3933402767717; E-mail: [pf.pietrofiaschi@gmail.com](mailto:pf.pietrofiaschi@gmail.com)

characteristics of these conditions are solely relegated to few case reports. In the present paper, we report a case of a cerebral vasospasm following elective clipping of a MCA bifurcation aneurysm in a 59-year-old woman who smoked the days following treatment, despite medical advice. With the aim of better characterize shared features and

mechanism that could be involved in such event we also performed a review of the present literature and analyzed aneurysm's features, surgical factors, treatments, recovery and of all reported cases of CVS after elective clipping.

**Table 1:** All cases analyzed.

Case	Author, year	Sex	Age (yrs)	Comorbidities	Aneurysm location	Aneurysm size (mm)	Multiple aneurysm	Previous SAH	CVS onset (postoperative days)	CVS location	Temporary clipping (min)	Number of clips	Other relevant surgical details	Relevant Imaging (CT/MRI)	Symptoms	Treatment	Outcome
1	Bloomfield, 1985	F	54	NA	right MCA bifurcation	7			9th		NA	2	aneurysm puncture after clipping, transient MCA focal spasm	none	left hemiparesis	hydration dexamethasone 4 mg/hrs for 5 days	Partial recovery
2	Gutierrez, 2001	F	55	NA	left ICA (ophthalmic segment)	3/5	no	NA	1st (16 hrs)	M1,M2, A1,A2	NA	NA	NA	none	severe right hemiparesis, aphasia, coma	papaverine instillation	Partial recovery (slight right hemiparesis)
3	Kitazawa, 2004 I	F	21	NA	left ICA (paraclinoid)	4	no	no	12th	left M2	use (unknown, several times)	1 straight (Sugita no.2)	bleeding from cavernous sinus	none	aphasia, Gerstmann	chemical angioplasty (papaverine hydrochloride 80 mg), triple H	Complete recovery
4	Kitazawa, 2004 II	F	63	NA	left ICA (paraclinoid)	5	no	no	9th	NA	use (unknown)	2	none	mild EDH (unknown if it requires surgery)	aphasia, right hemiparesis	chemical angioplasty (unknown), triple H	Complete recovery
5	Paolini, 2005	F	47	smoking (2/3 packs a day)	right MCA bifurcation	8			28th	distal M1	use (unknown)	2 straights	none	postop CT scan: right f-t ICH with brain swelling; on 28th day CT-subacute infarction in the MCA periventricular areas	left faciobrachiorural hemiparesis	hydration, antiplatelet	Complete recovery
6	Yang, 2011	F	41	NA	left ICA bifurcation	5			28th	left distal ICA, A1 and M1	use (3 (su art hr??error?)	2	none	none	aphasia, right facial numbness	hydration, antiplatelet, chemical angioplasty (unknown drug)	partial recovery (minimal aphasia)
7	Yang, 2012	F	61	NA	left MCA bifurcation	6			10th	NA	use (?)	3	none	none	aphasia, mental change	hydration, antiplatelet, chemical anicardipina 8 mg)	partial recovery (minimal aphasia)
8	Hashimoto, 2015	F	62	NA	left ICA-PCA	5			11th (radiological 8th)	diffuse: bilateral A1, left M1, right M3-M4, bilateral PCA	no	NA	residual neck wrapped by temporal muscle graft	none the postop CT; a Ct scan performed at 8th postop day showed M1 vasospasm+left hemispheric edema, 11th day MRI: left MCA ictus	disorientation, aphasia, right hemiplegia	hypervolemic+antiplatelet therapy	partial recovery (acalculia, paraphasia)
9	Tsyben, 2016	F	53	NA	left M1	5			2nd (30 hrs)	left MCA	no	1	reposition of clip 3 times	none, until MRI on the 6th postop day:left MCA stroke	dysphasia, fluctuant right hemiparesis (> upper limb)	chemical angioplasty (verapamil)	Partial recovery (minimal dysphasia, right upper limb paresis)
10	Tsyben, 2016	M	70	DM type II, essential hypertension, smoking	ACoA, two small left MCA	NA	yes		2nd	left M2 and M3	yes (both A1 for 4min)	unknown	old xanthochromic arachnoid staining near one small MCA an., resection of gyrus rectus	none	decrease of consciousness, aphasia, right hemiparesis	chemical angioplasty (verapamil 20 mg), 3 days of hyperphesion and hypervolemia, 21day of nimodipine	Complete recovery
11	Present Case	F	59	smoking (2/3 packs a day), hypertension	left MCA bifurcation	5	yes: 3mm left ICA	no	6th	left M1 and MCA bifurcation	yes (M1 for 6min)	1 curved Sugita clip	none	left frontobasal and temporal ipodensity on postop CT scan	aphasia, right hemiparesis	chemical angioplasty (nimodipine)	Partial recovery

Abbreviations: **ACoA**: Anterior communicating artery, **CT**: computed tomography, **EDH**: epidural haematoma, **ICA**: internal carotid artery, **ICH**: intraparenchymal haematoma, **MCA**: middle cerebral artery, **MRI**: magnetic resonance imaging, **NA**: Not Available.

## Material and Methods

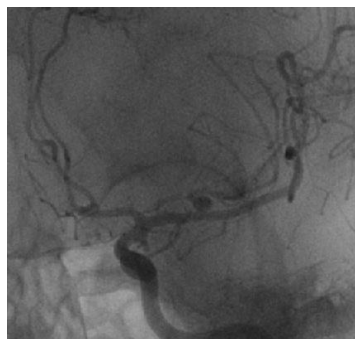
A search of MEDLINE from 1985 to present has been performed. Search terms were: “cerebral vasospasm” and “unruptured aneurysm” and “after elective aneurysm clipping”. Inclusion criteria were: 1) No evidence of a ruptured aneurysm or SAH in pre-operative CT scan and intraoperatively, 2) clinically evident vasospasm, 3) angiographically proven vasospasm. We found ten cases comparable to ours with angiographic-proven and clinically evident cerebral vasospasm after

uneventful elective clipping [2, 8-14]. All cases, together with our, are summarized in (Table 1).

## Case Description

A 59-year-old female was admitted for elective clipping of a 5 mm left MCA bifurcation aneurysm (Figure 1 & Figure 2). She had a history of hypertension and she was a heavy smoker with a consumption of 30 cigarettes per day for since she was 30-year-old. The aneurysm was incidentally discovered during the investigation for an occasional

headache and dizziness. Exams revealed also another smaller aneurysm located at the left internal carotid artery (ICA) (about 3 mm of maximum diameter) regarding which a conservative approach was chosen. No clinical or radiological signs of previous SAH were detected during preoperative workup. The patient underwent a pterional craniotomy for the exposition of the left MCA aneurysm, which was performed through a proximal-to-distal dissection. The aneurysm was clipped with a 7 mm Sugita curved clip, a temporary six-minutes-long M1 clipping was performed. There were no vessels sacrifice, nor intraoperative evidence of bleeding. The patency of the parent vessels and the complete aneurysm exclusion were verified with an intraoperative Doppler exam. Local papaverine was used as per local protocol. The postoperative neurological exam was negative, and the patient quickly resumed the ability to walk yet on the 2nd postoperative day. Since that moment, against medical advice, the patients smoked many cigarettes (about 4 per day). A first postoperative computer tomography (CT) scan scheduled for the 6<sup>th</sup> postoperative day was negative for SAH and showed only a small hypodensity in the left front - basal and temporal area of the brain, not associated with any clinical events. On the same day, she developed motor aphasia with right side hemiparesis and underwent a new CT scan, that resulted unchanged compared to the previous one.



**Figure 1:** 3D angiogram showing a left MCA bifurcation aneurysm and a left ICA aneurysm.



**Figure 2:** Angiogram showing a left MCA bifurcation aneurysm (white arrow).

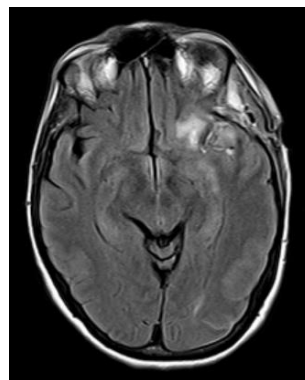


**Figure 3:** Angiogram showing a narrowing on M1 tract of left MCA.

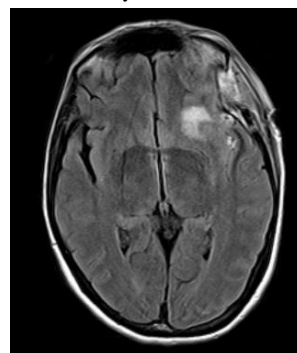
Considering a possible diagnosis of vasospasm, the patient underwent a cerebral angiography that confirmed an initial vasospasm of the left M1 and MCA bifurcation (Figure 3). An urgent chemical angioplasty with nimodipine was therefore performed (Figure 4). A subsequent cerebral magnetic resonance imaging (MRI) carried out a few hours later showed initials signs of parenchymal suffering on ischemic basis (Figure 5 & Figure 6). The next CT exam, performed on the 8<sup>th</sup> postoperative day, showed a front insular ischemic area, associated with a left MCA's diameter reduction. The vasospasm was then followed with daily transcranial Doppler (TCD) exams (initial values on left M1 250mm/s; MCA bifurcation 270 mm/s) showing a progressive normalization of the values in about two weeks. The patient was discharged on the 25th postoperative day with improved clinical signs. At the time of discharge, she was able to walk independently; the speech had phonemic and nominal paraphasia and occasional speech arrest. On long-term follow up (one year) the patient further improved, and she was able to return to work.



**Figure 4:** Light reduction of cerebral vasospasm on M1 tract of left MCA after chemical angioplasty with nimodipine.



**Figure 5:** MRI FLAIR sequence showing an ischemic area in the left MCA territory.



**Figure 6:** Other MRI FLAIR sequence showing a front insular ischemic area.

## Results

Among eleven patients ten patients were female, only one was a male; this is probably due to the greater number of women that suffers from UIA compared to men. The mean patient's age was 53, 2 years ranged (21-70 years). Three cases were reported to be smokers. Our case was the sole in which early smoking during hospitalization is reported. One patient suffered type II diabetes and hypertension also. The mean aneurysm size was 5, 4 mm and all were in the anterior circulation with left prevalence ranged (4-8 mm, 5 at left ICA, 2 at right MCA bifurcation, 3 at left MCA bifurcation/M1 and 1 at anterior communicating artery (ACoA)). Only two patients had associated aneurysms (3 mm left ICA aneurysm in our case and two small left MCA aneurysms in case number 10).

No patients suffered previous SAH or exhibited intraoperative or radiological sign of bleeding (authors of the case no. 10 reported the presence of old xanthochromic arachnoid staining near one small MCA aneurysm, but no evidence of any recent SAH). Regarding the surgical technique, temporary clipping was performed in 7 patients and multiple clips (mean value 2, 2 clips) were used in 5 cases. Peculiar intraoperative events included transient MCA focal spasm after post-clipping aneurysm puncture in one case, cavernous sinus bleeding in another case, wrapping with a temporal muscle graft of the residual neck of the aneurysm was performed in the case reported by Hashimoto et al. and the definitive clip was repositioned 3 times in the ninth case and in 1 time in our case [8, 12, 14]. The onset of CVS was reported to occur between 1 and 28 days following surgical treatment with the mean time to onset of 10, 6 days (median 9 days).

Vasospasm was diffuse in only two cases, meanwhile in the others it was localized near the site of surgery in the proximal segments of ICA, MCA and anterior cerebral artery (ACA) (2 in distal ICA, 6 in M1, 3 in M2, 3 in A1, 1 in A2 and 1 in M3). The symptoms included aphasia in 9 patients, right hemiparesis in 5 patients, left hemiparesis in 2 patients, right hemiplegia in 1 patient, Gerstmann's syndrome in 1 patient, disorientation in 1 patient, decrease of consciousness in 1 patient. CVS treatment included chemical angioplasty (2 patients with verapamil, 2 patients with papaverine, 1 patient with nimodipine, 1 patient with nicardipine and 2 patients with unknown drugs), triple H therapy, hydration and antiplatelet therapy. After treatment, 4 patients had a complete recovery and 7 patients had a partial recovery.

## Discussion

Classic mechanisms of CVS following SAH have been widely studied. The hemoglobin released from subarachnoid blood clots triggers intracellular entry and release of calcium with subsequent actin and myosin cross-linkage and basal smooth muscle contraction [15]. The contractile proteins protein kinase C, Rho kinase, and protein tyrosine kinase and their corresponding signal transduction pathways have been implicated in vasospasm models when their activation shifts the contractile mechanism toward increased shortening in the absence of high intracellular calcium levels. The presence of reactive oxygen species (ROS) and free hemoglobin induce the reduction of nitric oxide (NO) production by the endothelial cells, which has been demonstrated to have a direct effect on arterial smooth muscle contraction and in the regulation of regional cerebral flow [11, 13]. Endothelin-1 (ET-1) has

the greatest role in vasoconstriction; ET-1 levels have been found to be elevated in the cerebrospinal fluid (CSF) of patients in whom vasospasm and brain ischemia develops.

However, these mechanisms are implicated in presence of subarachnoid blood around arterial vessels. In all the cases we analyzed, no subarachnoid bleeding occurred, as demonstrated in pre and postoperative CT scans and intraoperatively. Various theories on the possible mechanism have been advanced summarized in (Table 2).

**Table 2:** Proposed Theories of CVS.

	Proposed Theories of CVS
1	Intraoperative bleeding around vessels
2	Spasmogenic blood breakdown products from aneurysm sac
3	Allergic reaction to metal's clip
4	"hypothalamic" theory
5	Trigemino-cerebrovascular reflex (TCVS)
6	Mechanical stress (temporary clipping, multiple clips, etc.)

i. During elective surgery, certainly cerebral arteries are exposed to a small amount of blood and although some cases of CVS after resection of skull base tumors or pituitary adenomas with a small amount of postoperative SAH surrounding blood vessels are reported, it seems to be unlikely that the amount of intraoperative extravasated blood would be alone responsible for CVS, as supported by the wide temporal range of vasospasm onset reported (1-28 days) [8, 13].

ii. Other factors may be implicated, and many hypotheses have been proposed. DeLong, based on the clinical observation that resecting rather than simply closing the aneurysm sac seems to be accompanied by a lower incidence of postoperative vasospasm, hypothesized that spasmogenic blood breakdown products might diffuse into the arterial wall not only from the subarachnoid cisterns but also from the inside of the aneurysm once this has been secured [16]. This presumes a very long process, but the early time of onset and the extremely rare occurrence of the CVS after elective clipping would seem to make this mechanism unlikely, except for the cases in which was observed a delayed CVS (Table 1).

iii. Hashimoto et al, in light with the existence of transient vasculitis caused by allergic reaction to a metal, like nickel and titanium, tested their patient for allergic reactions to 3 different clips but no cases resulted positive [14]. We used a 7 mm Sugita curved clip. We did not test our patient for allergic reaction to metal, but she has negative allergy history. Also, in the other cases, there was not reported any history of allergy, so this event seems to be much rarer than CVS after elective clipping itself.

iv. Some authors advocated the "hypothalamic" theory. According to this theory, mechanical or vascular impairment of the hypothalamus could promote the release of vasospastic mediators [2, 8-10]. If this hypothesis could explain CVS in aneurysms arising from structures near the midline (such as ACoA or paraclinoid tract of ICA), on one other hand, it seems less conceivable for CVS after clipping of more peripheral aneurysm (as in our case) on the other.

It is demonstrated that meninges and cranial vessels receive a trigeminal innervation, especially through the ophthalmic branch [17]. This

trigemino-cerebrovascular system (TCVS) is part of a complex nerve network surrounding the arteries of the circle of Willis. It seems to be involved in maintaining a normal vessel diameter in response to arterial vasoconstriction by a constant release of vasodilatory peptides such as substance P and calcitonin gene-related peptide (CGRP) [9]. The concentration of CGRP in the external jugular venous blood and CSF strictly correlate with the grade of vasospasm revealed by transcranial Doppler [13].

iv. Hypothetically, stimulation of the TCVS nerve by chemical factors, i.e. hemoglobin or prostaglandins, or mechanical stretching of the arterial wall could produce a failure of the “trigemino-cerebrovascular reflex” with onset of CVS [9, 13].

v. An interesting aspect about CVS pathogenesis is endothelial damage produced by mechanical factors. Aggressive manipulation of the vessel wall during surgery may cause a distention or a damage in the endothelium, that could induce an imbalance between vasoactive agents, with the preponderance of the vasoactive ones, like in the post-SAH CVS [13]. Therefore, it could be argued that local pressure of the clips on aneurysm wall or occlusion of a vessel by a temporary clip, may produce endothelial damage. The vascular stress may be severe especially in the case of use of multiple clips or if there are multiple attempts before the definitive clipping or if the temporary clipping last longer. Kitazawa et al. found a statistically significant correlation between CVS after elective clipping and the number of clips used and temporary occlusion of the ICA [8].

On the other hand, a recent paper of Malinova et al found that temporary clipping did not contribute to a higher rate of TCD-vasospasm, DIND, or delayed cerebral ischemia (DCI) in comparison with rates in patients without temporary clipping; it's worth to mention that this study included only patient underwent a clipping of ruptured cerebral aneurysm and so a different context compared to our case [18]. The use of a temporary clip or multiple clips is a common practice in aneurysm surgery. In our case, we used a temporary clip for 6 minutes and the definitive clip was replaced 1 time. In our analysis, only in 7 cases a temporary clip was used, and multiple clips were used in 5 cases. In our opinion, it would be interesting to understand if the time of use of a temporary clip or the numbers of attempts to place the definitive clip could be statistically correlated with CVS. Moreover, in our case the exposition of the UIA was done thanks to a proximal-to-distal dissection, and this could have increased the surgical manipulation of the vessel and, indeed the endothelial damage due to mechanical factors.

Secondly, areas of turbulence within the aneurysm could produce mechanical stress on the vascular wall with consequent endothelial damage and NO production impairment [19]. Also, ROS could be produced in this area of turbulent flow because of the presence of relatively hypoxic blood [20]. At the same time, several experimental studies demonstrated that, apart from causing vascular endothelial dysfunction, cigarette smoke causes physical damage to the vascular endothelium by contraction or death of endothelial cells [21]. Chronic exposure to cigarette smoking might damage the blood-brain barrier (BBB) and inflammatory effects produced by exposure to cigarette smoke may favor perivascular inflammation. In two previous case was reported smoking habit, but we have no information about the temporal correlation between smoking and onset of symptoms. In our case, the

patient smoked few days after she underwent surgical clipping. This early exposure to cigarette smoke may have contributed and amplified the endothelial alteration produced by the set of events mentioned above, even if probably the acute effect of smoke on the endothelial alteration of the arteries is much less important than the chronic one (promotion of atherosclerosis and alteration of vessel function).

The paper presents several limitations. Firstly, the incidence of CVS after clipping of UIA is unpredictable due to the lack of data regarding the amount of surgical clipping performed every year in Europe or US. It could be helpful create a nationwide register of UIA clipping procedures. Secondly, the limited number of the reported cases prevent to make any statistical analysis. As well as what concern CVS following SAH, an early diagnosis and treatment could be reasonably suggested for the management of CVS after elective clipping, despite the limited numbers and the various treatment performed in reported cases.

## Conclusion

It seems reasonable that CVS following elective clipping of unruptured aneurysm is a multifactorial phenomenon involving some mechanical and biochemical factors cause of vascular injury, production of vasoactive agents and failure of arterial wall response. Although the pathogenesis is unclear, clinicians should keep in mind the existence of this event, that is rare, but it could be seen in the clinical practice of every neurosurgery ward. Indeed, in our opinion, it's worth to know this possible post-operative complication because, when suspected clinical signs and symptoms of DIND arising after elective clipping, early diagnosis and treatments seem critical to improve clinical outcome.

## Ethics Approval and Consent to Participate

Ethics approval and consents were not needed as this study was retrospective and all data were de-identified.

## Consent for Publication

Consent for publication was obtained from all individual participants included in the study.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

## Competing Interests

The authors declare that they have no competing interests.

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None.

## Author Contribution

Marco Ceraudo and Monica Truffelli conceived of the presented idea. Pasquale Anania and Alessandro Prior developed the theory and



performed the computations. Monica Truffelli and Marco Ceraudo wrote the manuscript with support from Pietro Fiaschi. Alessandro D'Andrea and Gianluigi Zona supervised the project. All authors discussed the results and contributed to the final manuscript.

### Conflicts of Interest

None.

### Abbreviations:

**ACA:** Anterior cerebral artery.

**ACoA:** Anterior communicating artery.

**BBB:** Blood brain barrier.

**CGRP:** Calcitonin gene related peptide.

**CSF:** Cerebrospinal fluid.

**CT:** Computed tomography.

**CVS:** Cerebral vasospasm.

**DIND:** Delayed ischemic neurological deficit.

**ET-1:** Endothelin-1.

**ICA:** Internal carotid artery.

**MCA:** Middle cerebral artery.

**MRI:** Magnetic resonance imaging.

**NO:** Nitric oxide.

**ROS:** Reactive oxygen species.

**SAH:** Subarachnoid haemorrhage.

**TCVS:** Trigemino-cerebrovascular system.

**UIA:** Unruptured intracranial aneurysm.

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