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Trends in Cerebrovascular Surgery and Interventions

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Trends in Cerebrovascular Surgery and Interventions

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History of the European-Japanese Cerebrovascular Congress

Tetsuya Tsukahara

The European-Japanese Cerebrovascular Congress originally started as a Swiss-Japanese joint conference on cerebral aneurysm. The Congress was held in Zürich, Switzerland, from 5–7 May 2001 with Prof. Y. Yonekawa of Zürich and Prof. Y. Sakurai of Sendai as the presidents.

At that time, Japanese National Hospitals received Health Sciences Research Grants for Medical Frontier Strategy Research from the Japanese Ministry of Health, Labour and Welfare regarding multi-center studies on the treatment of unruptured cerebral aneurysms. Since an international cooperative study was organized between Prof. Yonekawa of the Department of Neurosurgery of Zürich University and Japanese National Hospitals, the congress was planned as a research meeting for the theme.

The first day offered a unique opportunity to gather European and Japanese neurosurgeons to discuss the treatment of unruptured cerebral aneurysms. Presentation of these new clinical experiences facilitated intensive discussions in order to clarify updated and appropriate ways to focus the treatment. The second day provided updated information on neurocritical care as well as endovascular and surgical treatment modalities carried out in daily practice in Zürich and Japan. Roundtable discussions encouraged interactive communication between the participants and faculties (Fig. 1).

Three years later, in July of 2004, the second meeting was also held at Zürich, with wide-ranging conference topics on cerebral stroke surgery.

The first day was to discuss the treatment of cerebral aneurysms and subarachnoid hemorrhage.

The discussion on the second day focused on the treatment of intracranial arteriovenous malformations, and discussion on the third day was on cerebral revascularization (Fig. 2).

Publication of the proceedings books of the conference as supplements of *ACTA Neurochirurgica* is one of the main reasons we have been able to continue this conference for almost 20 years. We sincerely thank Prof. Steiger for his continuous and generous cooperation as the series Editor of *ACTA Neurochirurgica*.

The third meeting at Zürich in 2006 was the key congress for future development. The conference was expanded to the European-Japanese Joint Conference for Stroke Surgery (Fig. 3).

As the year of 2006 was the 70th Anniversary of the Department of Neurosurgery, University Hospital Zürich, Prof. Krayenbühl, Prof. Yasargil, and Prof. Yonekawa introduced the impressive history of the Department of Neurosurgery at the conference. We were all impressed by the contribution of Zürich University to the development of neurosurgery in Europe, Japan, and throughout the world.

Symposiums on the treatment of moya moya disease, aneurysms, AVM, and AVF were held at the same time.

The AVM randomized trial (ARUBA) was introduced by Prof. J. P. Mohr of New York. Professor A. Valavanis of Zürich gave a lecture on the endovascular treatment of AVM, and Prof. E. Motti of Milano gave a lecture on AVM treatment using Gamma knife. An epidemiological survey of dural AV fistula in Japan was described by Prof. N. Kuwayama of Toyama.

The natural history and annual rupture rate of unruptured intracranial aneurysms were discussed by Prof. M. Yonekura of Nagasaki.

At the fourth European-Japanese Joint Conference on Stroke Surgery we moved from Zürich to the beautiful Nordic city of Helsinki, with Prof. Juha Hernesniemi as the conference president. The participants presented papers and discussed surgery for cerebral aneurysms and the management of subarachnoid hemorrhage and stroke, arterial dissection, intracranial arteriovenous malformations, and fistulas. Microsurgical extra-intracranial bypass surgery and revascularization techniques were also discussed. On the same

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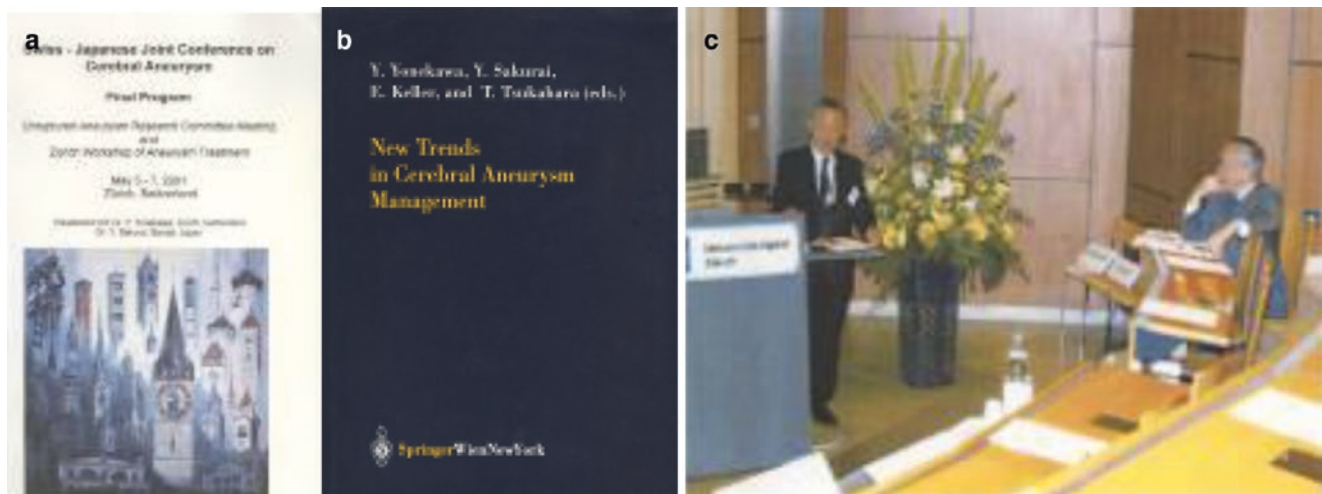
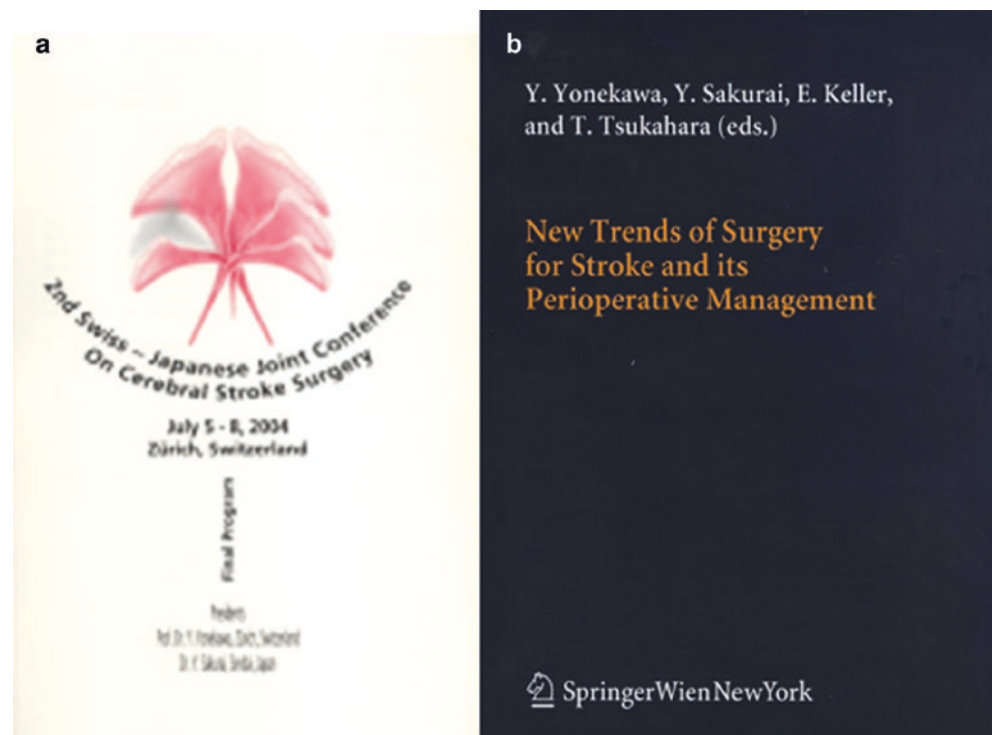


Fig. 1 Conference program (a) and the proceedings book of the first meeting: Yonekawa Y, Sakurai E, Keller E, Tsukahara T, eds. *New Trends in Cerebral Aneurysm Management*. ACTA Neurochirurgica

Supplement 82. Springer-Verlag/Wien; 2002. (b). Prof. Y. Yonekawa of Zürich and Prof. Y. Sakurai of Sendai in the Saal of Zurich University at the first meeting (c)

Fig. 2 Conference program (a) and the proceedings book of the second conference: Yonekawa Y, Sakurai E, Keller E, Tsukahara T, eds. *New Trends for Stroke and its Perioperative Management*. Acta Neurochirurgica Supplement 94. Springer-Verlag/Wien; 2005. (b)



occasion, we visited Prof. Hernesniemi's world-famous operating room in Helsinki (Fig. 4).

The fifth joint conference was held at Düsseldorf am Rein with Prof. Hans-Jakob Steiger as the conference president. Management of cerebral and ventricular hemorrhage, sub-arachnoid hemorrhage, extra-intracranial bypass surgery, surgical and endovascular treatment of arterial occlusive disease, and embolization and microsurgery of AVM and dural AV-fistula were the main themes. Special topics of the conference were cerebral and ventricular hemorrhage and cere-

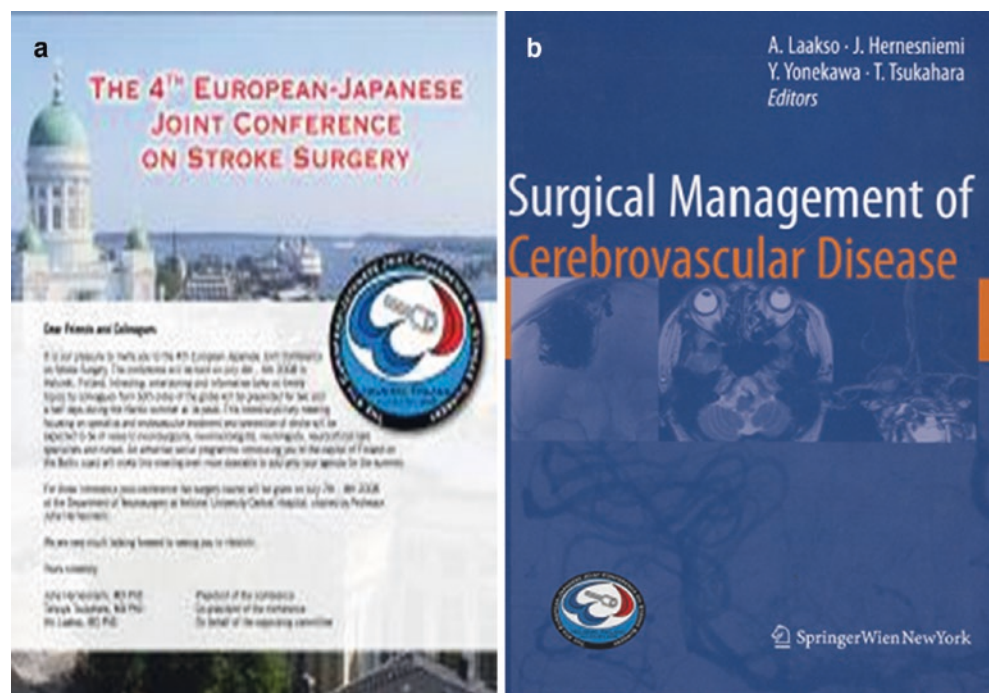
bral vascular reconstruction. In order to strengthen the focus on new trends, an open invitation for submission was made. A number of emerging concepts were presented and discussed in the resulting meeting (Fig. 5).

The sixth conference, named "The European-Japanese Stroke Surgery Conference" (EJSSC), was held in Utrecht, The Netherlands. Professor Luca Regli and Prof. Gabriel Rinkel were the conference presidents. The main topics of the conference comprised surgical and endovascular management of intracranial

Fig. 3 Conference program (a) and the proceedings book of the third conference: Yonekawa Y, Tsukahara T, Valavanis A, Khan N, eds. *Changing Aspects in Stroke Surgery: Aneurysms, Dissections, Moyamoya Angiopathy and EC-IC Bypass*. ACTA Neurochirurgica Supplement 103. Springer-Verlag/Wien; 2008. (b)



Fig. 4 Conference program (a) and the proceedings book of the fourth conference: Laakso A, Hernesniemi J, Yonekawa Y, Tsukahara T, eds. *Surgical Management of Cerebrovascular Disease*. Acta Neurochirurgica Supplement 107. Springer-Verlag/Wien; 2010. (b)



aneurysms and arteriovenous malformations; current concepts in cerebrovascular reconstruction; and new developments in cerebrovascular imaging. A number of emerging concepts were also presented and discussed at this meeting (Fig. 6).

The seventh European-Japanese Stroke Surgery Conference (EJSSC) was held in the beautiful city of Verona, Italy with Presidents Prof. Alberto Pasqualin and Prof. Giampietro Pinna. The main topics of the conference

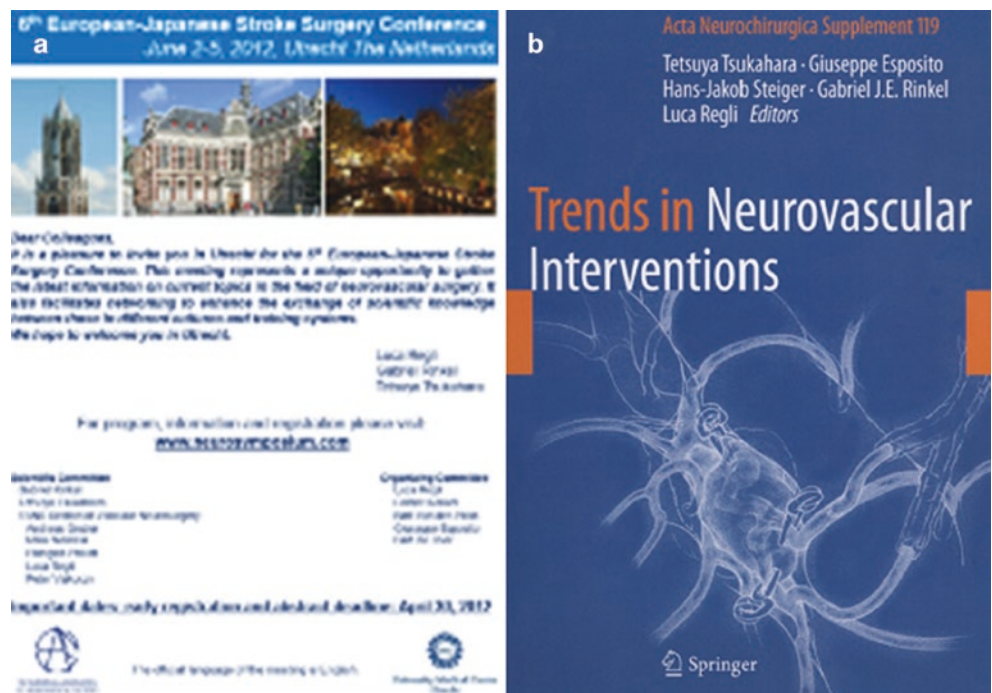
were surgical and endovascular management of intracranial aneurysms and arteriovenous malformations and cerebrovascular reconstruction. We also enjoyed beautiful paintings by Veronese and opera at the ancient Arena de Verona (Fig. 7).

The eighth European-Japanese Cerebrovascular Congress (EJCVC) came back to Zürich in the year 2016 with Prof. Luca Regli as the president. The main topics of the conference consisted of management of



Fig. 5 Conference program (a) and the proceedings book of the fifth conference: Tsukahara T, Regli L, Hänggi D, Turowski B, Steiger H-J, eds. Trends in Neurovascular Surgery. Acta Neurochirurgica Supplement 112. Springer-Verlag/Wien; 2011. S (b)

Fig. 6 Conference program (a) and the proceedings book of the sixth conference: Tsukahara T, Esposito G, Steiger H-J, Rinkel GJE, Regli L, eds. Trends in Neurovascular Interventions. Acta Neurochirurgica Supplement 119. Springer-Verlag/Wien; 2014. (b)



intracranial aneurysms, arteriovenous malformations, cavernoma and dural arteriovenous fistulas, and hemorrhagic and ischemic stroke, current trends in cerebrovascular reconstruction and cerebrovascular

neuroanatomy, and new concepts in cerebrovascular imaging.

At the same time, the Cerebral Blood Flow Meeting and Microsurgery Course Zürich were organized (Fig. 8).



Fig. 7 Conference program (a) and the proceedings book of the seventh conference: Tsukahara T, Pasqualin A, Esposito G, Regli L, Pinna G, eds. Trends in Cerebrovascular Surgery. Acta Neurochirurgica Supplement 123. Springer International Publishing Switzerland; 2016. (b)

Fig. 8 Conference program (a) and the proceedings book of the eighth conference: Esposito G, Regli L, Kaku Y, Tsukahara T, eds. Trends in the Management of Cerebrovascular Diseases. Acta Neurochirurgica Supplement 129. Springer International Publishing; 2018. (b)



The ninth European-Japanese Cerebrovascular Congress (EJCVC) was held in the historical room of Grande Ospedale Metropolitano Niguarda Milan, Italy, on 7–9 June 2018, with Prof. Marco Cenzato as the president. The main theme of the congress was preventive cerebrovascular surgery. A number of emerging concepts were presented and discussed by European and Japanese participants. Very fruitful presentations and discussions will be published as the proceedings book of ACTA Neurochirurgica Supplement, the same as with previous meetings (Fig. 9).

The tenth European-Japanese Cerebrovascular Congress (EJCVC) will be held in Kyoto, Japan with Prof. Tetsuya Tsukahara and Prof. Yasuhiko Kaku as the presidents. Due to the pandemic crisis of Covid-19, the 10th EJCVC in Kyoto has been postponed to November 2021.

It will be the first meeting in Japan of the European-Japanese Cerebrovascular Congress (EJCVC). A number of European and Japanese participants will be expected to join the congress and have fruitful discussions on New Trends of Cerebrovascular treatment.

Conflict of Interest The author declares that I have no conflict of interest.



Fig. 9 Program of ninth conference

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Part I

Intracranial Aneurysms



When Is Diagnostic Subtraction Angiography Indicated Before Clipping of Unruptured and Ruptured Intracranial Aneurysms? An International Survey of Current Practice

Martina Sebök, Jean-Philippe Dufour, Marco Cenzato, Yasuhiko Kaku, Michihiro Tanaka, Tetsuya Tsukahara, Luca Regli, and Giuseppe Esposito

Introduction

Digital subtraction angiography (DSA) is considered the gold standard for understanding the angioanatomy in ruptured and unruptured intracranial aneurysms (IAs) [1–5]. More recently, computed tomography angiography (CTA) has been introduced as an alternative imaging modality for ruptured aneurysms [6]. Sensitivities ranging from 77–97% and specificities ranging from 87–100% for the identification of ruptured aneurysms using CTA have been reported [3, 4, 7–9]. High-resolution magnetic resonance angiography (MRA), on the other hand, is frequently used for unruptured aneurysms as an alternative noninvasive modality [10]. In a systematic review [11] of studies evaluating the value of MRA for the diagnosis of intracranial aneurysms, a pooled sensitivity of 95% and pooled specificity of 89% have been reported. By comparison, in 2000 the very first meta-analysis

[12] reported a per-aneurysm pooled sensitivity and specificity of MRA of 87% and 95% for the detection of IAs, respectively. Both CTA and MRA can in many cases provide the necessary information for the preoperative planning of intracranial aneurysms, comparable to DSA [10, 11, 13, 14]. In cases of mural calcifications, CTA has a sensitivity superior to that of MRA [10, 15].

The goal of this survey is to investigate the daily practice regarding indications for DSA before clipping of ruptured and unruptured IAs in an international panel of neurovascular specialists.

Methods

Survey Development and Distribution

We elaborated an anonymous survey containing 23 multiple-choice questions (see Appendix) to investigate when and why cerebrovascular specialists consider a DSA to be indicated before the clipping of ruptured and unruptured IAs.

The survey was structured as follows. First, general questions about the responder's specialty and institution were asked: country, specialty of responder, number of treated aneurysms as main surgeon, and number of treated ruptured and unruptured aneurysms per year at responders' institution. Second, questions regarding the choice of aneurysm treatment and the quality of imaging modalities at the responders' institutions were asked. Third, responders were asked the situations (unruptured aneurysms/ruptured aneurysms/ruptured aneurysms with life-threatening hematoma) and aneurysm locations (MCA or locations other than MCA) in which microsurgical treatment is to be performed without preoperative DSA. Finally, responders were asked to select factors which in their view influence the need for preoperative

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DSA, from a list of aneurysm-, patient-, and treatment-related factors (Table 5).

A paper version of this survey was distributed to the attendees of the ninth European–Japanese Cerebrovascular Congress (EJCVC—www.ejvc2018.com), which took place in Milan, Italy at 7–9 June 2018 and was thereafter collected. The EJCVC is a biennial cerebrovascular meeting initiated in Zurich in 2001 and represents a unique opportunity to gather the latest updates on neurovascular surgery and interventions for cerebrovascular diseases.

Data Analysis

Data were manually imported into a digital database (Statistical Package for the Social Science) (SPSS) version 24 for Windows (IBM, Armonk, New York, USA). The various results were reported as value or proportion (%). Descriptive statistics were used to analyze the collected data. Categorical data were analyzed using the χ^2 test. Statistical significance was defined at $p < 0.05$.

Results

Baseline Characteristics of Survey Responders

The total number of participants at the EJCVC was 152. The survey was offered to all participants at the entrance to the conference auditorium. A total of 93 surveys were distributed and 67 (72%) completed surveys were returned during the three days of the conference. The responders worked in 13 different countries. The baseline characteristics are shown in Table 1.

Eighty-five percent of all responders were neurosurgeons, 7.5% neurointerventionalists, and 7.5% hybrid neurosurgeons. A hybrid surgeon is a cerebrovascular specialist able to treat aneurysms both by microsurgical and by endovascular methods.

Seventeen percent of responders had treated more than 500 aneurysms as main surgeon, 18% between 200 and 500 aneurysms, 10% between 100 and 200 aneurysms, 23% had treated between 20 and 100 aneurysms, and 12% between 1 and 20 aneurysms. Twenty percent of responders had never treated an aneurysm as a main surgeon.

Twenty-eight percent of all responders worked at institutions that treated 50–100 unruptured aneurysms per year, while 48% of all responders worked at institutions that treated 20–50 unruptured aneurysms per year.

Twenty-seven percent of all responders worked in institutions where the number of ruptured aneurysms treated per year is 50–100, while 54% of responders worked at an institution treating 20–50 ruptured aneurysms per year.

Table 1 Baseline characteristics of 67 respondents to the survey

	Number of respondents (%)
Continent	
Europe	50 (75)
Japan	16 (24)
Other	1 (1)
Specialty	
Neurosurgeon	57 (85)
Neurointerventionalist	5 (7.5)
Hybrid surgeon	5 (7.5)
Number of aneurysms treated as a main surgeon	
None	13 (20)
1–20	8 (12)
20–100	15 (23)
100–200	7 (10)
200–500	12 (18)
>500	11 (17)
Number of treated UNRUPTURED aneurysms at institution per year	
<20	14 (21)
20–50	32 (48)
50–100	19 (28)
>100	2 (3)
Number of treated RUPTURED aneurysms at institution per year	
<20	11 (16)
20–50	36 (54)
50–100	18 (27)
>100	2 (3)
Final decision for the type of treatment	
Interdisciplinary	53 (80)
Neurosurgeon	10 (15)
Neurointerventionalist	1 (2)
Hybrid surgeon	2 (3)

Concerning the final decision for the type of treatment, 80% of responders assume an interdisciplinary approach (on neurovascular boards or by directly discussing the cases among neurosurgeons, neuroradiologists, and neurologist).

Ninety-one percent of all responders worked at institutions offering good quality CTA and 97% at an institution with a good quality MRA (at least 1.5 T). Good quality neuroimaging is defined as imaging capable of displaying every vessel of the circle of Willis in high definition. In cases where a preoperative DSA is considered indicated, 82% of responders also request tridimensional rotational sequences.

No statistical differences were seen in the baseline characteristics between survey responders from Europe and Japan.

Impact of Aneurysm Location and Rupture Status

For MCA aneurysms, 64% of survey responders would treat unruptured aneurysms without preoperative DSA, and 60%

Table 2 Crosstab of surgical aneurysm treatment without preoperative DSA based on aneurysm location—all survey responders

Aneurysm location	Number of respondents (%)		
	Unruptured aneurysm	Ruptured aneurysm	In case of life-threatening hematoma
MCA	43 (64)	40 (60)	65 (97)
Other location	45 (68)	49 (73)	64 (96)

of responders would treat ruptured MCA aneurysms without preoperative DSA. Ninety-seven percent of responders would treat ruptured MCA aneurysms with life-threatening hematoma without preoperative DSA (Table 2).

Regarding aneurysms in locations other than the MCA, 68% of survey responders would treat unruptured aneurysms without preoperative DSA, and 73% of responders would treat ruptured aneurysms without preoperative DSA. Ninety-six percent of all responders would treat ruptured aneurysms in other locations than the MCA with life-threatening hematoma without preoperative DSA (Tables 2 and 3). There were no statistically significant differences in decision-making regarding preoperative DSA for aneurysm treatments between European and Japanese neurosurgeons.

Because 20% of all responders never treated an aneurysm as a main surgeon, in Table 3 we adapted a crosstab of surgical aneurysm treatment without preoperative DSA based on aneurysm location and performed a calculation excluding survey responders who never treated an aneurysm as main surgeon. Results do not show significant changes if one does not consider the surgeons who never clipped an aneurysm (Tables 2 and 3).

Impact of Surgeon Experience on Decision to Perform a Preoperative DSA

The benchmark for an experienced surgeon was set at 100 treated aneurysms as main surgeon. Forty-five percent of survey responders classify as experienced aneurysm surgeons. Table 4 represents a crosstab of the impact of a surgeons' experience on the decision to perform a preoperative DSA. Because in cases of life-threatening hematoma nearly all survey responders decide to waive a preoperative DSA (Tables 2 and 3), the impact of experience in these cases was not calculated.

In cases of unruptured aneurysms in locations other than the MCA, experienced neurosurgeons treat aneurysms significantly more often without a preoperative DSA, compared to less experienced colleagues (experienced vs. less-experienced: 80% vs. 43%, $p = 0.002$).

In cases of unruptured MCA aneurysms, a similar trend is seen: Experienced neurosurgeons perform surgeries without

Table 3 Crosstab of surgical aneurysm treatment without preoperative DSA based on aneurysm location—excluding survey responders who never treated an aneurysm as main surgeon

Aneurysm location	Number of respondents (%)		
	Unruptured aneurysm	Ruptured aneurysm	In case of life-threatening hematoma
MCA	37 (70)	36 (68)	51 (96)
Other location	39 (74)	39 (74)	51 (96)

Table 4 Impact of surgeon's experience to treat aneurysm without preoperative DSA

Aneurysm location	Experienced surgeon (n (%))		p -value
	YES ($n = 30$)	NO ($n = 37$)	
MCA			
Unruptured	23 (71)	22 (49)	0.08
Ruptured	24 (80)	25 (68)	0.20
Other location			
Unruptured	24 (80)	16 (43)	0.002
Ruptured	22 (73)	19 (51)	0.18

preoperative DSA more often than less experienced colleagues (experienced vs. less-experienced: 71% vs. 49%, $p = 0.08$).

For ruptured MCA aneurysms and ruptured aneurysms in other locations, the data again show differences in absolute numbers, whereby preoperative DSAs are less frequently requested by experienced neurosurgeons (but without reaching significant differences between the experienced and less-experienced group).

Factors Influencing the Decision to Perform a Preoperative DSA

Table 5 summarizes aneurysm-related factors, patient-related factors, and treatment-related factors that influence the choice of survey responders to perform a preoperative DSA.

The most important aneurysm-related factors indicating a preoperative DSA examination are: aneurysmal shape (fusiform or dissecting aneurysms: >80% of responders ask for a preoperative DSA); infectious aneurysm etiology (72% of responders); maximum aneurysm diameter >25 mm (85% of responders); paraclinoidal or posterior circulations aneurysms (>70% of responders); possible perforators and vessels arising from aneurysm sac (85% of responders for both); intra-aneurysmal thrombus (73% of responders); and previous treatment (90% of survey responders).

There are no patient-related factors (age, clinical status) (Table 5) that influence the decision for a preoperative DSA.

Table 5 Aneurysm-, patient- and treatment-related factors influencing the choice to perform a preoperative DSA

	Number of respondents answering YES (%)
Aneurysm-related factors	
<i>Aneurysm location</i>	
• Middle cerebral artery (MCA) proximal (M1-M2 segments)	29 (43)
• Middle cerebral artery (MCA) distal (M3-M4 segments)	31 (46)
• Carotid-posterior communicating artery (PCom)	35 (52)
• Carotid-anterior choroidal artery (ACho)	41 (61)
• Carotid-T	34 (51)
• Carotid-hypophyseal	41 (61)
• Carotid-paraclinoidal (ophthalmic)	48 (72)
• Anterior cerebral artery (ACA) proximal (A1-A2 segments)	31 (46)
• Anterior cerebral artery (ACA) proximal (A3-A4 segments)	29 (43)
• Anterior communicating artery (ACom)	
– Anterior projecting	31 (46)
– Posterior projecting	39 (58)
– Superior projecting	37 (55)
– Inferior projecting	33 (49)
• Posterior circulation:	
– posterior inferior cerebellar artery (PICA)	47 (70)
– others (anterior inferior cerebellar artery, superior cerebellar artery, basilar artery, posterior cerebral artery)	51 (76)
<i>Aneurysmal morphology</i>	
• Etiology:	
– Saccular	25 (37)
– Fusiform	54 (81)
– Dissecting	58 (87)
– Infectious (i.e., mycotic)	48 (72)
• Shape:	
– Irregularity (bleb/lobulation/daughter aneurysm)	40 (60)
– Broad neck	41 (61)
• Maximum diameter (single):	
– <5 mm	22 (33)
– >10 mm	35 (52)
– >25 mm	57 (85)
• Possible perforators arising from the aneurysm	57 (85)
• Efferent vessels arising from aneurysmal sac	57 (85)
• Calcification/atherosclerotic plaque of the aneurysm wall	26 (39)
• Intra-aneurysmal thrombus	49 (73)
• Recurrence/previous treatment	60 (90)
• Computational fluid dynamic analysis based decision	20 (30)
Patient-related factors	
• Patient age:	

Table 5 (continued)

	Number of respondents answering YES (%)
– <40	20 (30)
– 40–60	18 (27)
– >60	18 (27)
• Clinical situation:	
– SAH	22 (33)
– Cranial nerve deficit	23 (34)
– Clinical mass effect	26 (39)
– Radiological mass effect	23 (34)
– Previous SAH	29 (43)
Treatment-related factors	
• Bypass contemplated	52 (78)
– Visualization of possible donor artery (e.g. STA)	51 (76)
– Visualization of possible recipient artery	47 (70)
• Collateral circulation	57 (85)

Regarding treatment-related factors, 78% of responders would ask for a DSA preoperatively in cases where a flow-replacement bypass is contemplated as a treatment option. Similarly, 85% of responders would ask for a preoperative DSA to assess the collateral circulation in cases where the possibility of bypass is evaluated.

Discussion

The goal of the survey was to investigate, among an international panel of neurovascular specialists participating at the ninth EJCVC, the workup and in particular the indication for preoperative DSA for patients undergoing microsurgical treatment of ruptured or unruptured intracranial aneurysms.

The analysis of the survey showed that in more than 80% of responders, the final decision for the type of aneurysm treatment at the responder's institution is taken in an interdisciplinary setting.

Tables 2 and 3 show a crosstab of microsurgical aneurysm treatment without preoperative DSA based on aneurysm location and rupture status. For MCA aneurysms, approximately 60% of responders perform microsurgery without preoperative DSA, regardless of rupture status. For aneurysms in locations other than MCA, microsurgery is done without preoperative DSA in 68% of unruptured and 73% of ruptured cases. In the case of ruptured MCA and non-MCA aneurysms with life-threatening hematoma, the vast majority of the responders (96% and 97%, respectively) perform surgery without preoperative DSA.

This high percentage of responders who do not perform a DSA in cases of life-threatening hematoma is to be expected.

In these cases there is no time for a DSA examination: the hematoma must be evacuated and the brain decompressed.

For MCA aneurysms without life-threatening hematoma, 40% of responders ask for a DSA preoperatively. This is quite a high percentage, especially if one considers the possible complications of a DSA: According to the literature, neurological complications after a DSA examination occur in 2.63% of cases, where 0.14% of these are strokes with permanent disability [16].

Our survey results suggest that a surgeons' experience plays a role in deciding whether a preoperative DSA is indicated. A clear difference between experienced (>100 treated aneurysms as main surgeon) and less experienced neurosurgeons is seen especially in cases of unruptured aneurysms: experienced surgeons ask for a preoperative DSA significantly less frequently in these patients.

Regarding the difference in requests for a preoperative DSA in MCA aneurysms, an almost-significant difference is seen in unruptured aneurysms ($p = 0.08$) and a trend toward statistical significance is seen in ruptured aneurysms ($p = 0.20$) between experienced surgeons and less experienced surgeons.

To simplify our questionnaire and the statistical workup, we separated the aneurysm location into MCA and locations other than the MCA. As a consequence, the non-MCA group includes a heterogeneous group of aneurysms from the anterior and posterior circulation.

According to the consensus among neurovascular specialists, a preoperative DSA is performed more often for aneurysms of the posterior circulation. Our survey confirms this trend: $\geq 70\%$ of survey responders perform a preoperative DSA in patients with posterior circulation aneurysms. Therefore, the higher percentage of survey responders performing surgeries without DSA in locations other than the MCA compared to MCA aneurysms regardless of rupture status (unruptured locations other than MCA vs. unruptured MCA aneurysms: 68% vs. 64%; ruptured locations other than MCA vs. ruptured MCA aneurysms: 73% vs. 60%) is a surprising finding.

Factors which in a high percentage of responders (>70%) lead to the request for a preoperative DSA are: location of the aneurysm in the posterior circulation or paracaloid aneurysms, non-saccular aneurysmal shape (fusiform or dissecting), infectious aneurysm etiology, maximum diameter of the aneurysm >25 mm, possible perforators or efferent vessels arising from the aneurysm sac, intra-aneurysmal thrombus, previous treatment of the aneurysm, bypass contemplated, and to assess the collateral circulation. All these factors could be considered as characteristics of complex aneurysms. This is an expected finding since a general consensus among the cerebrovascular specialists exists wherein any angioanatomical feature indicating the presence of a complex aneurysm should lead to a more detailed workup,

including preoperative DSA. The aneurysmal complexity is namely related to at least one of the following features: (1) size ≥ 2.5 cm, (2) anatomic location (vertebral, basilar, paracaloid), (3) involvement of critical perforating or branch vessels, (4) previous treatment (endovascular or surgical), (5) dissecting, fusiform, saccular lesions with very broad neck, (6) intraluminal thrombosis, and (7) atherosclerotic plaques and calcifications of the aneurysm wall and/or neck [17–24]. There are no patient-related factors (except clinical status) that influence the decision for a preoperative DSA. This is an expected finding because in cases of bad clinical status, often caused by life-threatening hematoma, there is no time for a preoperative DSA.

One of the aims of the survey was to assess in which direction the use of diagnostic DSA before microsurgical management of ruptured and unruptured cerebral aneurysms is moving among European and Japanese neurosurgeons. Several advantages of both noninvasive CTA and invasive DSA are known and should be considered, as well as the possible complications of DSA. Previous studies introduced CTA as an alternative imaging modality for ruptured IAs and reported sensitivities ranging from 77–97%, and specificities ranging from 87–100% [3, 4, 7, 8]. The most recent meta-analysis by Menke et al. [8] was published in 2011 and encompassed 45 previous studies, for a total of 3643 patients with ruptured and unruptured aneurysm. This meta-analysis reported an overall CTA sensitivity of 97.2% and a specificity of 97.9%, as well as a per-aneurysm sensitivity of 95% and specificity of 96.2%.

In a comparative analysis between CTA and DSA for the diagnosis of ruptured intracranial aneurysms, Philipp et al. [25] concluded that the accuracy of CTA for the diagnosis of ruptured intracranial aneurysm may be lower than previously reported: in fact they found a low sensitivity of CTA (57.6%) for aneurysms smaller than 5 mm in size, located adjacent to bony structures, and for those arising from small caliber parent vessels.

The “Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms” from the American Heart Association/American Stroke Association [9] recommend that due to its high sensitivity and specificity, even for smaller aneurysms, CTA can be considered as an initial diagnostic test for aneurysm detection and screening. However, the reconstruction methods may not accurately depict the true neck/dome/adjacent small vessel anatomy, but CTA is very useful in identifying mural calcification and thrombus, which can have a significant impact on treatment decisions [15, 26].

Several other advantages of CTA and MRA over DSA have been recognized, including reduced cost, avoidance of arterial injury and stroke, rapid acquisition, and retrospective manipulation of data. Furthermore, it is important to mention that both the radiation dosage and the volume of contrast

media is inferior with CTA than DSA (one-third to one-half for a single CTA compared to a four-vessel DSA) [10, 15].

The most appropriate use of the above-mentioned imaging modalities, especially CTA and DSA, in guiding medical decision-making for treatment of ruptured and unruptured intracranial aneurysms, remains an issue of debate.

Limitations

Our survey has several limitations, particularly with regard to responder bias and generalizability. First, the survey was distributed to participants of the EJCVC 2018 and therefore the results represent the current European and Japanese practice but might not be generalizable to other regions. Second, responses were voluntary and could lead to a selection bias for people with a particular interest and/or knowledge in these issues. Finally, 20% of all responders never treated an aneurysm as a main surgeon, indicating a possible limited experience in preoperative decision-making. Nonetheless, this subgroup of responders could have answered by using the decision-making algorithm of their working institution, which was the reason we included them in our analysis. However, we adapted a crosstab of surgical aneurysm treatment without preoperative DSA based on aneurysm location and performed a calculation excluding the responders who never treated an aneurysm as main surgeon. The results do not show significant changes if one does not consider the surgeons who never clipped an aneurysm (Tables 2 and 3).

Conclusion

There is still a high variability in the surgeons' preoperative decision-making regarding the indication for DSA before clipping of intracranial aneurysms, except in case of ruptured aneurysms with life-threatening hematoma, where most of the responders perform surgery without preoperative DSA. For MCA aneurysms, approximately 60% of responders perform microsurgery without preoperative DSA, regardless of rupture status. For aneurysms in locations other than MCA, microsurgery is done without preoperative DSA in 68% of unruptured and 73% of ruptured cases.

The factors favoring the execution of a DSA before clipping are related to the complexity of the aneurysm: aneurysmal shape (fusiform, dissecting), etiology (infectious), size (>25 mm), possible presence of perforators or efferent vessels arising from the aneurysm, intra-aneurysmal thrombus, previous treatment, location (posterior circulation or paraclinoid), and flow-replacement bypass contemplated for final aneurysm treatment.

Moreover, a surgeons' experience plays a role in the decision-making regarding preoperative DSA, with experienced surgeons (>100 aneurysms treated as main surgeon) requesting preoperative DSAs less frequently. This effect is especially pronounced in patients with unruptured aneurysms.

Appendix: Survey Questions

1. **In which country do you work?**
.....
2. **At which institution do you work? (if you want to answer)**
.....
3. **Which specialist are you?**
 - (a) neurosurgeon
 - (b) neurointerventionist (interventional neuroradiologist)
 - (c) hybrid surgeon
 - (d) neurologist
 - (e) neurointensivist (Neuro Intensive Care)
 - (f) other:
4. **What is your position?**
 - (a) chairman
 - (b) senior consultant (attending clinician)
 - (c) junior consultant (attending clinician)
 - (d) fellow
 - (e) resident
 - (f) other:
5. **How many aneurysms have you treated in your career as main surgeon?**
 - (a) none
 - (b) 1–20
 - (c) 20–100
 - (d) 100–200
 - (e) 200–500
 - (f) >500
6. **How many patients with unruptured intracranial aneurysms are treated at your department per year?**
 - (a) <20
 - (b) 20–50
 - (c) 50–100
 - (d) >100
7. **How many patients with ruptured intracranial aneurysms are treated at your department per year?**
 - (a) <20
 - (b) <50
 - (c) 50–100
 - (d) >100

8. **Who takes the final decision for the type of treatment?**
- interdisciplinary (boards or discussion of the case among neurosurgeons, neuroradiologists, neurologists)
 - neurosurgeon
 - neurointerventionalist (interventional neuroradiologist)
 - hybrid surgeon
 - neurologist
 - neurointensivist (Neuro Intensive Care)
 - others:
9. **Do you (or surgeons at your institution) nowadays treat surgically only aneurysms of the middle cerebral artery (MCA)?**
- yes
 - no
 - I do not know
10. **Have you (or surgeons at your institution) treated surgically in the past also intracranial aneurysms in other locations (i.e., not MCA aneurysms)?**
- yes
 - no
 - I do not know
11. **Does the neurosurgeon at your institution sometime decide by himself to treat a MCA aneurysm surgically without having involved the neurointerventionist in the decision-making?**
- yes
 - no
 - I do not know
12. **Does the neurosurgeon sometime decide by himself to treat an aneurysm in other locations (i.e., not MCA aneurysms) surgically without having involved the neurointerventionist in the decision-making?**
- yes
 - no
 - I do not know
13. **Does the neurointerventionist sometimes decide by himself to treat an aneurysm endovascular without having involved the neurosurgeon in the decision-making?**
- yes
 - no
 - I do not know
14. **Have you at your institution good quality Computed Tomography Angiography (CTA)?**
- yes
 - no
15. **Have you at your institution good quality Magnetic Resonance Angiography (MRA) with at least 1.5 T or more?**
- yes
 - no
16. **Do you treat surgically unruptured MCA aneurysms without preoperative Digital Subtraction Angiography (DSA)?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
17. **Do you treat surgically unruptured aneurysms in other locations (i.e., not MCA-aneurysms) without preoperative DSA?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
18. **Do you treat surgically ruptured MCA aneurysms without preoperative DSA?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
19. **Do you treat surgically ruptured aneurysms in other locations (i.e., not MCA-aneurysms) without preoperative DSA?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
20. **Do you operate ruptured MCA aneurysms without preoperative DSA in case of life-threatening hematoma?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
21. **Do you operate ruptured aneurysms in other locations (i.e., not MCA-aneurysms) without preoperative DSA in case of life-threatening hematoma?**
- yes
 - no
 - I do not clip
 - I have not clipped yet
22. **By preoperative DSA, do you always ask for tridimensional rotational sequences?**
- yes
 - no
 - I do not clip
 - I have not clipped yet

23. Which of the following criteria influence your choice to perform a preoperative DSA? If you do not know one or more answer, please do not cross the relative box.

Aneurysm-related factors

Aneurysm location

- Middle cerebral artery (MCA) proximal (M1-M2 segments) yes no
- Middle cerebral artery (MCA) distal (M3-M4 segments) yes no
- Carotid-posterior communicating artery (PCoM) yes no
- Carotid-anterior choroidal artery (ACho) yes no
- Carotid-T yes no
- Carotid-hypophyseal yes no
- Carotid-paraclinoidal (ophthalmic) yes no
- Anterior cerebral artery (ACA) proximal (A1-A2 segments) yes no
- Anterior cerebral artery (ACA) proximal (A3-A4 segments) yes no
- Anterior communicating artery (ACoM)
 - Anterior projecting yes no
 - Posterior projecting yes no
 - Superior projecting yes no
 - Inferior projecting yes no
- Posterior circulation: posterior inferior cerebellar artery (PICA) yes no
- Posterior circulation: others (anterior inferior cerebellar artery, superior cerebellar artery, basilar artery, posterior cerebral artery) yes no

Aneurysmal morphology

- Etiology:
 - Saccular yes no
 - Fusiform yes no
 - Dissecting yes no
 - Infective (i.e.: mycotic) yes no
- Shape:
 - Irregularity (bleb/ lobulation/daughter aneurysm) yes no
 - Broad neck yes no
 - Others yes no
- Maximum diameter (single)
 - < 5mm yes no
 - >10 mm yes no
 - >25mm yes no
- Possible perforators arising from the aneurysm yes no
- Efferent vessels arising from aneurysmal sac yes no
- Calcification/atherosclerotic plaque of the aneurysm wall yes no
- Intra-aneurysmal thrombus yes no
- Recurrence/previous treatment yes no
- Computational fluid dynamic analysis based decision yes no

Patient-related factors

- Patient age:
 - <40 yes no
 - 40-60 yes no
 - >60 yes no
- Clinical situation:
 - SAH yes no
 - Cranial nerve deficit yes no
 - Clinical mass effect yes no
 - Radiological mass effect yes no
 - Previous SAH yes no
 - Others: yes no

Treatment-related factor

- Bypass contemplated yes no
 - Visualization of possible donor artery (e.g. STA) yes no
 - Visualization of possible recipient artery yes no
- Collateral circulation yes no
- Others: yes no

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Current Strategies in the Treatment of Intracranial Large and Giant Aneurysms

Matthias Gmeiner and Andreas Gruber

Introduction

Very large and giant intracranial aneurysms are defined as aneurysms with a diameter >20 mm and >25 mm [1] respectively. Giant aneurysms constitute approximately 2–5% of all intracranial aneurysms [2–4]. The natural history of these lesions is poor, with reported mortalities ranging from 66–80%. The worst outcomes have been observed in untreated posterior circulation giant aneurysms [3–5]. The majority of patients harboring very large and giant intracranial aneurysms (50–80%) present with thromboembolic events or symptoms of mass effect [3, 6], whereas subarachnoid hemorrhage (SAH) occurs in approximately 20–30% [6].

In view of the poor natural course of these lesions, aggressive treatment aiming for both aneurysm occlusion and relief of mass effect has been recommended [6, 7]. The benefits of active aneurysm therapy must be weighed against the inherent risks of treatment. Whereas surgical management carried a significant morbidity and mortality in the past [3], recent meta-analyses reported good clinical outcomes in as many as 80% of the patients when individualized treatment strategies—including both surgical and endovascular techniques—were adopted [2]. The risk-benefit assessment, however, will favor active therapy only when treatment is performed at high-volume cerebrovascular centers, where the capacities of both neurosurgery and neurointervention are available and individualized treatment concepts considering anatomic location (cavernous vs. subarachnoid, anterior circulation vs. posterior circulation), clinical presentation (SAH vs. mass effect vs. incidental presentation), patient

demographics (age), and aneurysm morphology can be applied [6, 7].

Both reconstructive (clipping, coiling, stent-assisted coiling, flow diversion [FD]) and deconstructive techniques (parent artery occlusion [PAO], PAO in conjunction with bypass surgery, and strategies of flow modification) are available for the treatment of cerebral aneurysms [8]. The aim of this paper is to review the current literature on the management of very large and giant aneurysms and to describe representative cases—treated by the senior author, who has been dually trained and is cross-experienced in both microsurgical and endovascular techniques—to illustrate possible treatment strategies.

Reconstructive Techniques

Reconstructive techniques are usually the preferred treatment strategy in the management of intracranial aneurysms, since these procedures do not compromise the patency of the parent vasculature and in turn do not interfere with cerebral blood flow distal to the aneurysm site. In the management of very large and giant aneurysms, open surgical strategies of direct aneurysm occlusion have proven technically difficult but often highly effective, whereas technically less challenging endovascular procedures, e.g., intrasaccular coil embolization, have proven ineffective in the long run. The role of more advanced endovascular strategies, e.g., FD stents and intra-aneurysmal FD, is still in the process of being defined.

Clipping and Clip Reconstruction

Direct surgical clip ligation of the neck with preservation of the parent vasculature remains the ideal reconstructive treatment strategy in the majority of very large and giant saccular aneurysms. Procedural outcomes usually depend on aneurysm morphology (calcifications, intrasaccular thrombus,

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complex anatomy), aneurysm location, parent artery caliber, and perforator anatomy [4, 6, 9, 10].

In the management of very large and giant middle cerebral artery (MCA) aneurysms, direct surgical clipping is considered the most effective and durable treatment, whereas coiling was identified as an independent risk factor for retreatment in a recent study describing the management of 106 large and giant MCA aneurysms [11]. Coiling of MCA aneurysms carries a higher recurrence risk even in smaller lesions. In detail, the recurrence risk following coil embolization of >7 mm MCA aneurysms was 17.5% [12], and that of MCA aneurysms ≥ 11 mm was 46% in recent publications [13]. Long-term instability of MCA aneurysm occlusion was reported in 3% of the patients receiving surgical clipping and in >45% of the patients receiving intrasaccular coiling [14].

The success of direct clipping of very large and giant aneurysms depends on the ability to soften the aneurysmal sac intraoperatively, usually achieved by temporary clipping of the parent vasculature or measures inducing transient cardiac standstill (i.e., pharmacologically induced hypodynamic standstill using Adenosine or electrically induced hyperdynamic standstill using rapid ventricular pacing). In cases of extensive intrasaccular thrombosis, aneurysmotomy and subsequent thrombectomy under pharmacologic cerebroprotection are required for successful clip reconstruction [6]. Multiple clips applied in different techniques (tandem clipping, stacked multiple clips, overlapping clips) are usually required (Fig. 1a–c) [15, 16].

Coil Embolization

Coil embolization has proven ineffective in the treatment of very large and giant aneurysms. Low initial complete occlusion rates (10–60%) and high recanalization rates (56–90%) have been demonstrated in several studies [17, 18]. Mechanisms of recanalization include coil compaction, coil migration, and aneurysm regrowth [18, 19].

In a previous study assessing the results of coil embolization in patients with very large or giant aneurysms, the senior author reported a 71% complete or nearly complete angiographic occlusion rate immediately after the intervention. Of note, a single embolization served as definitive treatment for only 12.5% of the giant and only 31% of the very large aneurysms in the long run [17]. In partially thrombosed aneurysms presenting with mass effect, selective coiling reportedly resulted in continuous aneurysm growth in 18% of the cases, whereas only 7% of the aneurysms decrease in size [20]. Coiling had little if any effect on the relief of symptoms of mass effect.

The current body of literature strongly suggests that the initial angiographic occlusion rate after coil embolization is related to the risk of re-rupture [21]. Ruptured aneurysms

with angiographic occlusion rates >90% 6 months after coiling had low rates (0.4%) of recurrent SAH within the subsequent 8 years [22]. In large and giant aneurysms, the reported annual rebleeding rate of 1.9% after coil embolization was substantially higher [23]. A retrospective study reporting outcomes after surgical or endovascular therapy of 184 very large or giant aneurysms identified the following as risk factors for incomplete angiographic obliteration: (1) fusiform aneurysm morphology, (2) aneurysm location in the posterior circulation, and (3) endovascular treatment (coiling or stent-assisted coiling) [24].

Stent-Assisted Coiling

Intrasaccular coil embolisation has significant limitations in wide-necked aneurysms due to comparably lower packing densities and subsequently higher rates of recanalization. Therefore, alternative techniques using so-called neck bridging devices have been introduced (Fig. 1d–f). The technique of stent-assisted coiling uses a stent—which per se is a non-occlusive device—to provide a scaffold to hold the coils within the aneurysmal sac [25]. Meta-analyses revealed that in patients harboring very large and giant aneurysms, occlusion rates were significantly higher following stent-assisted coiling [73%] when compared to coiling alone (59%) [26]. Of note, significantly higher treatment morbidities have been reported following stent-assisted coiling when compared to regular intrasaccular coil embolization [27]. Stent-assisted coiling has nowadays become a routine procedure that can be performed safely and effectively in expert hands. Since the implanted device is endoluminal rather than intra-aneurysmal, peri-interventional management of coagulation is of major importance and procedure-related complications of in-stent thrombosis and subsequent distal thromboembolism are still relevant issues. When compared to flow diversion [FD], stent-assisted coiling of giant aneurysms has the potential to further increase aneurysmal mass effect. It should be pointed out that stent-assisted coiling of a giant aneurysm can be a very expensive undertaking.

Flow Diversion

Flow diverters have become an attractive alternative for the endovascular treatment of complex aneurysms in selected cases [28–31] because the technique does not suffer from the aforementioned shortcomings of intrasaccular coil embolization [17, 18, 20, 28]. Flow diverters initially received FDA approval for the treatment of large and giant aneurysms extending from the petrous to the superior hypophyseal segment of the internal carotid artery [32] (Fig. 1g–i). Currently, however, a variety of aneurysms—including those previously

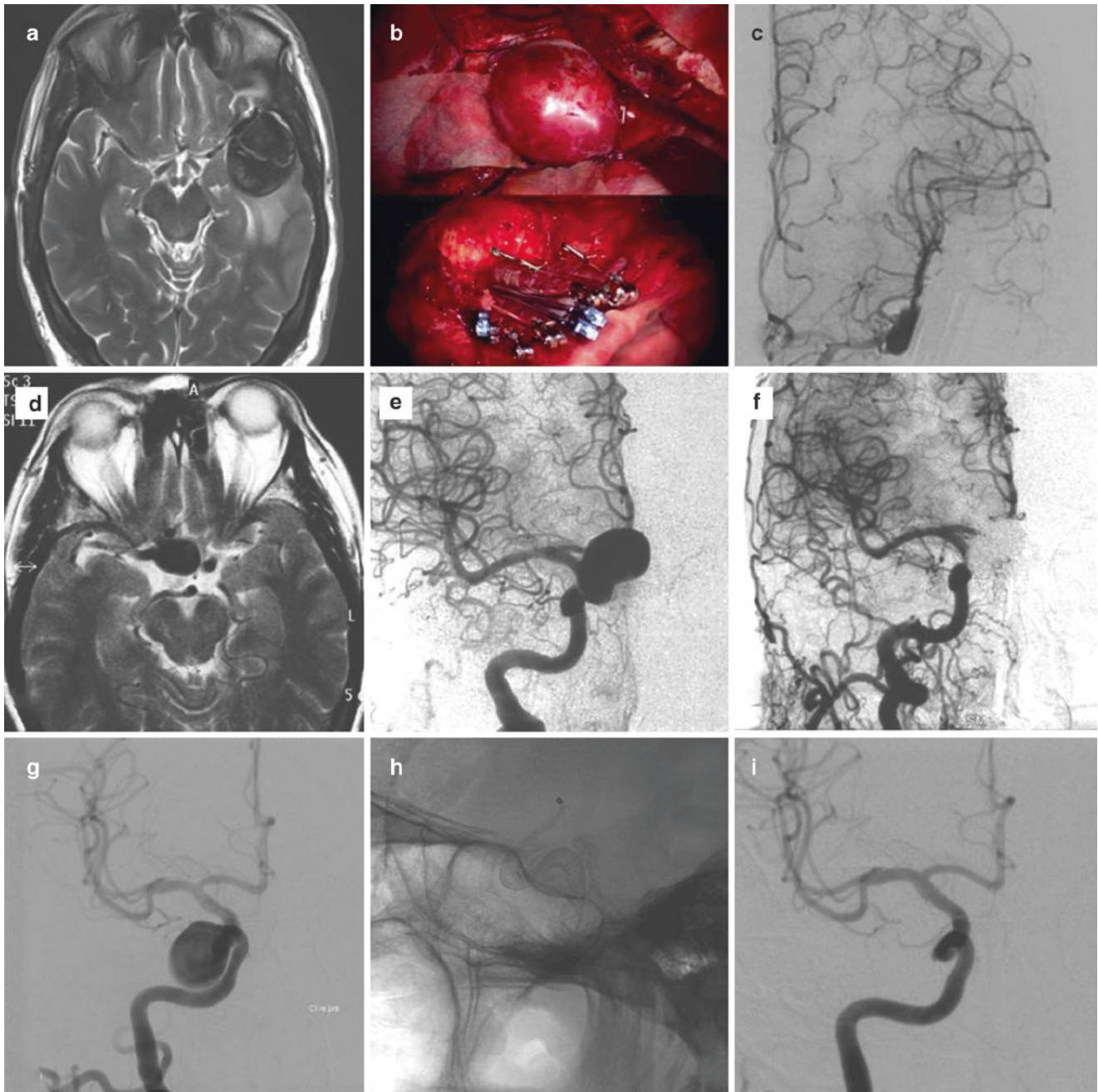


Fig. 1 Reconstructive surgical and endovascular techniques. (a–c) Microsurgical clipping. Fifteen years after uneventful clipping of a 7 mm left MCA bifurcation aneurysm, a 40 mm partially thrombosed aneurysm recurrence is detected on MRI (a). Since STA donor branches were of insufficient caliber and three M2 branches were incorporated into the aneurysm sac, the decision was made to treat the aneurysm by direct surgical clipping after temporary trapping, aneurysmotomy, and thrombectomy under pharmacologic cerebroprotection (b). Intraoperative left ICA angiograms demonstrate sufficient aneurysm obliteration (c) (A.G., procedure performed at the Kepler University Hospital Linz). (d–f) Stent-protected coil embolization. MRI (d) and right ICA angiograms (e) depict a 20 mm ICA aneurysm at the branch-

ing site of the superior hypophyseal artery. Aneurysmal mass effect resulted in optic nerve compression and subsequent visual field deficits. The patient was treated by stent-protected coil embolization (f) and regained vision over the following months, an effect attributable to aneurysm shrinkage after embolization (A.G., procedure performed at the Medical University Vienna). (g–i) Flow diversion. Right ICA angiograms (g) demonstrate a very large intracavernous ICA aneurysm that resulted in partial ophthalmoplegia from mass effect and intracavernous cranial nerve compression. The patient was treated by FD stenting (h), which resulted in complete aneurysm occlusion (i) and delayed resolution of ophthalmoplegia due to post FD aneurysm shrinkage (A.G., procedure performed at the Medical University Vienna)

treated, acutely ruptured, small sized, located within the posterior circulation, as well as non-saccular lesions including fusiform, dissecting, and pseudoaneurysms—are treated using FD techniques. For the time being, indications for FD treatment are unclear, and many procedures, especially those expanding FD indications from untreatable giant aneurysms to comparably easy surgical cases, must still be considered off-label uses of the device.

Similar to stent-assisted coiling, FD stenting relies on an endoluminal device creating an interface between the aneurysmal sac and the parent vasculature. Aneurysm occlusion thereby occurs in a delayed fashion over weeks to months [23] by intra-aneurysmal flow modification, thrombus formation, and subsequent endothelial overgrowth of the aneurysm neck. Peri-interventional management of coagulation, i.e., dual antiplatelet medication, is of major concern, and in turn FD stents have limited if any value in the management of patients with acutely ruptured aneurysms [33]. Since intra-aneurysmal thrombosis occurs progressively over time and intra-aneurysmal pressures will remain elevated even after the initial angiographic occlusion—which is due to stagnant aneurysmal inflow rather than to aneurysm obliteration (“a flow diverter is not a pressure diverter”) [34]—patients managed using FD stents in the acute phase after aneurysmal SAH are still at risk for early rebleeding.

Possible strategies to circumvent the problem of dual anti-platelet medication for FD treatment in acutely ruptured aneurysms include (1) techniques of intra-aneurysmal FD and (2) staged procedures consisting of partial protective coiling of the aneurysm dome in the acute phase followed by later definitive FD treatment. Such staged procedures were both safe and effective in a recent series of 31 patients with acutely ruptured intracranial aneurysms [35].

Unexplained cases of early post-interventional hemorrhages after FD treatment—occurring also in initially unruptured aneurysms and with often fatal consequences under dual anti-platelet medication—may also be explained by intrasaccular processes of active thrombus formation and degradation affecting the integrity of the aneurysm wall [36–38]. These mechanisms remain speculative, however, since any residual flow within the aneurysm may per se trigger further aneurysm growth or rupture [39]. In line with these findings, a recent study demonstrated significantly improved occlusion rates in absence of post-interventional hemorrhages in patients undergoing FD stenting in conjunction with concomitant coiling when compared to FD treatment alone (88.9% versus 61.5% complete occlusion rate, respectively) [31].

Similar mechanisms may trigger early giant aneurysm growth after FD treatment. A recent retrospective study found that 6 out of 45 aneurysms managed by FD stenting had increased >20% in size during the first 6 months and produced symptoms of intracranial mass-effect [36]. Since other

sources indicate that all aneurysms that underwent FD stenting either collapsed completely (in 90% of cases) or decreased significantly in size (in 10% of cases) between 6 and 18 months after the intervention, it is likely that the aforementioned mechanisms of post-FD stenting aneurysm expansion are transient in nature [38].

A recent study reported a 95.2% complete occlusion rate in complex internal carotid artery aneurysms undergoing FD stenting in absence of hemorrhagic or ischemic cerebrovascular events [28]. In the same patient cohort, the complete aneurysm occlusion rate after 180 days was 73.6% [28, 40]. Other reports have demonstrated complete aneurysm occlusions in as many as 76% of the giant aneurysms treated using FD stents. This success, however, came at the cost of comparably higher treatment morbidities when compared to those of conventional coil embolization. In detail, the reported procedure-related mortality was 5% and the overall ischemic stroke rate was 6%. Perforator strokes occurred in 3% and patients with posterior circulation aneurysms were more likely to be affected. In basilar artery aneurysms, perforator territory strokes were encountered in 14% [41]. The rates of post-procedural SAH or parenchymal hemorrhage were 3% each [29]. Aneurysm morphology may further influence the success of FD treatment. Recent data indicate that permanent complete aneurysm occlusion is less likely in aneurysms incorporating arterial side branches, i.e., in lesions where major arteries arising from the aneurysm are jailed during FD stent placement [42]. It should therefore be pointed out that the clinical safety of FD devices is still in a process of being defined [23]; e.g., a multicenter randomized care trial and registry was recently halted due to safety and efficacy concerns [43].

Deconstructive Techniques

Deconstructive measures are indicated only in those cases where reconstructive treatment of cerebral aneurysms is impossible or associated with unacceptable treatment morbidities. As previously mentioned, these strategies include [10, 44] therapeutic surgical or endovascular parent artery occlusion (PAO), PAO in conjunction with flow replacement bypass surgery, as well as techniques of flow modification (e.g., deliberate basilar trunk occlusion to induce flow reversal for the management of otherwise untreatable very large and giant basilar apex aneurysms).

Parent Artery Occlusion

As demonstrated in Fig. 2a–c, PAO relies on competent crossflow via anterior and posterior communicating artery collaterals as well as leptomeningeal anastomoses. The

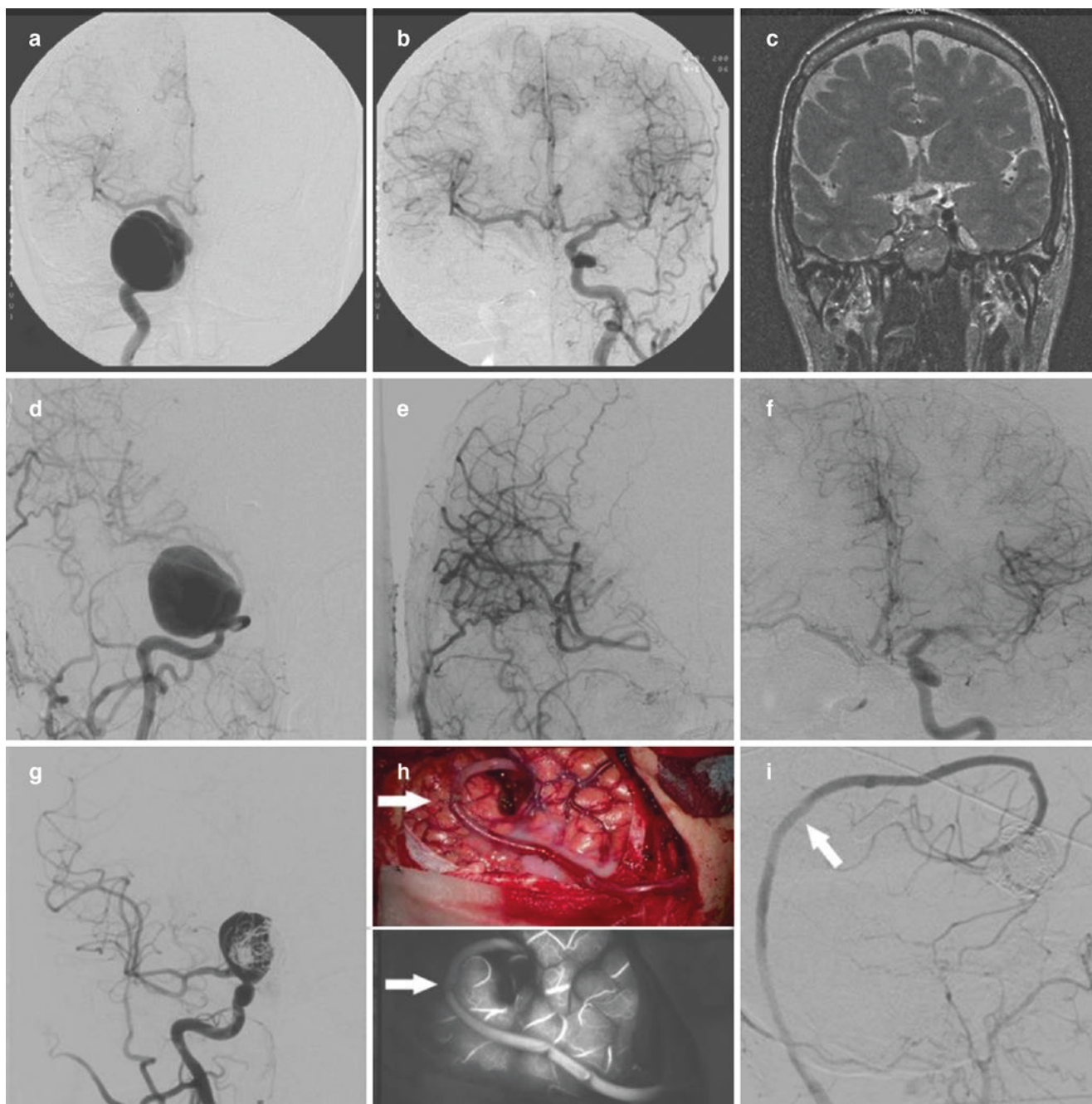


Fig. 2 Deconstructive surgical and endovascular techniques. (a–c) Parent artery occlusion. Right ICA angiograms (a) demonstrate a giant intracavernous ICA aneurysm that exerted local mass effect and resulted in complete right-sided ophthalmoplegia. The patient was managed by endovascular parent artery occlusion after successful balloon test occlusion. Left ICA angiograms (b) depict sufficient crossflow via the anterior communicating artery to supply the right hemisphere after therapeutic parent artery sacrifice (b). The intracavernous giant aneurysm decreased in size significantly as depicted on follow-up MRIs (c) and the patient’s ophthalmoplegia gradually resolved over time (A.G., procedure performed at the Medical University Vienna). (d–f) Parent artery occlusion under low-flow bypass protection. Right ICA angiograms demonstrate a giant intracavernous ICA aneurysm (d) that became symptomatic by local cranial nerve compression and manifested in partial oculomotor nerve palsy. The patient was managed by

STA–MCA double-barrel low-flow bypass revascularization (e) 48 h before successful awake balloon test occlusion and subsequent endovascular parent artery occlusion. The bypass in conjunction with pre-existent anterior communicating artery crossflow (f) was sufficient to revascularize the right hemisphere after therapeutic endovascular parent artery sacrifice (A.G., procedure performed at the Medical University Vienna). (g–i) Parent artery occlusion under venous high-flow bypass protection. Right ICA angiograms depict a partially coiled, recurrent very large aneurysm of the right ICA at the branching site of the superior hypophyseal artery, exerting progressive optic nerve compression and resulting in right-sided visual loss (g). The patient was managed by saphenous vein high-flow bypass revascularization (h, i) followed by parent artery occlusion during the same procedure. The patient recovered gradually but never regained vision in her right eye (A.G., procedure performed at the Kepler University Hospital Linz)

safety and feasibility of this strategy is assessed during balloon test occlusions [BTO] in the awake patient prior to definitive surgical or endovascular vessel sacrifice. Many surgeons, however, prefer revascularization in all cases that require major vessel sacrifice [44]. PAO is often followed by a significant reduction of aneurysm size and alleviation of aneurysmal compressive mass effect (Fig. 2a–c).

Parent Artery Occlusion in Conjunction with Bypass Surgery

In the vast majority of the cases, however, spontaneous collateral crossflow is inadequate to provide sufficient hemispheric blood flow distal to the point of PAO. In these cases, cerebral revascularization is required prior to PAO. Generally speaking, cerebral bypasses can be stratified according to their function (flow replacement bypass, flow augmentation bypass), their donor grafts (pedicled, interpositional, in situ), the sites of anastomosis (extracranial [EC]–intracranial [IC], EC–IC) and the flow provided (low-, intermediate-, and high flow) [44]. The revascularization technique selected for flow replacement bypass surgery in the management of intracerebral aneurysms depends on the treatment strategy chosen. In cases in which bypass surgery is performed in conjunction with surgical PAO during the same procedure (i.e., cases where neurologic assessment of the awake patient is not possible), high-flow bypass surgery is usually performed. It is reasonable to “oversize” the bypass rather than to face ischemic complications due to insufficient low-flow bypass revascularization (Fig. 2g–i). In those cases, however, where the therapeutic strategy involves cerebral revascularization 1–2 days ahead of BTO and endovascular PAO, other bypass techniques (i.e., double barrel STA–MCA bypass in cases of anterior circulation aneurysms, OA–PCA or OA–PICA bypasses in cases of posterior circulation aneurysms) may be justified. The senior author has successfully performed this technique in over 40 cases (Fig. 2d–f). Anterior and posterior communicating artery crossflow as well as leptomeningeal collaterals frequently contribute further to post PAO hemispheric revascularization.

The occlusion rates reported with indirect aneurysm treatment are high. A recent series described the management of 82 patients with complex intracranial aneurysms using both EC–IC and IC–IC bypasses and reported aneurysm obliteration rates of over 97% with low treatment-related morbidities [9]. Aneurysms managed by PAO in conjunction with bypass revascularization usually shrink in size over time. A recent multi-center study observed an average delayed volume reduction of 55.2% in giant aneurysms treated by PAO and bypass revascularization [1].

Whereas revascularization of multiple vascular territories distal to the site of PAO is usually easily obtained using

the STA–MCA double-barrel technique (e.g., temporal and frontoparietal territories in cases of M1/M2 bifurcation aneurysms), this may be difficult in cases of—single-barrel—high-flow revascularization. Recent publications have reported a multiple reimplantation technique for the reconstruction of complex and giant MCA bifurcation aneurysms, where the efferent M2 branches are serially reimplanted into the saphenous vein donor graft [45]. The technical nuances of indirect surgical aneurysm occlusion were addressed in a recent publication, describing 18 different bypass strategies for the treatment of 30 complex MCA aneurysms, all managed with excellent surgical and clinical results [16].

Perforator occlusion in conjunction with PAO-induced thrombosis is always a major concern. A recent case series describing the management of 141 giant aneurysms reported thrombotic occlusion of perforators or branching arteries in 7% of the aneurysms receiving indirect treatment [10]. In those cases, where complete surgical trapping or endovascular coil embolization of the aneurysm is impossible due to delicate perforator anatomy, proximal or distal occlusions may be performed. This strategy relies on intra-aneurysmal flow modification to reduce the risk of aneurysm rupture, to induce slow aneurysm thrombosis, and to preserve flow into the perforating branches [10, 46]. In some cases, however, postoperative aneurysm ruptures with devastating consequences have been reported with this technique [47].

Periprocedural ischemia due to prolonged temporary clipping times while suturing the anastomosis is another important issue. The larger the caliber of the donor graft (i.e., during high-flow bypass surgery), the larger—and thus more proximal—the recipient artery should be. In turn, the more proximal the recipient artery, (1) the larger the vascular territory rendered ischemic during temporary clipping for suturing the anastomosis, and (2) the more difficult and usually time-consuming the suturing of the anastomosis will be. To overcome this problem, the technique of excimer laser-assisted non-occlusive anastomosis [ELANA] bypass was introduced to provide high-flow revascularization without cross-clamping related distal ischemia or stroke. The role of this technique, usually reserved for the most challenging lesions, is still in a process of being defined [44, 48]. In many cases, originally considered suitable for the ELANA procedure, FD stenting and other innovative reconstructive endovascular techniques have proven effective as well.

Conclusion

Very large and giant intracranial aneurysms are among the most challenging pathologies in neurosurgery. Patients harboring such lesions should be managed at high-volume cerebrovascular centers by multidisciplinary teams trained in all techniques of open and endovascular neurosurgery.

In view of the poor natural history, active management using multiprofessional individualized approaches [4, 6, 7, 9–11, 15, 16, 44–46, 48–50] is required to achieve complete aneurysm occlusion, relief of mass effect, and obliteration of the embolic source with acceptable treatment morbidities [7]. Microsurgical and endovascular techniques are complementary rather than competitive strategies that can ideally be combined in hybrid procedures. Both microsurgery [6, 7, 15, 16] and neurointervention are still improving in technique and outcome. With an increasing endovascular caseload, neurosurgeons working in the field of cerebrovascular disease may find themselves in a “low case scenario” in the near future, where innovative strategies of surgical training—including haptic and virtual models of simulation [51]—will be of major importance to maintain the current levels of technical skill and procedural quality.

Conflict of Interest The authors declare that they have no conflict of interest or a financial disclosure.

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Computational Fluid Dynamics for Cerebral Aneurysms in Clinical Settings

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Introduction

Computational fluid dynamics (CFD) is a computational science which connects experiment and theory. Therefore, it is important to understand the need of validation and verification of CFD for cerebral aneurysms when the hemodynamic results are applied to surgical decision-making in clinical settings.

CFD for a cerebral aneurysm using the patient-specific geometry model was first reported by DA Steinman et al. in 2003 [1], and it has been revealing that hemodynamics contributes to understanding aneurysm pathology including initiation, growth, and rupture [2–10]. On the other hand, CFD has not permeated into a clinical setting of cerebral aneurysms due to several limitations including analysis time and complicated process. Therefore, we present our practical application of CFD for the treatment planning of cerebral aneurysms.

CFD Process for Cerebral Aneurysms

The CFD process for cerebral aneurysms is the following [2, 11, 12]: the digital imaging and communication in medicine (DICOM) datasets of 3D CT angiography and 3D rotational angiography are loaded into Mimics Innovation Suite

(Materialise Japan, Kanagawa, Japan) to extract aneurysm geometry as stereolithography (STL). The STL file is integrated into 3-matic (Materialise Japan, Kanagawa, Japan) and geometry in the region of interest is segmented. In addition, the geometry is remeshed by a triangle measuring 0.25 mm at the maximum length for correction of a distortion comprising the STL. The fluid domain is meshed using ANSYS ICEM CFD (ANSYS Inc. Canonsburg, Pennsylvania) to create tetrahedral elements that are established as 0.6 mm at maximum and 0.1 mm at minimum using the Octree's method. On the geometry surface, six prism layers are added with total heights of 0.148 mm. The inlet is prolonged vertically at the surface to establish fully developed laminar flow according to Poiseuille's law.

Numerical modeling is performed using ANSYS CFX (ANSYS Inc. Canonsburg, Pennsylvania). For the fluid domain, 3D laminar flow fields are obtained by solving the continuity and Navier-Stokes equations, and discretization is made by the finite volume method. Blood is assumed to be an incompressible Newtonian fluid with a density of 1056 kg/m³ and a viscosity of 0.0035 Pa s. Typical flow waveform of phase-contrast MR imaging is scaled to the inlet and a flow rate is proportional to achieve a physiological wall shear stress (WSS). Traction-free boundary conditions are applied to the outlets. The time steps are 0.0001 s and transient analysis with an initial value specification is performed.

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Rupture Status

A lot of CFD studies were reported regarding the rupture status of cerebral aneurysms. Compared with unruptured aneurysms, ruptured aneurysms had significant characteristics such as low WSS [12–15], high oscillatory shear index (OSI) [12, 14], low aneurysm formation indicator (AFI) [12], prolonged relative residence time (RRT) [16], complex

flow pattern, unstable flow pattern [17], and high oscillatory velocity index [18]. Among these hemodynamic parameters, low magnitude of WSS is the most noticeable hemodynamic characteristic associated the rupture status. Since the magnitude of WSS was quantified as time-averaged value, spatial minimum and maximum values on the dome, normalized WSS and low shear area ratio, we should recognize that the distribution of low WSS would be an unchanged observation. However, comparison of the magnitude of WSS in clinical practice should be carried out as an optimal quantification. For instance, time-averaged WSS would be allowed to investigate the rupture status of multiple cerebral aneurysms in a patient with subarachnoid hemorrhage. In particular, mirror aneurysms are a useful disease model to predict the rupture site of an aneurysm. On the other hand, normalized WSS would be recommended for measuring WSS of aneurysms at different locations.

Hyperplastic Remodeling of Aneurysm Wall

Ku described OSI that was a hemodynamic parameter to evaluate fluctuation of WSS vectors in 1985 [19]. The studies using the pulsatile flow data in a Plexiglas model and intimal plaque thickness in five human carotid bifurcations revealed that oscillations in the direction of wall shear may enhance atherogenesis. Aside from OSI, RRT and AFI can also evaluate oscillation of WSS vectors. These hemodynamic parameters were examined regarding hyperplastic remodeling of aneurysm wall. Since these hemodynamic parameters showed similar distribution to high oscillatory WSS vector (Fig. 1), we can use any of these variables as the preoperative predictor of thick aneurysm wall. In addition, we should recognize that a high OSI region corresponds to a low WSS region.

The prediction of hyperplastic remodeling lesions using CFD [6, 11, 16] would contribute to avoiding intraoperative risks such as inadequate temporary clipping and obstruction of small branches (Fig. 2).

Recurrence of Coiled Aneurysms

Coil embolization of cerebral aneurysms is widely used; however, recanalization and re-treatment occur more often compared with surgical clipping. Several risk factors for recanalization and re-treatment have been reported, such as a large aneurysm, wide neck width, minor recurrence on cere-

bral angiogram early after coil embolization, and lower packing density.

A number of authors reported hemodynamic risk factors associated with coiled aneurysms. High WSS observed near the remnant neck of partially coiled aneurysms are more likely to have recanalization [20]. However, since the geometry of neck remnant is obtained only after coiling, it is impossible to predict the recurrence risk as presurgical decision-making based on this method. In a clinical setting, it is desirable that hemodynamic evaluation using presurgical geometry models can predict recanalization of coiled aneurysms. Sugiyama et al. demonstrated the correlations between the hemodynamics before coil embolization and the outcomes after treatment for basilar tip aneurysms [21]. In their study, aneurysmal inflow rate coefficient (AIRC) was calculated by the following equation:

$$\text{AIRC} = \frac{Q_a}{Q_b}$$

where Q_a and Q_b were the aneurysmal inflow rate and the basilar artery flow rate, respectively.

In 57 basilar tip aneurysms, AIRC was significantly higher in the recanalized group and correlated to the types of basilar bifurcation configuration. Although it was sensible to make a decision for coil embolization based on these findings, packing density should be considered simultaneously. Therefore, CFD using porous media modeling was developed to predict recurrence of coil embolization. Umeda et al. calculated residual flow volume (RFV) to quantify the residual aneurysm volume after simulated coiling, which has a mean fluid domain above 1.0 cm/s [22]. In 37 unruptured cerebral aneurysms, the recurrence group had significantly larger RFV than the stable group. Receiver-operating characteristic (ROC) curve analyses showed that the cut-off value of RFV was 20.4 mm³ and that the area under the ROC curve was 0.86. Although this study was retrospective, these findings could be applied to indicate a target packing density. In addition, CFD using double porous media modeling was developed to simulate stent-assisted coiling (Fig. 3) [23]. Since these porous media modeling have discrepancies between actual distribution of placed coil and expanded strut in the aneurysm, large-scale clinical studies are required to confirm the accuracy of the prediction for recurrence of coiled aneurysms.

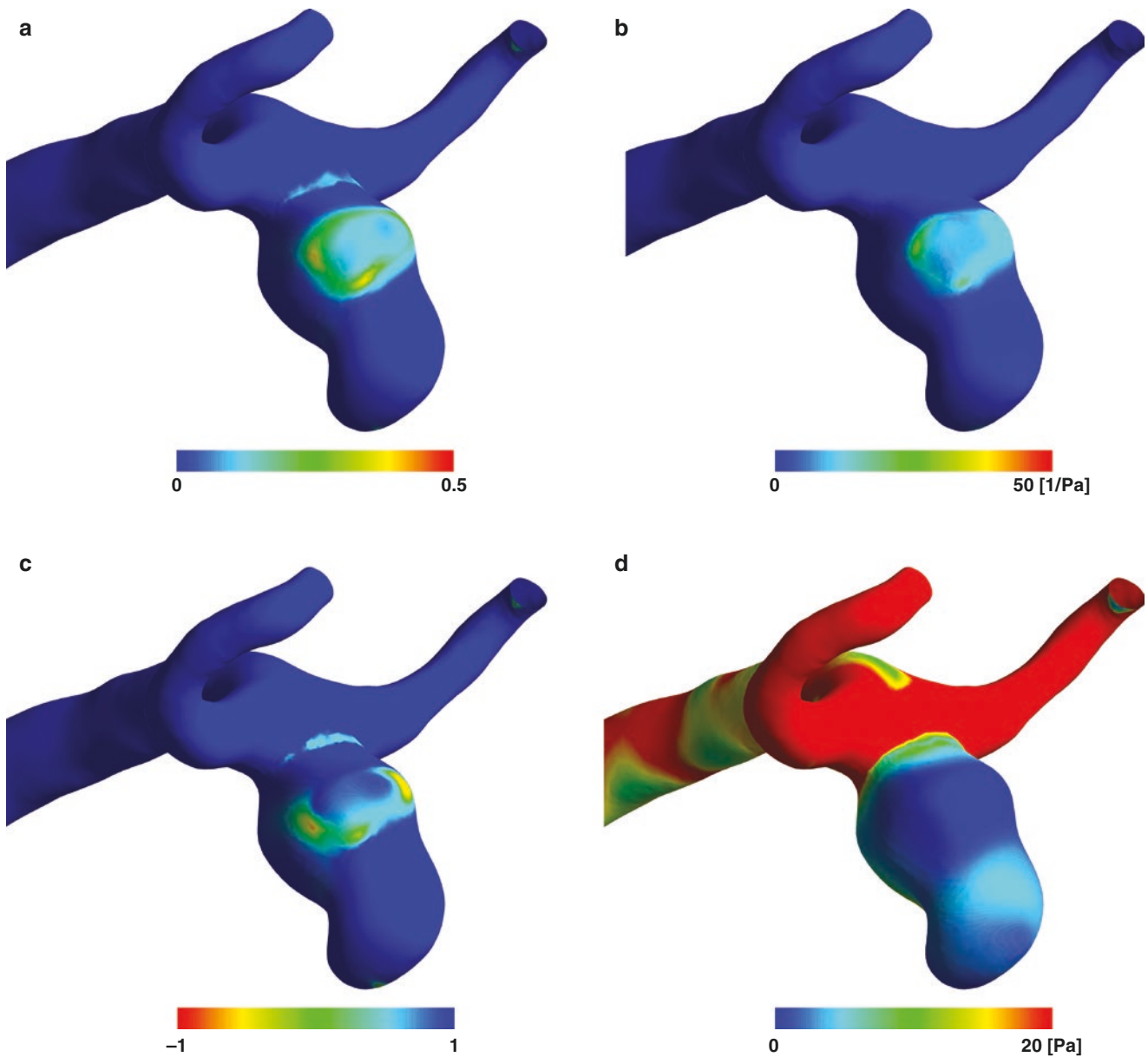


Fig. 1 Comparison of hemodynamic parameters to evaluate the fluctuation of WSS vector in a patient of ruptured middle cerebral artery aneurysm: (a) visualization of OSI, showing high OSI near the neck; (b) visualization of RRT; (c) visualization of AFI, in which low AFI has

similar distribution to prolonged RRT and low WSS; (d) visualization of WSS, in which high OSI, prolonged RRT and low AFI regions are depicted in the low WSS area

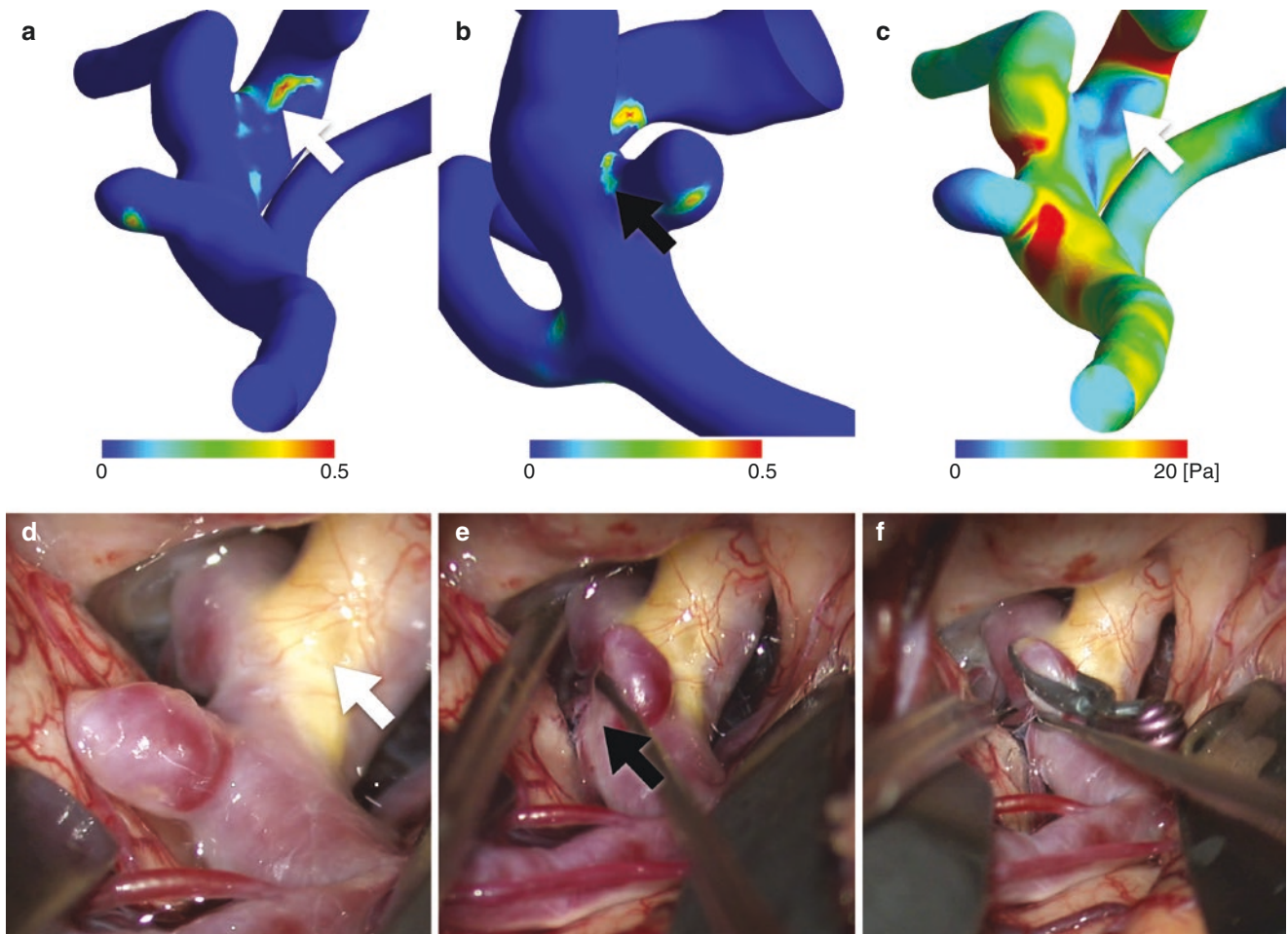


Fig. 2 Seventy-six-year-old man with unruptured left internal carotid artery-anterior choroidal artery bifurcation aneurysm: (a, b) visualization of OSI, showing high OSI at the parent artery (white arrow) and the backside of the aneurysm neck at which anterior choroidal artery arises (black arrow); (c) visualization of time-averaged WSS, showing distribution of low WSS (white arrow) which is similar to that of high OSI;

(d, e) intraoperative photography, demonstrating atherosclerotic lesions of the parent artery (white arrow) and at the backside of the aneurysm neck (black arrow), respectively, which correspond with high OSI regions; (f) aneurysm clip is applied with an intended space to keep blood flow of the anterior choroidal artery

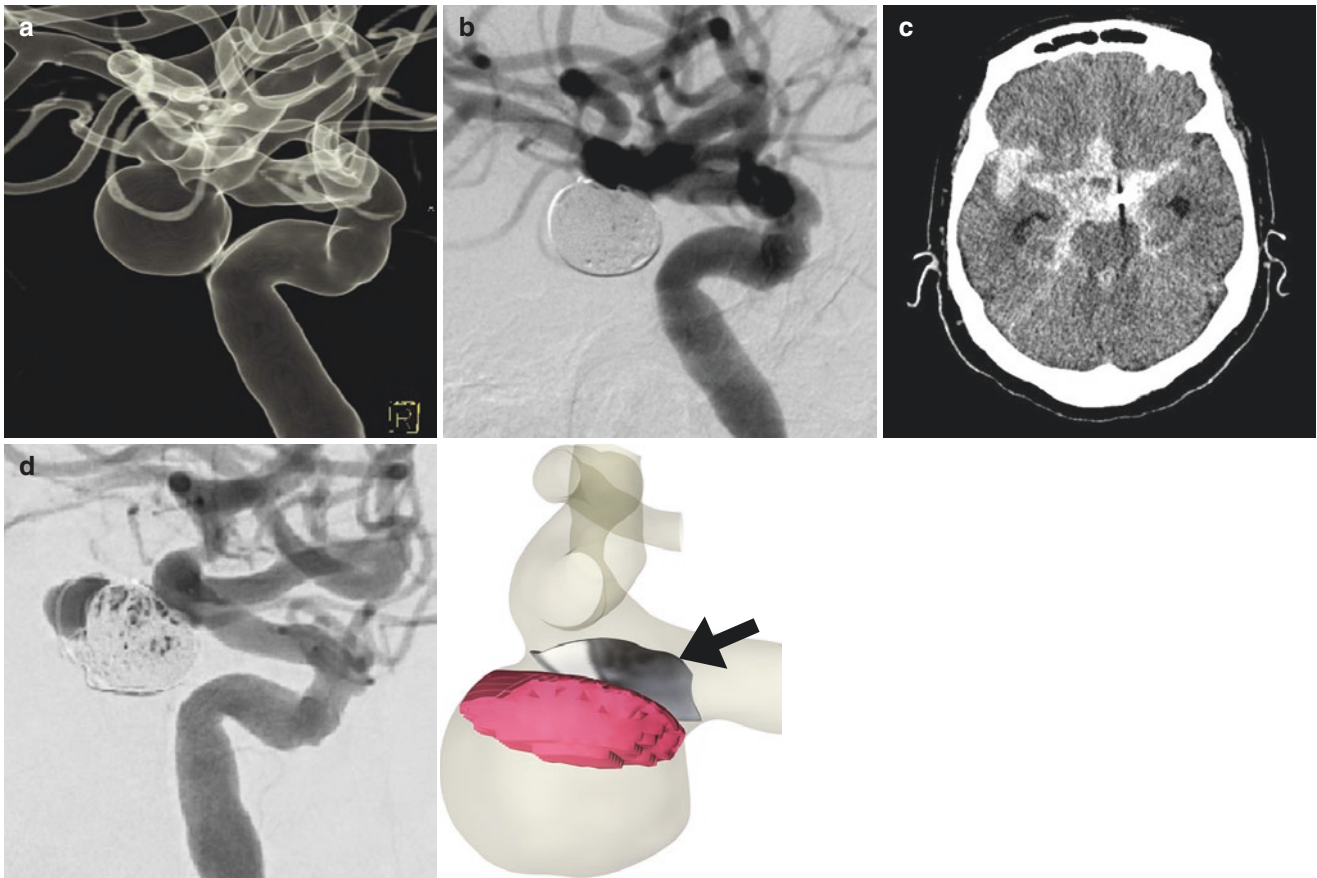


Fig. 3 Seventy-nine-year-old woman with left internal carotid artery-posterior communicating artery bifurcation aneurysm: (a) 3D surface rendering image of rotational angiography; (b) angiography after stent-assisted coiling of the aneurysm with a packing density of 35.9%; (c) head CT revealing subarachnoid hemorrhage 19 months after the coiling; (d) left internal carotid artery angiography revealing the recanalization of the coiled aneurysm; (e) retrospective CFD findings using

double porous media setting, one of which is a porous media setting for the coiled aneurysm and another of which is that for an intracranial stent (arrow), to evaluate the hemodynamic changes of stent-assisted coiled aneurysm. Residual flow volume (pink domain) is 62.3 mm^3 , which is larger than the cut-off value to predict the recurrence of coiled aneurysms

Conclusions

This review describes the practical application of CFD to treatment planning of cerebral aneurysms. Several hemodynamic parameters have valuable aspects not only in an endovascular treatment but also in a direct clipping. Although prospective trials are needed to evaluate the rupture risk of unruptured cerebral aneurysms determined using CFD, recent knowledge of hemodynamics of cerebral aneurysms would enhance the decision-making ability and precision in several clinical settings.

Conflict of Interest The authors declare that they have no conflict of interest.

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Microneurosurgical Management of Posterior Inferior Cerebellar Artery Aneurysms: Results of a Consecutive Series

Mattia Del Maestro, Sabino Luzzi, and Renato Galzio

Introduction

PICA aneurysms are rare. Their incidence accounts for 0.49–3% of all intracranial aneurysms [1–3]. However, they are most common within the posterior circulation ones after those of the basilar tip. Most are left-sided due to the prevalence of the vertebral artery. The saccular geometry is usually the most frequent, but dissecting or fusiform aneurysms are also relatively more common than in other cerebral arteries [2, 3]. PICA has a complex and variable course among all of the intracranial arteries, it has a small diameter, projecting along the brainstem and cerebellum. According to Lister et al., five segments are classically described [4]. Because of the proximity to the lower cranial nerves and frequent involvement of perforating arteries from the proximal segments, both microsurgical and endovascular treatment of PICA aneurysms are challenging.

In 1953, Rizzoli and Hayes first reported successful surgical treatment of a PICA aneurysm operated in 1947 [5, 6]. Since then, several reports on the surgical management of PICA aneurysms were published, but only a few of them were based on a large patient's cohort. The aim of this retro-

spective study is to analyze the results of 25 PICA aneurysms surgically treated, mainly focusing on the choice of the approach and technical nuances.

Materials and Methods

Between 2008 and 2018, 25 patients harboring 25 PICA aneurysms were surgically treated by the senior author (R.G.) at two institutions: San Salvatore City Hospital, L'Aquila, Italy, and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. Only patients harboring saccular aneurysms were selected and retrospectively reviewed. Aneurysms were classified according to the five PICA segments reported by Lister et al. [4]. Proximal aneurysms were defined as those arising from the vertebral artery-PICA junction to the tonsillo-medullary segment, the remnants being considered as distal. Factors affecting the choice of the approach were also analyzed. Overall neurological outcome was reported as good, moderate, severe, and death, on the basis of an mRS score of 0–2, 3–4, 5, and 6, respectively. The outcome evaluation was also reported according to the clinical onset and the involved PICA segment. The angiographic outcome was evaluated on the basis of the complete exclusion of the aneurysm at the sixth-month follow-up.

Results

Nineteen patients were females and the average age was 43 years (range 18–69). Nine patients suffered from hypertension, two from diabetes, three from hypercholesterolemia, and one from obesity. Nineteen patients were smokers. In one patient, familiar history of aneurysms was found. Admission computed tomography (CT) angiography and digital subtraction angiography (DSA) were performed by default in all patients. A contrast-enhanced MRI was performed in all large

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Table 1 Demographic and clinical presentation

Patients			
	No. of Patients [no. 25]	Ruptured aneurysms [no. 15]	Unruptured aneurysms [no. 10]
Gender			
Females	19 (76%)	11	8
Males	6 (24%)	4	2
Age: mean 43 years old (18–69)			
Comorbidities			
Hypertension	9	7	2
Diabetes	2	2	1
Hypercholesterolemia	3	2	–
Obesity	1	1	–
Smokers (76%)	19	16	3
Clinical presentation			
Ruptured Aneurysms	15		
SAH			
Hunt Hess scale I–III	11		
Hunt Hess scale IV	3		
Hunt Hess scale V	1		
Cerebellar life threatening hematoma	4		
Unruptured Aneurysms	10		
Vertigo and gait instability	3		
Asymptomatic	7		

and giant aneurysms to reveal intraluminal thromboses. In 15 aneurysms (72%) subarachnoid hemorrhage (SAH) was the onset, four of which being associated with a life-threatening cerebellar hematoma. Three giant aneurysms presented with vertigo and gait instability and seven further aneurysms were incidental. Table 1 summarizes demographics and clinical presentation data of the present series (Tab. 1) Nine aneurysms were small (<7 mm), 11 medium (7–14 mm), two large (15–24 mm) and three giant (>25 mm). Nineteen aneurysms were proximal and, among these, ten involved the VA-PICA junction. Six involved the anterior-medullary segment and three the lateral-medullary segment. Of the remaining distal aneurysms, two were located on the tonsillo-medullary segment, one on the telovelotonsillary segment, and one on the cortical segment. Peculiar patient characteristics involving PICA segment and bony anatomy were the main factors influencing the choice of approach. Far-lateral approach was the approach of choice for all proximal aneurysms, while median or paramedian suboccipital approaches were used for distal ones. An early surgery (within 24 h) was performed in all ruptured aneurysms. Since 2012, in all elective cases, intraoperative neurophysiological monitoring involving somatosensory, motor, and brainstem auditory-evoked potentials was implemented, adopting a defined protocol that is also used in all intracranial aneurysms and

brain arteriovenous malformations [7–15]. But we strongly believe that neurovascular training is the most important tool by far to improve the technique and avoid complications [16] Exclusion of the aneurysm was achieved in 23 cases treated by clipping. Two complex aneurysms underwent to an in situ PICA-PICA bypass before the trapping. Table 2 reports the overall data about the surgical management of the present series (Tab. 2). Neuronavigation and endoscope-assisted techniques were commonly employed, the latter being useful for both the aneurysms having a huge blind spot and those very close to perforating arteries. Micro-Doppler (20 MHz System, Mizuho Medical Co., Ltd., Tokyo, Japan) ultrasound-based evaluation of the flow was implemented. Indocyanine green video angiography (Flow 800 Infrared Module, OPMI Pentero 800, Zeiss, Oberkochen, Germany) and fluorescein angiography (Yellow 560 Fluorescence Module, Kinevo 900, Zeiss, Oberkochen, Germany) were also introduced since 2009 and 2018, respectively. Sixth-month postoperative DSA was available in all but one patient. Total exclusion of the aneurysm was achieved by means of a single procedure in 22 cases. In three cases, a remnant was revealed imposing a redo surgery. No recurrences occurred during the follow-up.

A good overall outcome was achieved in all but one unruptured aneurysm and in 60% of those ruptured. A moderate outcome was observed in 16% of patients, whereas a severe outcome occurred in one patient who suffered by a permanent deficit of the lower cranial nerves. One patient, having a giant ruptured proximal PICA aneurysm, died. Table 3 reports the overall outcome of the present series (Tab. 3).

Illustrative Cases

Case 1 The case of a medium VA-PICA aneurysm is reported (Fig. 1). A 35-year-old patient had an incidental finding of a left VA-PICA unruptured aneurysm after a mild traumatic brain injury (Fig. 1a). CT angiography and DSA demonstrated the involvement of PICA (Fig. 1b, c). A left far-lateral transcondylar approach was performed and the aneurysm was clipped (Fig. 1e, f). Postoperative CT angiography documented the complete exclusion of the aneurysm with a preserved flow into the left PICA (Fig. 1g). Patient had a good recovery (mRS 1).

Case 2 The case of a giant distal PICA aneurysm is reported (Fig. 2). A 64 years-old patient suffering from a severe headache and dizziness underwent to an MRI showing a giant thrombosed aneurysm causing a right cerebellar compression (Fig. 2a). CT angiography and DSA demonstrated the involvement of the distal PICA (Fig. 2b, c). A median suboc-

Table 2 Overall data of the surgical management

Aneurysms			
	Aneurysms no.	Approach	Treatment
Size			
Small (<7 mm)	9		9 Clipping
Medium (7–14)	11		11 Clipping
Large (15–24)	2		1 Clipping 1 Trapping + PICA-PICA by-pass
Giant (>25 mm)	3		2 Clipping 1 Trapping + PICA-PICA by-pass
Anatomical distribution			
VA-PICA	10	Far lateral	
Anterior medullary	6	Far lateral	
Lateral medullary	3	Paramedian suboccipital	
Tonsillomedullary	2	Paramedian suboccipital	
Telovelotonsillary	1	Median suboccipital	
Cortical	1	Median suboccipital	

Table 3 Overall patient outcomes

mRS	Ruptured aneurysms		Unruptured aneurysms	
	Proximal	Distal	Proximal	Distal
0	–	1	3	1
1	2	3	4	–
2	4	1	–	–
3	3	–	1	–
4	1	–	–	–
5	1	–	–	–
6	1	–	–	–

cipital approach was performed and the aneurysm was clipped after thrombectomy, the indocyanine green video angiography confirmed the patency of the PICA (Fig. 2d–g). Postoperative CT and CT angiography documented the complete exclusion of the aneurysm (Fig. 2h, i). Patient had a good recovery (mRS 0).

Discussion

Historically speaking, posterior circulation aneurysms were always considered a tough dare for surgeons. In 1829, Cruvelhier reported the first description of a spherical aneurysm arising from the PICA-vertebral junction [17]. Afterward, in 1854, Fernet reported the first case of a distal PICA aneurysms [1]. The rarity of PICA aneurysms justifies the few large series reported [18–21]. Still today, with 146 cases, that of Peerless and Drake remains the largest ever reported series about PICA aneurysms. In these aneurysms, the need for treatment is dictated by their high risk of rupture, high mortality, and the usual younger age of the affected patients [19]. The mean reported age range is from 44.6–51 years [22, 23]. The average age was slightly lower in the present series, with a prevalence of female sex.

Interestingly, all but one of the distal aneurysms were ruptured, three of which of small size. Indeed, as already reported

about distal aneurysms at all, this aspect has to be probably related to the thinner walls of the distal ones [24–26]. The well-known risk of rebleeding of ruptured PICA aneurysms, up to 78%, imposes an early treatment. In this series, all hemorrhagic patients underwent surgery within 24 hours and, for patients with an impending-life hematoma, the indication for surgery was mainly based upon an evidence-based management algorithm about intracerebral hemorrhages reported by our group [27]. Regardless of the clinical onset, all the patients underwent CTA and DSA. A 4- or 6-vessel DSA is recommended for all PICA aneurysms, depending by the need for flow replacement, is recommended for all PICA aneurysms, also because of the well-known risk to miss very distal ones [28]. Indeed, one of the authors reported a very rare case of an extra-cranial small aneurysm of the PICA which was initially missed by CT angiography. The labyrinth of neurovascular bundles present in the posterior fossa makes the surgical exposure of PICA aneurysms really challenging. A careful preoperative evaluation of the patient’s vascular and bony anatomy is needed to tailor any approach, especially to assess the relationships between VA-PICA complex, the jugular tubercle, and the occipital condyle. The choice of the correct surgical approach has to be considered the crossroads in the microsurgical treatment of these aneurysms. In this series, 19 proximal aneurysms were exposed through a far-lateral approach without drilling of the condyle in most cases. Conversely, Bertalanffy et al. used the transcondylar approach as a rule [29]. Ambrosio et al. suggest the routine use of the extreme-lateral approach to reach the proximal PICA from a corridor remaining below the lower cranial nerves [30].

In the elective treatment of proximal PICA aneurysms, the use of the endoscope as an adjuvant tool has to be considered. Our group have already stressed the importance of endoscope-assisted techniques in the treatment of several neurosurgical pathologies [31, 32], but particularly in aneurysm surgery where, often, the endoscope view allows sparing perforating branches within blind spots.

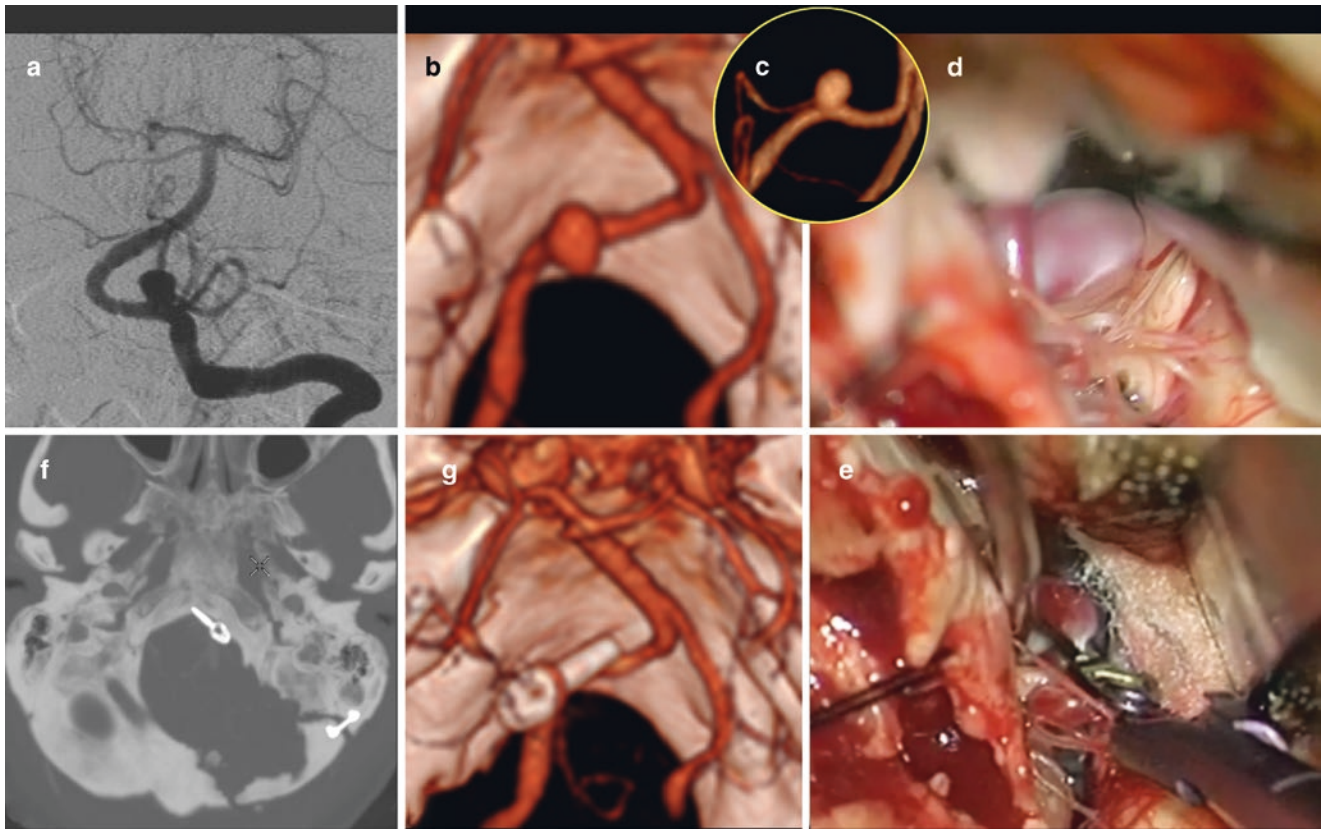


Fig. 1 CT angiography and DSA revealing a VA-PICA unruptured regular aneurysm (a–c). Left far-lateral transcondylar approach and clipping of the aneurysm (d, e). Postoperative CT and CT angiography documenting the complete exclusion of the aneurysm with a preserved flow into the left PICA (f, g)

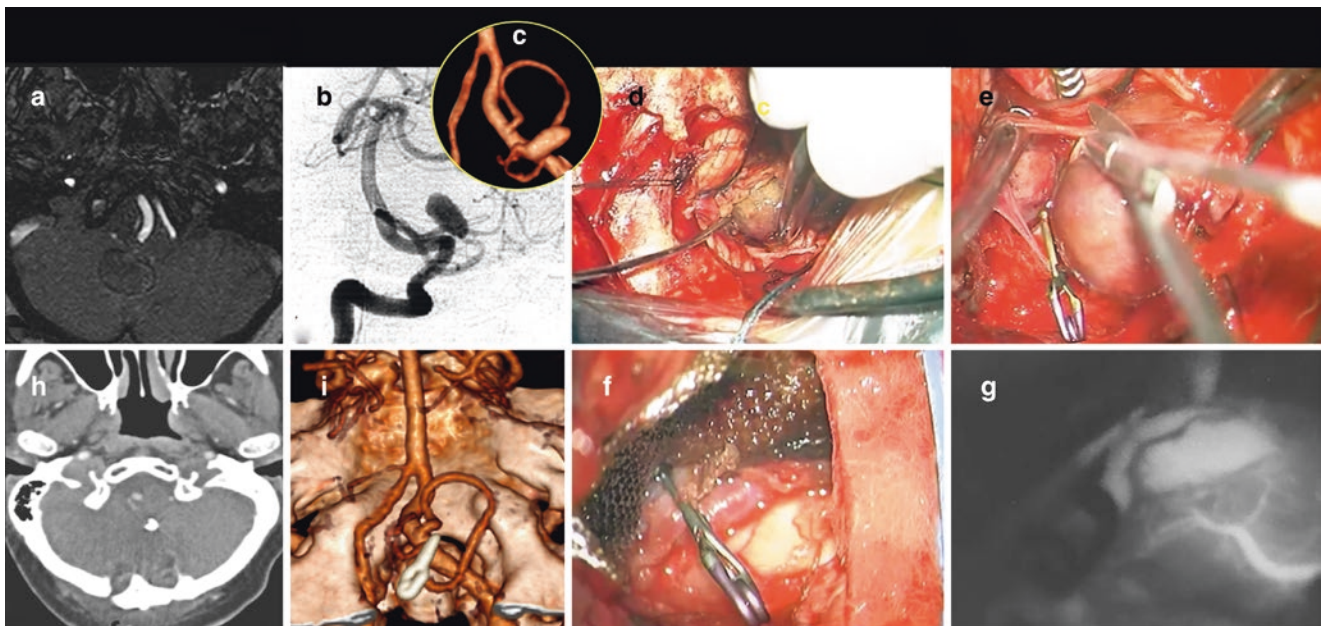


Fig. 2 MRI angiography showing a giant thrombosed aneurysm causing a right cerebellar compression (a). CT angiography and DSA demonstrating the involvement of the distal PICA (b, c). Median suboccipital approach, exposure of the thrombosed aneurysm, dissection, clipping and virtual videoangiography with indocyanine green (d–g). Postoperative CT and CT angiography documenting the complete exclusion of the aneurysm (h, i)

The six aneurysms arising from the distal PICA were approached by a median or paramedian suboccipital craniotomy according to the length and the tortuosity of PICA.

The results of the present series, although made up of 25 cases, endorse the prominent role of microneurosurgery for PICA aneurysms, both proximal and distal, especially in young patients. In experienced hands, direct clipping allows for a definitive and durable exclusion of the aneurysm. Outcomes are strictly related to the preoperative neurological status.

The charm of PICA aneurysms is strictly related to the high anatomical variability of this artery and to their rarity. Surgeons who want to deal with them must have a deep knowledge of skull base approaches, vascular anatomy, and a profound familiarity with all the microsurgical techniques of vessel reconstruction.

Ethical Approval This study was approved by the Internal Advisory Board.

Conflict of Interest Statement The authors declare that they have no conflict of interest.

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Posterior Circulation Aneurysms: A Critical Appraisal of a Surgical Series in Endovascular Era

Sabino Luzzi, Mattia Del Maestro, and Renato Galzio

Introduction

Posterior circulation aneurysms have a worse natural history than anterior aneurysms, mainly because of their higher risk of rupture and poor outcome [1]. This aspect imposes the need for treatment in most cases, especially in younger patients. The advent of the endovascular era and its constant refinement through the continuous improvement of the devices has dramatically changed the treatment standard for many but not all of the posterior circle aneurysms. Exceptions are aneurysms involving the distal segments of the cerebellar arteries, most basilar tip aneurysms, and the giant ones for which microneurosurgery remains a rational option. The aim of this study is a critical appraisal of the overall results of a retrospective surgical series aimed to identify those posterior circulation aneurysms for which microneurosurgery still today maintains a key role.

Materials and Methods

Collected data concerned demographics, clinical onset, the prevalence of site and size, approaches, and outcome of 149 patients surgically treated because they harbored one or more posterior circulation aneurysms have been retrospectively reviewed. All the patients were operated on by the senior author (RG) in three different hospitals over a period of 28 years between January 1990 and December 2018. Aneurysms were classified as proximal and distal. The proximal ones involved vertebral artery (VA), basilar artery (BA), and the proximal segments of the posterior cerebral artery (PCA) and cerebellar arteries. The remaining sites were considered as distal. For outcome evaluation, the patients were divided in to two groups: <65 and ≥ 65 years old. The Angiographic outcome was evaluated based on the complete exclusion of the aneurysm at a six-month follow-up. The Neurological overall outcome was reported according to patients' age, clinical onset, and site, and size of the aneurysms. Glasgow Outcome Score (GOS) 1 and 2 were considered as "good recovery," whereas GOS 3, 4, and 5 were considered as "moderate disability," "severe disability," and "death-vegetative state," respectively.

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Results

Patients Demographics and Clinical Data

Average patient age was 56.7 ± 14.2 years. Admission contrast-enhanced computed tomography (CT) angiography was the rule for all patients. Preoperative digital subtraction angiography (DSA) was performed in all unruptured or complex aneurysms. In elective cases, the need for a balloon test occlusion (BTO) was assessed on a case-by-case basis. A contrast-enhanced MRI was performed in all very large and giant aneurysms to reveal

Table 1 Site and Size Prevalence of Posterior Circulation Aneurysms

Site		N (%)	Size			
			Small (7 mm) N (%)	Regular (7–12 mm) N (%)	Large (13–24 mm) N (%)	Giant (25 mm) N (%)
Proximal	Basilar tip + PCA (P1) + SCA	91 (58%)	17 (18.7%)	57 (62.6%)	7 (7.7%)	10 (11%)
	Midbasilar trunk + proximal AICA	9 (5.7%)	2 (22.2%)	4 (44.4%)	2 (22.2%)	1 (11.1%)
	VB Junction	10 (6.4%)	2 (20%)	5 (50%)	2 (20%)	1 (10%)
	VA (V4) + proximal PICA (anterior + lateral medullary segment)	27 (17.2%)	5 (18.5%)	16 (59.3%)	3 (11.1%)	3 (11.1%)
Distal	PCA (P2-P3)	7 (4.5%)	1 (14.3%)	2 (28.6%)	1 (14.3%)	3 (42.9%)
	Distal SCA	3 (1.9%)	–	1 (33.3%)	1 (33.3%)	1 (33.3%)
	Distal AICA	4 (2.5%)	2 (50%)	1 (25%)	–	1 (25%)
	Distal PICA (tonsillo-medullary + telovelotonsillar + cortical segment)	6 (3.8%)	–	2 (33.3%)	2 (33.3%)	2 (33.3%)
Tot.		157	29 (18.5%)	88 (56.1%)	18 (11.5%)	22 (14%)

PCA (P1) proximal segment of the posterior cerebral artery, SCA superior cerebellar artery, AICA anterior inferior cerebellar artery, VB junction, vertebro-basilar junction, VA (V4) intradural segment of the vertebral artery, PICA posterior inferior cerebellar artery, PCA (P2-P3) distal segments of the posterior cerebral artery

eventual intraluminal thromboses. In 98 patients, a hemorrhagic onset occurred. The Average admission Hunt-Hess score was 2.17 ± 0.8 and the mean Fisher grade was 1.9 ± 0.8 . One hundred thirty-seven aneurysms were classified as proximal and 20 as distal. Table 1 reports the prevalence of proximal and distal posterior circulation aneurysms according to site and size (Table 1). About ruptured aneurysms—apart from rare cases of young patients having an impending life hematoma, for whom the indication for surgery was based mainly upon an evidence-based management algorithm about intracerebral hemorrhages reported by our group [2]—mainly patients with an admission Hunt-Hess score of 1–3 underwent surgery. In 92% of cases, an early surgery (within 24 h) was performed. One hundred fifty-seven aneurysms were consecutively operated on; six patients had two aneurysms and one patient harbored three different aneurysms. In three cases, two different procedures were performed on the same patient. A total of 152 procedures were performed.

Surgery

Approach Selection

Approaches were selected according to site and angioarchitecture. Pterional and cranio-orbital approaches were utilized to basilar tip, proximal (P1) PCA, and superior cerebellar artery (SCA). For these aneurysms, pterional approach was usually “extended” to comprehend wide drilling of the lesser sphenoid wing, a large opening of the sylvian fissure, an extradural or intradural anterior clinoidectomy, and an intradural posterior clinoidectomy. Cranio-orbital corridors were preferentially employed in large

and giant aneurysms. Al-Mefty’s combined petrosal approach [3] was employed for the midbasilar trunk and proximal anterior inferior cerebella artery (AICA). The Far-lateral retrocondylar approach was the corridor of choice for aneurysms involving VB junction, VA, and the proximal PICA, although the transcondylar variant was rarely necessary. Regarding the distal localizations, a subtemporal trans-tentorial approach was commonly used to treat P2-P3 PCA aneurysms. Conversely, aneurysms involving the distal segments of AICA, SCA, and PICA were elegantly treated by a retrosigmoid route.

Direct vs. Indirect Treatment

In all but three aneurysms a direct treatment was possible. A total of 128 aneurysms were successfully clipped. Trapping was the solution to aneurysms that were not amenable for clipping, under two conditions: if the patient tolerated the BTO, and the aneurysms were far distal having no need for revascularization. In one elective case of complex giant posterior projecting basilar tip aneurysm, an extracranial to intracranial (EC-IC) occipital artery (OA)—right P3 PCA bypass, with a radial artery graft, was performed. In two other elective patients, an intracranial to intracranial (IC-IC) PICA-PICA in situ bypass was carried out preceding, in both cases, the trapping of a complex VB junction aneurysm. Table 2 reports the types of treatment and the surgical techniques comprehensively employed in the current series (Table 2).

Temporary Clipping and Neurophysiological Monitoring

In the present series, the anesthesia protocol used by our group was specifically designed to allow the intraoperative neurophysiological monitoring during neurovascular surgery

Table 2 Type and Prevalence of the Employed Surgical Techniques

Type of treatment	Technique	N (%)
Direct	Clipping	128 (81.5%)
	Trapping	19 (12.1%)
	Wrapping	7 (4.5%)
Indirect	OA-P3 PCA bypass	1 (0.6%)
	PICA-PICA bypass	2 (1.3%)
Tot.		157

OA occipital artery, P3 PCA P3 segment of the posterior cerebral artery, PICA-PICA posterior-inferior cerebellar artery to posterior-inferior cerebellar artery side to side in situ by pass

and was the same as employed for brain arteriovenous malformations and giant aneurysms in general [4–13]. A combined somatosensory-motor-brainstem auditory evoked potentials and EEG-based intraoperative neurophysiological monitoring were implemented in 2012. Neurophysiological Monitoring was performed in all proximal or complex aneurysms electively treated.

Technological Adjuvants and Flow Assessment Techniques

Neuronavigation and endoscope-assisted techniques were commonly employed, the latter being useful for both the aneurysms having a huge blind spot and those very close to perforating arteries. Since 2007, a micro-Doppler (20 MHz System, Mizuho Medical Co., Ltd., Tokyo, Japan) ultrasound-based evaluation of the flow was implemented. Indocyanine green video angiography (Flow 800 Infrared Module, OPMI Pentero 800, Zeiss, Oberkochen, Germany) and fluorescein angiography (Yellow 560 Fluorescence Module, Kinevo 900, Zeiss, Oberkochen, Germany) were introduced in 2009 and 2018, respectively.

Neurological Outcome

The best outcome was achieved in patients <65 years old harboring an unruptured aneurysm. Table 3 reports the overall outcome according to the clinical onset and patient age (Table 3). The best results were also observed in small-to-regular aneurysms involving basilar tip, distal branches of the cerebellar arteries, VA, and the proximal PICA. Figures 1 and 2 report the overall patient outcomes in proximal and distal aneurysms, respectively, according to their site and size (Figs. 1 and 2).

Angiographic Outcome

Six-month postoperative angiography was available in all but 17 patients. If no remnants were revealed at the first postoperative angiography, patients underwent a CT angiography for further annual follow-ups.

In 88.5% of patients, total exclusion of the aneurysms was achieved using a single procedure. In three cases, a remnant was revealed, causing a redo surgery. Along with an average follow-up of 67.1 ± 61 months, no recurrences occurred.

Illustrative Case

The case of a left giant VA-PICA aneurysm is reported (Fig. 3). A 42-year-old patient suffering from long-lasting dizziness underwent a contrast-enhanced MRI that showed a left giant VA causing a brainstem compression (Fig. 3a). CT angiography and DSA demonstrated the involvement of PICA (Fig. 3b, c). No crossflow was revealed by BTO (Fig. 3d). A left far-lateral retrocondylar approach was performed and the aneurysm was clipped using stacking-seating technique (Fig. 3e, f). Postoperative DSA documented the complete exclusion of the aneurysm with a preserved flow into the left PICA (Fig. 3g). The patient had a good recovery (GOS 5).

Table 3 Patients' overall outcome according to the clinical onset and the patients' age

Outcome	Clinical onset		Patients' age	
	Hemorrhagic	Non-hemorrhagic	<65 years-old	≥65 years-old
Good Recovery [No. of patients (%)]	80 (81.6%)	45 (88.2%)	66 (83.5%)	33 (47.1%)
Moderate disability [No. of patients (%)]	4 (4.1%)	2 (3.9%)	8 (10.1%)	14 (20%)
Severe disability [No. of patients (%)]	3 (3.1%)	1 (2%)	1 (1.3%)	9 (12.9%)
Death-vegetative state [No. of patients (%)]	11 (11.2%)	3 (5.9%)	4 (5.1%)	14 (20%)

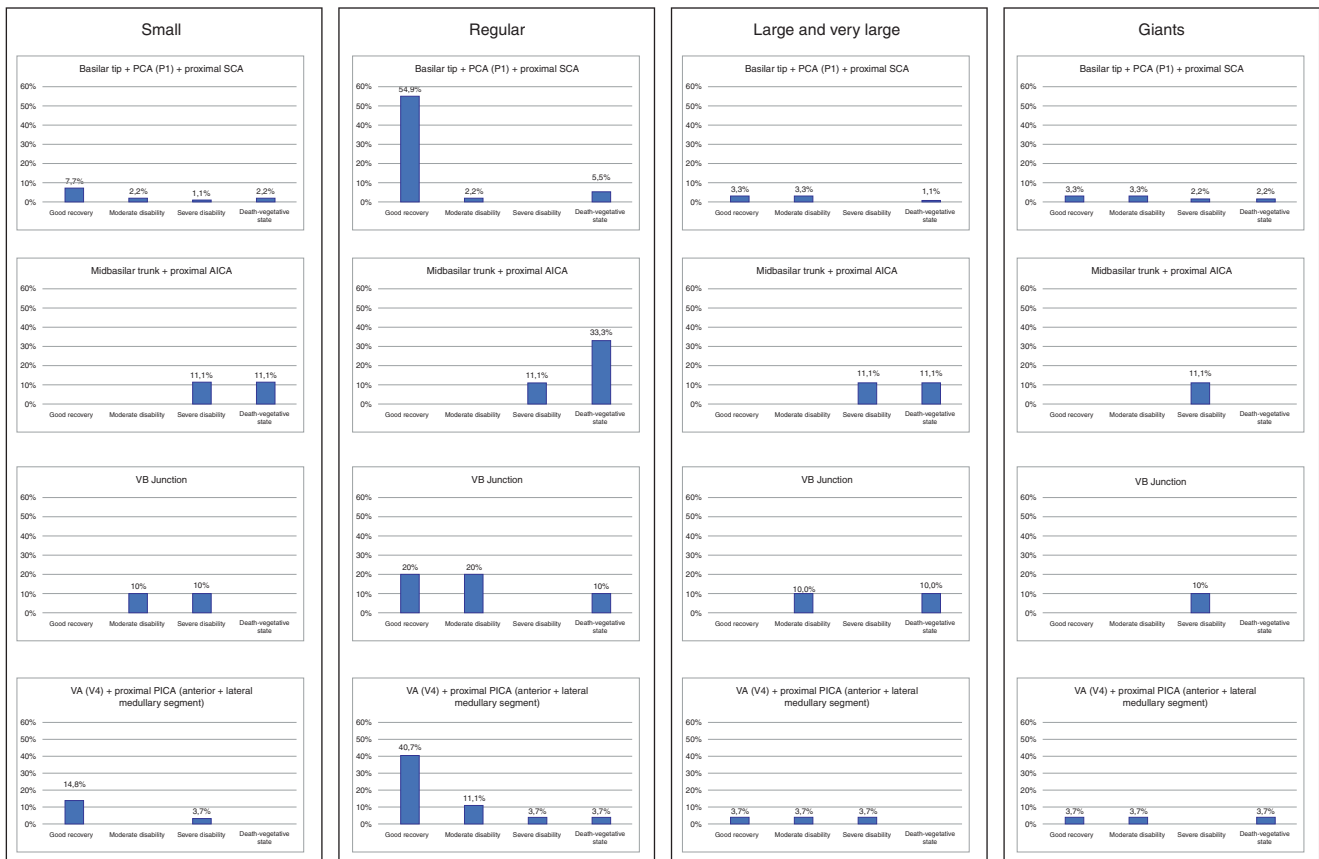


Fig. 1 Bar graph showing the overall patient outcome in proximal aneurysms according to their site and size

Discussion

Although not free from possible complications, neuroendovascular techniques have reached a level of effectiveness that certainly makes them suitable for a large part of posterior circulation aneurysms. Conversely, microneurosurgery still has a very important role in the treatment of aneurysms involving distal segments of the cerebellar arteries, giant aneurysms, a large number of aneurysms affecting basilar tip and proximal SCA, an equally large part of VA-PICA aneurysms and, more generally, complex aneurysms not amenable to endovascular treatment [6, 14–22]. Particularly, the well-established role that microneurosurgery plays in the treatment of distal infratentorial aneurysms is the same, in terms of durability, as its role in treating distal supratentorial ones [23].

The present retrospective series also confirms these data, suggesting that microneurosurgery should be considered as the treatment of choice especially for elective patients younger than 65 years old. Some technical aspects as follow ought to be considered to achieve the best results: First, a detailed static and dynamic preoperative evaluation of the aneurysm's angioarchitecture and the flow-related aspects are both imperative to plan the treatment strategy. A 4- or 6-vessel DSA, depending on the need for flow replacement, is recommended for all the posterior circulation aneurysms, and also addresses the well-known risk of missing very distal PICA ones [24]. Indeed, one of the authors reported a very rare case of an extracranial small aneurysm of the PICA which was initially missed by CT angiography. Second, a careful preoperative evaluation of the patient's vascular and bony anat-

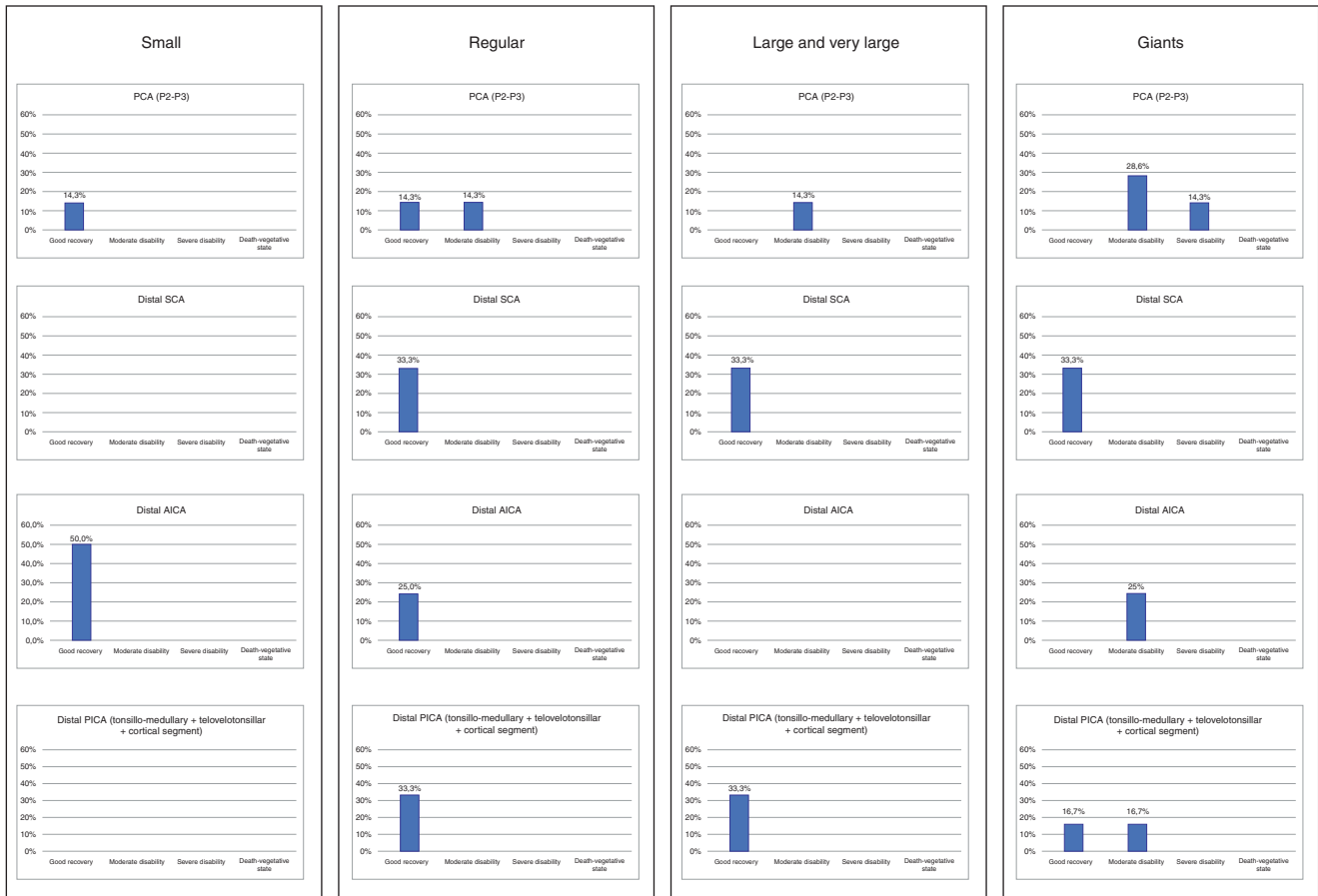


Fig. 2 Bar graph showing the overall patient outcome in distal aneurysms according their site and size

omy allows practical tailoring of any approach. The third remark regards the technological adjuvants, which are part of the surgeon’s armamentarium. For instance, our group has already stressed the importance of endoscope-assisted techniques in the treatment of several neurosurgical pathologies, but particularly aneurysm surgery where, often, the endoscope view prevents perforating branches within blind spots [25, 26]. Noteworthy, apart from the aforementioned aspects, a constant microneurosurgical training remains essential for aneurysms surgery, as already reported by our group [27].

The results of the present series confirm that microneurosurgery continues to have a paramount role in the treatment of many posterior circulation aneurysms, especially in

young patients. In experienced hands, direct clipping allows for a definitive and durable exclusion of the aneurysm. Microneurosurgery also leads to a flow replacement before trapping for those aneurysms not amenable to coiling, stenting, or clipping.

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Ethical Approval This study was approved by the Internal Advisory Board.

Conflict of Interest Statement The authors declare that they have no conflict of interest.

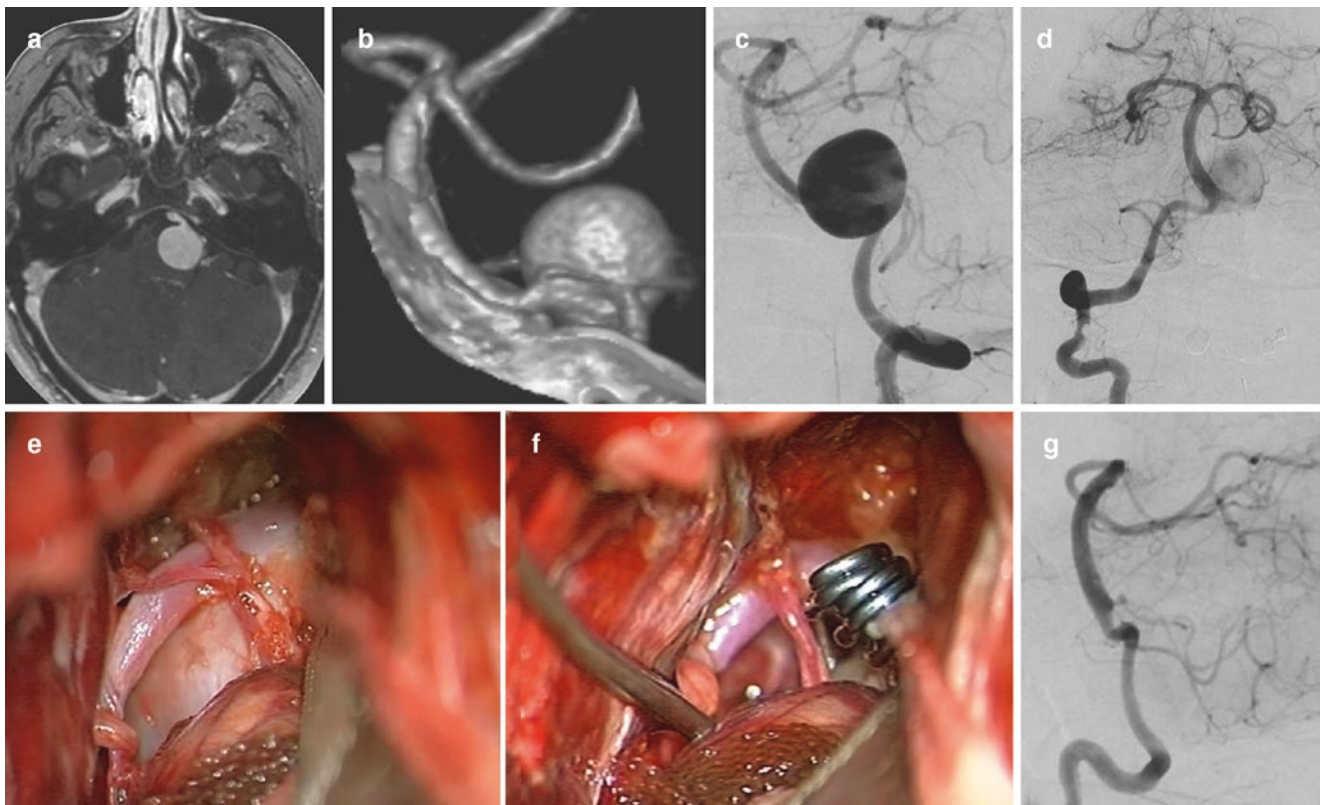


Fig. 3 Contrast-enhanced MRI showing a left giant VA causing a brainstem compression (a). CT angiography and DSA demonstrating the involvement of PICA (b, c). BTO revealing no crossflow (d). Left

far-lateral retrocondylar approach and clipping of the aneurysm (e, f). Postoperative DSA documenting the complete exclusion of the aneurysm with a preserved flow into the left PICA (g)

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Microneurosurgery for Paraclinoid Aneurysms in the Context of Flow Diverters

Sabino Luzzi, Mattia Del Maestro, and Renato Galzio

Introduction

Paraclinoid internal carotid artery (ICA) lies between the distal dural ring and the origin of the posterior communicating artery. Aneurysms involving this segment pose extraordinary challenges regarding the achievement of proximal hemodynamic control and safe intracranial exposure. The advent of the endovascular era, but especially the implementation of flow diverter (FD) stents in the last few years, have apparently shifted the treatment of paraclinoid aneurysms away from microneurosurgery. However, the not negligible number of reported complications related to endovascular techniques, the lack of randomized clinical trials, the relative brevity of experience with FD stents, their questionable use in hemorrhagic cases, and their yet undefined risk of ophthalmic artery occlusion, cause one to continue to consider microneurosurgery as a valuable option especially in young, visually symptomatic patients harboring large or giant aneurysms.

While admitting the actual achievements of FDs, the present study is aimed to critically review the results of microneurosurgery in a retrospective surgical series of paraclinoid aneurysms to differentiate those more indicated for

surgery from those instead of more suitable for endovascular therapy.

Materials and Methods

The present series employed Barami's classification of paraclinoid aneurysms (Table 1) [1]. Data about demographics, clinical onset, Barami's type site and size, approaches, as well the neurological and visual outcome of 53 patients consecutively operated for one or more paraclinoid aneurysms have been retrospectively reviewed. All the aneurysms were operated by the senior author (RG) in three different hospitals between January 1993 and December 2018. Because of their different natural history and particular characteristics, blister aneurysms were excluded from this study. Type IIIb and IV were also ruled out since nowadays these are certainly best managed by endovascular treatment. Neurological outcome was evaluated with the modified Rankin Scale [3], whereas angiographic outcome was evaluated upon the complete exclusion of the aneurysm at six-month follow-up. Visual outcome was measured based on the perimetry assessment at six-month follow-up.

Results

Demographics and Clinical Data

The Average patient age was 47.2 ± 12.6 years. Admission contrast-enhanced computed tomography (CT) angiography and digital subtraction angiography (DSA) were performed in all aneurysms, the former also providing details of the relationship between the aneurysm and anterior clinoid process. In non-hemorrhagic cases, the need for a DSA balloon test occlusion (BTO) was assessed on a case-by-case basis. A contrast-enhanced MRI was performed in

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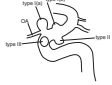
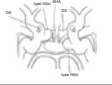

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Table 1 Barami classification of paraclinoid aneurysms [1]

Type	Carotid segment (according to Bouthillier Classification) [2]	Surface	Relation	Comments	Scheme
Ia	C6	Superior	Ophthalmic	Medial or lateral to ON	
Ib	C6	Superior	None	Lateral to ON	
II	C6	Ventral	None	Dome projects into CS roof	
IIIa	C6	Medial	SHA	Carotid cave aneurysms Project over DS	
IIIb	C5	Medial	SHA	Transitional aneurysms. Infradiaphragmatic	
IV	C5, C6	Ventral	None	Giant aneurysms extending between C5 and C6 segments. Widen distal dural ring	

CS cavernous sinus, DS diaphragma sella, ON optic nerve, SHA superior hypophyseal artery

all giant aneurysms to reveal eventual intraluminal thromboses. In 21 patients, subarachnoid hemorrhage was the clinical onset, the average admission Hunt-Hess score being 2.1 ± 1 and mean Fisher grade 1.8 ± 0.9 in these patients. Most of the aneurysms (47.4%) ranged between 7 and 12 mm in size, and Barami's type I was predominant. Table 2 reports the prevalence of Barami's types according to size (Table 2). In hemorrhagic cases, patients having an admission Hunt-Hess score ranging between 1 and 3 mainly underwent surgery. Exceptions regarded rare cases of young patients having an impending life hematoma. In these rare instances, the indication for surgery was based mainly upon an evidence-based management algorithm about intracerebral hemorrhages reported by our group [4]. In 94% of cases, an early surgery (within 24 h) was performed, the remaining cases being deferred because of evidence of vasospasm or poor neurological status. A total of 57 aneurysms were consecutively operated on; six patients had two aneurysms and one patient harbored three different aneurysms. In three patients, surgery was performed after initial endovascular coiling was ultimately incomplete or unsuccessful. Conversely, four previously operated patients underwent an endovascular treatment because of the need for retreatment of the same aneurysm or for a different aneurysm.

Surgery

Approach Selection and Proximal Hemodynamic Control

Pterional approach was used as a rule, although in selected cases of complex or giant aneurysms involving the back wall of the ICA, cranio-orbitary approaches were useful to maximize the handling.

Exposure of the cervical ICA was reserved to complex or giant aneurysms, especially if a hemorrhagic onset

Table 2 Prevalence of Barami types according to size

Barami type [1]	N (%)	Size			
		Small (7 mm) N (%)	Regular (7–12 mm) N (%)	Large and very large (13–24 mm) N (%)	Giant (25 mm) N (%)
Type Ia	35 (61.4%)	7 (20%)	16 (45.7%)	5 (14.3%)	7 (20%)
Type Ib	3 (5.3%)	–	2 (66.7%)	–	1 (33.3%)
Type II	6 (10.5%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)
Type IIIa	13 (22.8%)	1 (7.7%)	7 (53.8%)	3 (23.1%)	2 (15.4%)
Type IIIb	–	–	–	–	–
Type IV	–	–	–	–	–
Tot.	57	9 (15.8%)	27 (47.4%)	10 (7.5%)	11 (19.3%)

occurred. It also allowed for both for an eventual temporary occlusion and for the retrograde suction decompression, Dallas technique [5], used in some giant aneurysms. Intradural anterior clinoidectomy was always preferred to that extradural to decrease the risk of aneurysm rupture.

Direct vs. Indirect Treatment

A direct treatment was possible in 52 aneurysms (91.2%) and, in all these cases, it consisted of a clip ligation. In five aneurysms, an extracranial to intracranial high-flow bypass was performed before the trapping. The saphenous vein and the radial artery were the conduits in two and three cases, respectively. During direct treatment, temporary clipping of the parent vessel and bipolar aneurysm shrinking were the most frequently used techniques. Furthermore, stacking-seating clipping technique, retrograde suction-decompression, aneurysmorrhaphy, and aneurysmectomy were commonly employed, particularly for giant aneurysms. A total of 57 aneurysms were successfully treated.

Temporary Clipping and Neurophysiological Monitoring

In all cases of temporary clipping carried out in elective conditions, anesthesia protocol used for burst suppression and intraoperative neurophysiological monitoring was the same already reported by our group for most of the neurovascular pathologies [6–14]. A combined somatosensory-motor evoked potentials and EEG-based monitoring was introduced in 2012 and, since that time, routinely employed for all complex ICA aneurysms electively treated.

Technological Adjuvants and Flow Assessment Techniques

The Endoscope-assisted technique was utilized by default in all the aneurysms involving the back wall of the ICA. A rigid 0° or 30°, 4-mm endoscope was employed in all cases. The details of the endoscope-assisted technique for ICA aneurysms have been described elsewhere by our group [15, 16]. Flow assessment techniques were essential in all cases. They involved micro-Doppler ultrasound (MDU) (20 MHz System, Mizuho Medical Co., Ltd., Tokyo, Japan) since 2007, indocyanine green (ICG) video angiography (Flow 800 Infrared Module, OPMI Pentero 800, Zeiss, Oberkochen, Germany) since 2009, and fluorescein angiography (Yellow 560 Fluorescence Module, Kinevo 900, Zeiss, Oberkochen, Germany) since 2018. Charbel micro-flow probe (Intracranial Charbel Micro-Flow Probe, Transonic Systems Inc., New York, USA) was also used in some cases.

Neurological Outcome

An overall mRS of 0–2 was achieved in 77.3% of patients, 87.5% of which were elective. The best outcome was achieved in non-hemorrhagic cases and in patients <50 years old. Table 3 reports the overall outcome according to clinical onset (Table 3).

Visual Outcome

In patients suffering a preoperative visual impairment concern, visual field test appeared improved or unchanged in 36.3% and 63.6% of cases, respectively. Campimetry was

unchanged also in 76.1% of patients who had a preoperative normal visual field. Table 4 reports the visual overall outcome in unruptured aneurysms according to preoperative visual impairment (Table 4).

Angiographic Outcome

All but four patients underwent postoperative angiography at six-month follow-up. Apart from cases of remnants, all the patients underwent a CT angiography for further follow-ups. The total exclusion of the aneurysms with a single procedure was achieved in 93% of the patients. In four cases, two elective and two hemorrhagic, a remnant of a single aneurysm was revealed, and the patient underwent endovascular treatment. No recurrences were documented during an average follow-up of 54.1 ± 34 months.

Illustrative Cases

Case #1 Unruptured Giant Barami Type II Aneurysm in a Visually Symptomatic Patient. A 34-year-old female suffered a right eye progressive visual impairment (Fig. 1). CT angiography and DSA revealed a right giant Barami type II paraclinoid aneurysm (Fig. 1a–c). She also had a small basilar tip aneurysm (Fig. 1d). The patient passed the BTO of the right ICA and underwent surgery. A right pterional approach, comprehending an intradural anterior clinoidectomy, was performed, and the aneurysm was successfully clipped with three Yasargil standard clips (Fig. 1g). Basilar tip aneurysm was clipped also. The patient was discharged on the fifth postoperative day. At six-month DSA, a very small remnant was revealed, and the patient underwent radiological follow-up (Fig. 1i). Three months after surgery, the patient had completely recovered the preoperative visual field deficit (Fig. 1m, n).

Case #2 Ruptured Very Large Barami Type II Aneurysm. A 37-year-old female was diagnosed with a subarachnoid hemorrhage (Fig. 2). CT angiography and

Table 3 Neurological outcome according to the clinical onset

Clinical onset (N/%)		mRS 0–2 (N/%)	mRS 3–4 (N/%)	mRS 5 (N/%)	mRS 6 (N/%)
Non-hemorrhagic	32 (60.3%)	28 (87.5%)	3 (9.3%)	–	1 (3.1%)
Hemorrhagic	21 (39.6%)	13 (61.9%)	5 (23.8%)	1 (4.7%)	2 (9.5%)
Tot.	53	41 (77.3%)	8 (15%)	1 (1.8%)	3 (5.6%)

mRS modified Rankin Score

Table 4 Visual outcome in elective aneurysms

Preoperative visual impairment (N/%)		Improved (N/%)	Unchanged (N/%)	Worsened (N/%)	De Novo (N/%)
Absent	21 (65.6%)	–	16 (76.1%)	–	3 (14.2%)
Present	11 (34.3%)	4 (36.3%)	7 (63.6%)	2 (18.1%)	–
Tot.	32	4 (12.5%)	23 (71.8%)	2 (6.2%)	3 (9.3%)

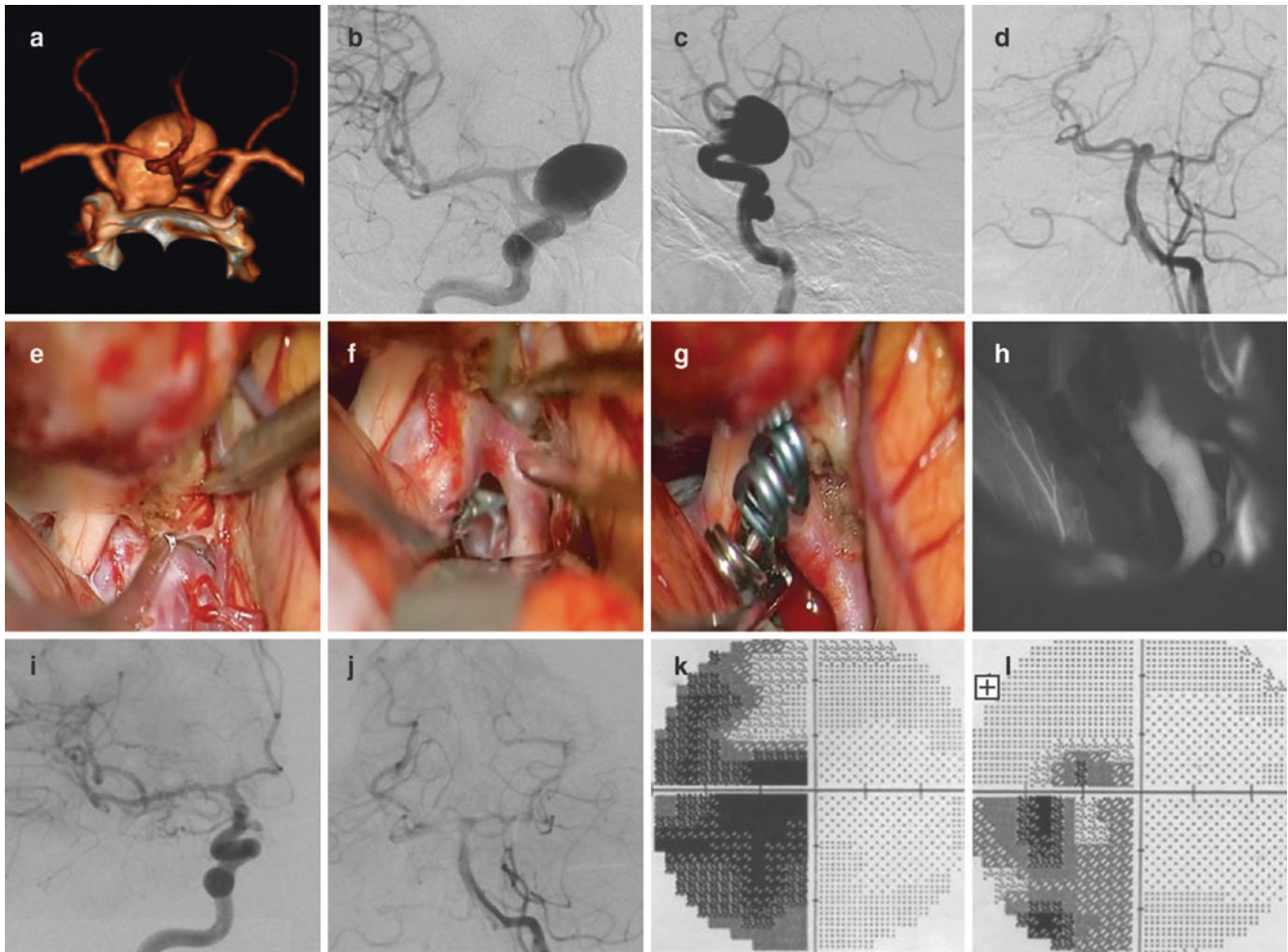


Fig. 1 Illustrative Case #1, regarding a 34-year-old female with a right eye progressive visual impairment. (a) CT angiography and DSA (b) of the right ICA in anterior-posterior and lateral (c) projection showing a right giant Barami type II paraclinoid ICA aneurysm. (d) DSA of the left VA showing a basilar tip aneurysm. (e) Intradural clinoidectomy during a right pterional approach. (f, g) Clipping of the aneurysms with the stacking-seating technique. (h) Intraoperative ICG videoangiogra-

phy showing the complete exclusion of the aneurysm. (i) Postoperative DSA of the right ICA in anterior-posterior projection showing a very small remnant of the aneurysm. (j) DSA of the vertebrobasilar system revealing a complete exclusion of the basilar tip aneurysm. Preoperative (k) and postoperative (l) visual field test of the right eye, confirming a dramatic improvement

DSA revealed a right very large Barami type II paraclinoid ICA aneurysm (Fig. 2a–c). Early surgery was performed, and the patient underwent a right fronto-temporo-orbital approach with an intradural anterior clinoidectomy after having exposed the ICA at the neck. The aneurysm was easily clipped with two tandem angled fenestrated clips (Fig. 2d–i). The Postoperative CT scan did not show ischemic complication (Fig. 2l) and the patient was discharged 10 days later without deficits. The

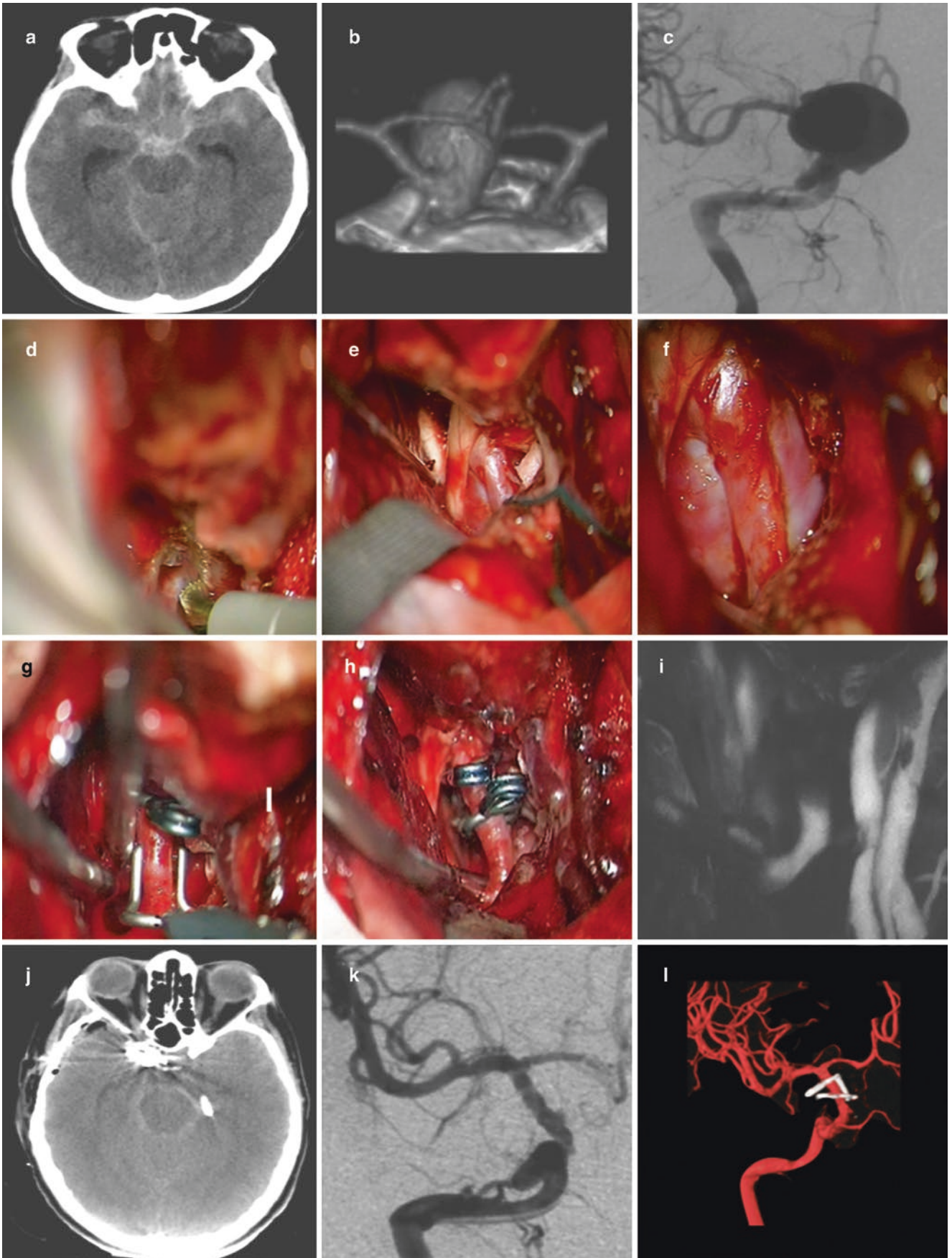
six-month DSA confirmed the complete exclusion of the aneurysm (Fig. 2m, n).

Discussion

The natural history of paraclinoid aneurysms is characterized by progressive and slow-growing until it reaches large or giant size without rupture. Hunterian ligation, with or

Fig. 2 Illustrative Case #2, regarding a 37-year-old female who was diagnosed with a subarachnoid hemorrhage (a). CT angiography (b) and DSA (c) of the right ICA showing a right large Barami type II paraclinoid aneurysm. An intradural clinoidectomy with a piezoelectric bone scalpel (d) during a fronto-temporo-pterional-orbital approach allowed to fully expose the aneurysm (e, f). (g, h) Clipping of the aneu-

rysm with the tandem angled fenestrated clipping technique. (i) Intraoperative ICG videoangiography confirming the complete exclusion of the aneurysm. (j) Late postoperative CT scan showing no ischemic complication. (k, l) DSA of the right ICA in anterior-posterior projection showing the optimal visualization of the paraclinoid ICA and ophthalmic artery and the exclusion of the aneurysm



without revascularization, has in the past been the treatment of choice for most of these lesions. However, as opposed to distal aneurysms, for which it has been reported to be usually decisive [17, 18], the straightforward proximal occlusion of the ICA is associated with an early recanalization of the aneurysm throughout the backflow. Accordingly, surgery shifted toward a direct treatment of this type of the aneurysms. The advent of the endovascular era has dramatically increased the spectrum of possible treatments for intracranial aneurysms, paraclinoid ones included. Moreover, with the introduction of FD stents, which find their main application right in ICA aneurysms, a quiet revolution within the endovascular techniques happened. A wide volume of literature confirms today the effectiveness and safety of FDs, especially for ICA aneurysms, therefore supporting them as the first-line treatment for most paraclinoid aneurysms [19–22]. Recently, FDs have also been associated with a high rate of visual improvement in symptomatic patients, without differences in terms of worsened vision or iatrogenic visual impairment as compared with clipping and coiling techniques [23]. While admitting the practical role of FDs in the treatment of a large part of ICA aneurysms as those wide-necked, fusiform, dissecting, blister-like, or ventral giant, the enthusiastic attitude toward the flow diversion ought to be counterbalanced by a series of drawbacks to be taken into account. First, FDs have been reported to be associated with a not negligible number of serious complications [24]; second, their use in hemorrhagic cases is still pioneering; third, the associated risk of ophthalmic artery occlusion in paraclinoid aneurysms is yet undefined; fourth, their actual effectiveness is not supported by high-quality evidence [25]. Last but not far from least, FDs require long-term or chronic anticoagulation, which is extremely inconvenient for patients with a long life expectancy.

All these aspects compel one to consider microneurosurgery as a still valuable option, especially in young and visually symptomatic patients harboring large or giant aneurysms. In addition to the undoubtedly proven durability of the microneurosurgical treatment, the results of the present series documented a very good neurological and visual outcome in patients <50 years old harboring dorsal paraclinoid ICA aneurysms but also type II ventral ones. These cases are essentially those for which microneurosurgery is primarily indicated because it offers some unquestionable advantages compared with flow diversion. Conversely, FDs should be considered as the first option in the superior hypophyseal artery and carotid cave aneurysms, especially if these are small, unruptured, or occur in older and asymptomatic patients. Although not reported in the present series, blister aneurysms also seem to have a clear indication to flow diversions even in hemorrhagic cases [26]. From a technical standpoint, the key aspect in

the management of these aneurysms is the anterior clinoidectomy. Regardless of the surgeon's preference for an extradural rather than an intradural approach, it should be stressed that anterior clinoidectomy plays the same role for paraclinoid aneurysms that condylectomy of jugular tuberculectomy play in the vertebro-basilar junction or vertebral artery-posterior inferior cerebellar artery aneurysms: both have been reported as an essential step to achieve the widest and most unobstructed view possible of the target [27, 28]. Indeed, the paramount concept of maximizing the bony removal to avoid mechanical retraction of the neurovascular structures is common to both skull base and neurovascular surgery. Paraclinoid aneurysms constitute a formidable challenging for which the mastery of neurovascular and skull base surgery techniques are mandatory, they being both achievable uniquely by means of a constant microneurosurgical training, as stressed by our group [29].

In conclusion, elective patients <50 years old, visually symptomatic, and harboring a Barami's type Ia, Ib or II paraclinoid aneurysm, especially if large or giant, are the best candidates for microneurosurgery. Conversely, older patients having a superior hypophysial, carotid cave, or blister aneurysm seem to be more likely for endovascular therapy, FDs first. Hemorrhagic cases are still a subject of discussion, however, and worthy of a multidisciplinary evaluation on a case-by-case basis.

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Ethical Approval This study was approved by the Internal Advisory Board.

Conflict of Interest Statement The authors declare that they have no conflict of interest.

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Part II

Cerebral Revascularization



Characteristic Pattern of the Cerebral Hemodynamic Changes in the Acute Stage After Combined Revascularization Surgery for Adult Moyamoya Disease: N-isopropyl-p-[¹²³I] iodoamphetamine Single-Photon Emission Computed Tomography Study

Miki Fujimura and Teiji Tominaga

Introduction

Moyamoya disease (MMD) is a unique cerebrovascular disease with unknown etiology characterized by progressive stenosis of the terminal portion of the internal carotid artery (ICA) and abnormal vascular network formation at the base of the brain [1–3]. Surgical revascularization by superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis is a standard surgical procedure especially for adult patients with MMD [1, 3–6]. The STA-MCA anastomosis not only prevents cerebral ischemic attack by improving cerebral blood flow (CBF), but could also reduce the risk of re-bleeding in patients with posterior hemorrhage who were known to have extremely high re-bleeding risk [7, 8]. Regarding surgical procedure, recent study indicates the superiority of direct/indirect combined revascularization surgery such as STA-MCA anastomosis with indirect pial synangiosis [9]. Despite its long-term favorable outcome, however, local cerebral hyperperfusion syndrome and perioperative cerebral infarction are potential complications of this procedure [10–16]. Therefore, routine hemodynamic study and intensive perioperative management, including strict blood pressure control and administration of neuroprotective agents, are essential to provide favorable outcome [3, 17, 18]. In the present study, we sought to clarify the characteristic pattern of cerebral hemodynamic changes in the acute stage after combined revascularization surgery for

adult MMD patients, who were treated by modern perioperative management protocol.

Materials and Methods

Inclusion Criteria of Patients and Surgical Procedure

The postoperative changes in CBF were investigated in 54 consecutive adult patients with MMD (21–76 years old, 43.1 average) surgically treated in 65 hemispheres by the same surgeon (M.F.) between July 2017 and June 2018. Surgical indication for MMD included all of the following items: the presence of ischemic symptoms (minor completed stroke and/or transient ischemic attack [TIA]) and/or posterior hemorrhage, the presence of hemodynamic compromise, independent activity of daily living (modified Rankin scale scores 0–2), and absence of major brain damage that exceed the vascular territory of one major branch of MCA.

Preoperative CBF was quantified by the autoradiographic method in most cases, and the CBF in each subregion using N-isopropyl-p-[¹²³I] iodoamphetamine single-photon emission computed tomography (¹²³I-IMP-SPECT) [10, 13]. All patients underwent STA-MCA (M4) anastomosis with encephalo-duro-myo-synangiosis (EDMS) [4]. Craniotomy was performed around sylvian fissure end, approximately 8 cm in diameter, and the stump of STA was anastomosed to the M4 segment of MCA, which was followed by EDMS. All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis, of the Ministry of Health, Labor, and Welfare, Japan [1, 3].

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Postoperative CBF Measurement and Perioperative Management Protocol

CBF was routinely measured by ^{123}I -IMP-SPECT at postoperative day (POD) 1 and 7 after surgery in all patients. The temporal profile of the postoperative cerebral hemodynamics was qualitatively classified into three patterns. First, the “local hyperperfusion-redistribution pattern” was defined as transient local hyperperfusion at the site of the anastomosis (POD1) and subsequent distribution of the improved CBF in wider vascular territory (POD7). Second, the “gradual CBF improvement pattern” was defined as none of minor improvement of CBF (POD1) which was followed by the moderate improvement of CBF on the affected hemisphere (POD7). All of the patterns that did not satisfied the above two patterns were defined as “others.” Postoperative computed tomography (CT) scan was routinely performed immediately after surgery and one day after surgery in all cases. 1.5-T or 3-T magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed within three days after surgery. MRI included diffusion-weighted images (DWI), T2-weighted images, and T2*-weighted images in all cases. The fluid attenuated inversion recovery was also performed in most cases. The criteria for “local hyperperfusion” included all of the following items: (1) The presence of a significant local CBF increase at the site of the anastomosis that exceeded the CBF value of the other supratentorial region of the bilateral hemispheres. (2) Apparent visualization of STA-MCA bypass by MRA. (3) The absence of other pathologies such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis and CBF increase secondary to seizure.

All 54 patients operated on 65 hemispheres were prospectively subjected to prophylactic intensive blood pressure lowering (100–130 mmHg of systolic blood pressure) according to standardized postoperative management protocol to prevent cerebral hyperperfusion syndrome using 1–10 mg/h continuous intravenous drip infusion of nicardipine hydrochloride as previously described [17]. All patients were managed by intraoperative and postoperative intravenous administration of minocycline hydrochloride (200 mg/day) until 7 days after surgery, in order to avoid the deleterious effects of cerebral hyperperfusion, and to reduce the potential risk of cerebral ischemia at remote area [18]. To avoid the unfavorable effect of intensive blood pressure lowering on the contralateral hemisphere and/or ipsilateral remote areas, we routinely administered anti-platelet agents (100 mg aspirin/day) starting the day after surgery in all cases [17, 18]. Based on the temporal profile of ^{123}I -IMP-SPECT and MRI/MRA findings, we gradually allowed a return to normo-tensive conditions within 7–10 days after surgery [17, 18].

Table 1 Patterns of cerebral hemodynamic changes after 65 consecutive direct/indirect revascularization surgeries for adult moyamoya disease

	Hemisphere	Incidence
Local hyperperfusion (POD1)-redistribution (POD7)	37/65	56.9%
Gradual increase in CBF (POD1-POD7)	20/65	30.8%
Others	8/65	12.3%

CBF cerebral blood flow, POD postoperative day

Results

The outcome of 65 surgeries was favorable in all cases except for one (1.5%), which manifested as delayed intracerebral hemorrhage due to local hyperperfusion and did not affect the patient’s long-term activity of daily living. The postoperative ^{123}I -IMP-SPECT revealed the characteristic CBF improvement pattern with local hyperperfusion (POD1) and subsequent distribution of CBF in wider vascular territory (POD7) on 37 hemispheres (56.9%, 37/65). “Gradual CBF improvement pattern” was found on 20 hemispheres (30.8%, 20/65), and eight hemispheres were classified into the “others” (12.3%, 8/65). The result is summarized in Table 1, and the representative case with “local hyperperfusion-redistribution pattern” is shown in Figs. 1 and 2. None of the patients developed perioperative cerebral infarction, while one patient suffered transient ischemic change by DWI at the cerebral cortex adjacent to the site of the anastomosis that resolved within 2 weeks.

Discussion

The present prospective study by routine ^{123}I -IMP-SPECT revealed the characteristic CBF improvement pattern in the acute stage after STA-MCA anastomosis with indirect pial synangiosis for adult MMD patients. We found that local hyperperfusion at the site of the anastomosis (POD1) and subsequent distribution of CBF in wider vascular territory (POD7), so-called “local hyperperfusion-redistribution pattern,” was the most common hemodynamic pattern as evident on 37 hemispheres (56.9%, 37/65) after combined revascularization surgery for adult MMD. Under the strict perioperative management by blood pressure control (100–130 mmHg of systolic blood pressure) and the administration of neuro-protective/anti-inflammatory agent (minocycline hydrochloride) [17, 18], the outcome of 65 surgeries was generally favorable despite the presence of transient local hyperperfusion, except for one (1.5%, 1/65) manifesting as delayed intracerebral hemorrhage due to local hyperperfusion. We thus recommend intensive perioperative care with routine CBF measure-

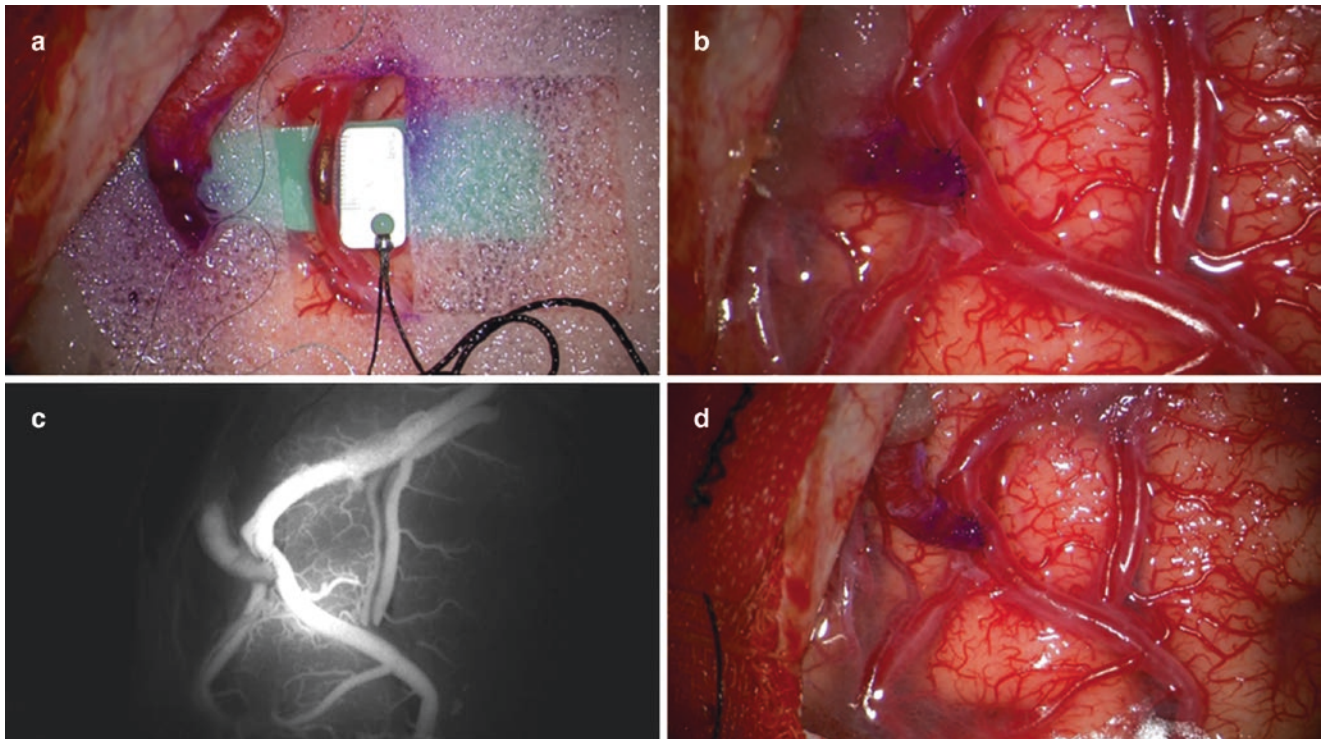


Fig. 1 Intraoperative microscopic view of right superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis for a 47-year-old patient. (a, b, d) The stump of STA was anastomosed to M4 segment of left MCA with 1.1 mm in diameter, with the temporary

occlusion time of 26 min. (c) Intraoperative indocyanine green video-angiography after the anastomosis showing apparently patent STA-MCA bypass

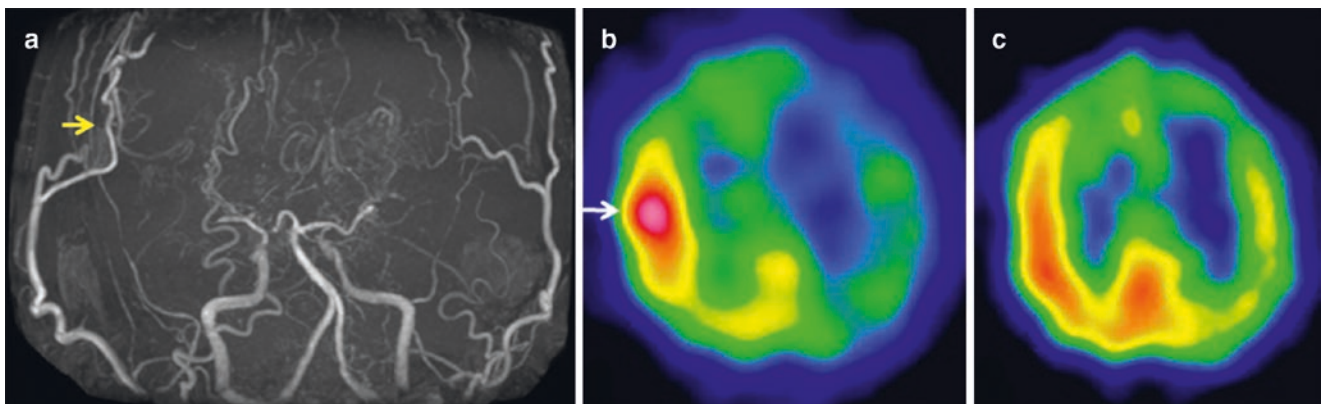


Fig. 2 (a) Magnetic resonance angiography on postoperative day 2 showing the patency of right STA-MCA bypass (arrow). (b, c) N-isopropyl-p-[¹²³I] iodoamphetamine single-photon emission com-

puted tomography on postoperative day 1 (b) showing focal cerebral hyperperfusion in the right frontal lobe (arrow), which is significantly relieved with favorable distribution 7 days after surgery (c)

ment to avoid the deleterious effect of transient local hyperperfusion within 7 days after STA-MCA anastomosis for adult MMD patients.

Surgical complications of MMD include perioperative cerebral ischemia and cerebral hyperperfusion syndrome [1, 3, 5]. Perioperative cerebral ischemia could be caused by at least three distinct mechanisms: “watershed shift phenom-

non” [14, 19], thrombo-embolism at the site of the anastomosis [13], and mechanical compression of the brain surface by swollen temporal muscle used for indirect bypass procedure [20]. Besides perioperative cerebral ischemia, rapid local increase in CBF at the site of the anastomosis could result in focal hyperemia associated with vasogenic edema and/or hemorrhagic conversion, especially in adult MMD

[11–13, 15, 16]. We have reported that the incidence of cerebral hyperperfusion syndrome after STA-MCA bypass was significantly higher in MMD patients than that in patients with atherosclerotic occlusive cerebrovascular diseases [13]. Prognosis of the focal neurological deficit due to hyperperfusion is generally favorable, but it could lead to delayed intracerebral hemorrhage in a rare occasion [12]. In fact, the present study included one complication case with delayed intracerebral hemorrhage even under the modern perioperative management protocol. In light of the risk factors for hyperperfusion syndrome in MMD such as adult-onset [11, 16], increased preoperative cerebral blood volume [16], hemorrhagic-onset [11], operation on the dominant hemisphere [18], and smaller diameter of the recipient artery [18], it is particularly important to manage adult MMD patients with these factors promptly to avoid deleterious effects of hyperperfusion during the perioperative period.

In conclusion, the direct/indirect combined revascularization surgery is generally a safe and effective treatment for adult MMD under modern perioperative management. In light of the characteristic CBF improvement pattern with local hyperperfusion (POD1) and subsequent distribution of CBF in wider vascular territory (POD7) on 37 hemispheres in the present series (56.9%, 37/65), transient local hyperperfusion should be strictly managed by intensive perioperative care in adult MMD patients.

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Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Informed Consent Informed consent was obtained from individual participants included in the study.

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Outcomes of Balloon Angioplasty and Stenting for Symptomatic Intracranial Atherosclerotic Stenosis at a High Volume Center

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Introduction

Intracranial atherosclerotic stenosis is an important etiological factor for cerebral infarction, and its incidence is reportedly high in Asians [1]. According to the Japanese Stroke Databank 2015, intracranial atherosclerotic stenosis was observed in approximately 18% of patients with cerebral infarction. For medical treatment of symptomatic intracranial atherosclerotic stenosis, antiplatelet drugs are primarily used, but the recurrence rate is high and the annual incidence of cerebral infarction is approximately 10% [2] (Figs. 1 and 2).

Regarding neuroendovascular treatment for intracranial atherosclerotic stenosis, the usefulness of balloon angioplasty was reported following the development of balloon catheters for the intracranial cerebral blood vessels in the early 1990s [3, 4]. Thereafter, the development of intracranial stents was promoted, and the results of a randomized controlled trial of Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis (SAMMPRIS) showed that aggressive medical management was superior to angioplasty and stenting with the use of the Wingspan stent system. Indeed, the 30-day rates of stroke and death were 14.7% (10.2% ischemic, 4.5% hemorrhagic) with stenting versus 5.8% with aggressive medical management. However, even in the medical management group, the risk is high. When the perioperative strokes were excluded, the rates of subsequent ischemic strokes were almost the same in the two groups.

On the other hand, in Japan, the Wingspan stent was approved in July 2014, and it has been increasingly used. In this study, we retrospectively compared the results of neuroendovascular treatment for symptomatic intracranial atherosclerotic stenosis before and after Wingspan stent approval at our hospital.

Materials and Methods

At our hospital, 256 sessions of neuroendovascular treatment were performed for 217 patients with symptomatic intracranial atherosclerotic stenosis between 1999 and 2017. This treatment was indicated for patients meeting the following conditions: (1) $\geq 70\%$ stenosis, (2) a history of cerebral infarction or repeated transient ischemic attacks (TIAs), and (3) written informed consent obtained from the patient or his/her family. Furthermore, acute-phase patients within three days after the onset of cerebral infarction were excluded. In addition, indication criteria for a Wingspan stent in Japan include: (1) emergency treatment for vascular dissection or acute/impending occlusion during angioplasty and (2) additional treatment after angioplasty under circumstances in which there is no other effective treatment method.

The subjects were divided into two groups: early-phase (from August 1999 until June 2014, before Wingspan stent approval) and late-phase (from July 2014 until December 2017, after Wingspan stent approval) groups. We compared initial treatment results and perioperative complications within 30 days after treatment between the two groups. In the late phase, we also examined restenosis and recurrent cerebral ischemic events.

Neuroendovascular treatment was performed under local/intravenous anesthesia. For femoral artery puncture, a 6-F guiding sheath or 8-F guiding catheter was used. As the stenotic blood vessel-dilating procedure,

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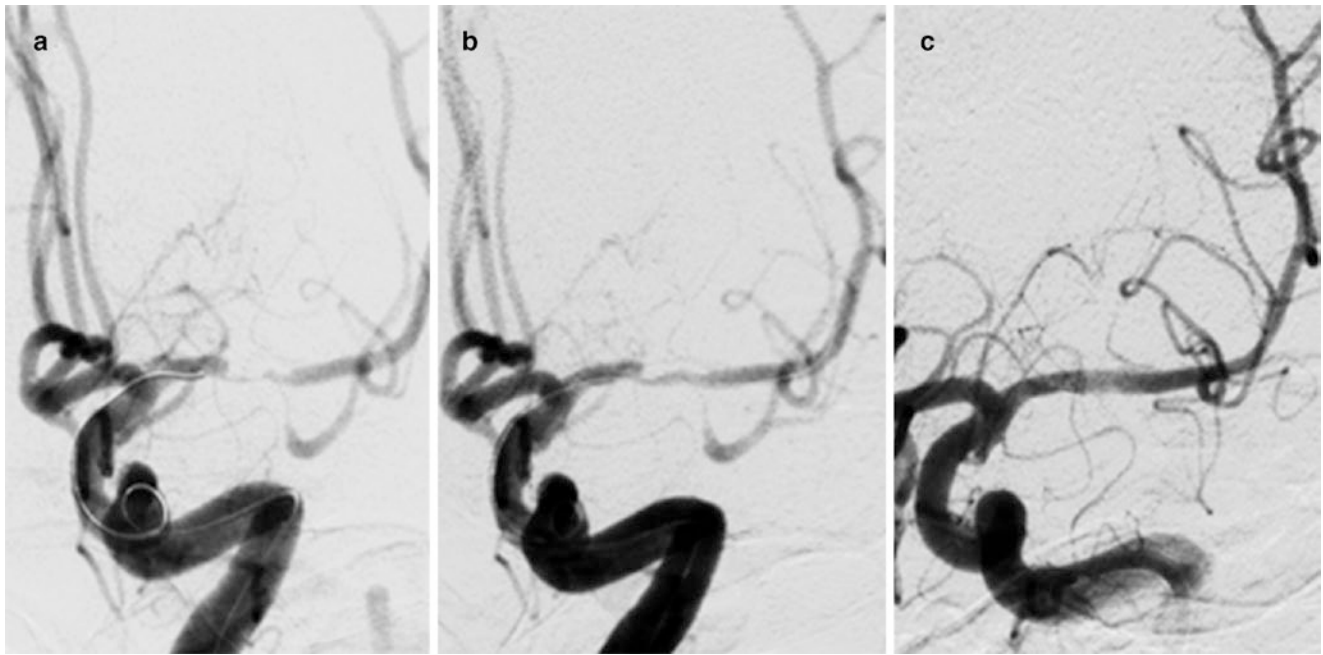


Fig. 1 A 73-year-old patient with a history of minor stroke and recurrent right hemispheric transient ischemic attacks under double antiplatelet therapy. (a) Angiography demonstrates high-grade stenosis of the left middle cerebral artery. (b) Residual stenosis after balloon angioplasty. (c) Widening of the lumen after deployment of the Wingspan stent

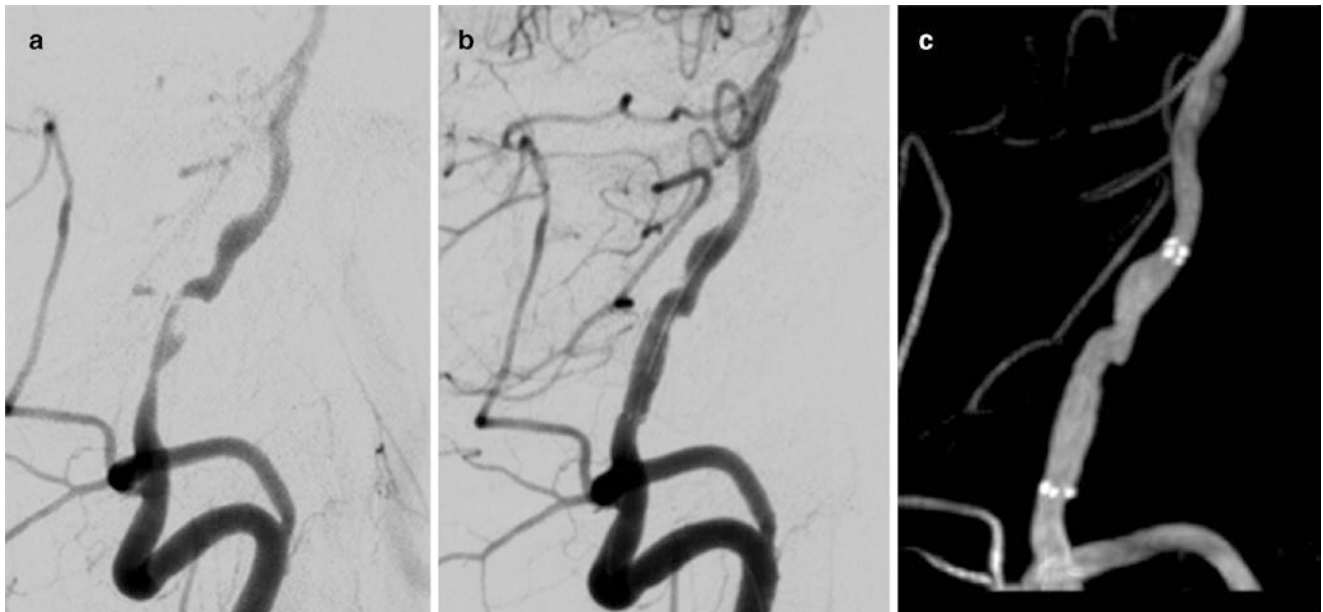


Fig. 2 A 68-year-old patient with recurrent brain stem and cerebellar infarction under double antiplatelet therapy. (a) Angiography shows high-grade stenosis of the left vertebral artery. (b) After balloon angioplasty and deployment of the Wingspan stent, there is minimal residual stenosis. (c) The radio-opaque stent end-makers are well visualized

balloon angioplasty alone was performed for initial treatment, as a rule. For balloon angioplasty, dilation at 6 atm at maximum was conducted for 60–90 s using a balloon catheter measuring 1.5–4.0 mm in diameter (Gateway balloon catheter, Stryker, Maple Grove, MN, U.S.A. or Unryu balloon catheter, Kaneka Medics,

Tokyo, Japan). When dilation after balloon angioplasty was insufficient or when acute occlusion related to vascular dissociation occurred, a stent for the coronary artery was used in the early phase and a Wingspan stent (Stryker, Maple Grove, MN, U.S.A.) was used in the late phase for treatment.

Two antiplatelet drugs were administered for 1 week prior to treatment. Two-drug administration was continued for 1 month after surgery for patients who underwent balloon angioplasty, and for 6 months to 1 year after surgery for those who underwent stenting. Subsequently, this therapy was switched to monotherapy. Magnetic resonance imaging (MRI) was performed before treatment and within 3 days after treatment. In the late-phase group, cerebral angiography was conducted 6 months after treatment if possible.

Results

In the early phase, 188 sessions of treatment were performed for 163 patients (mean age: 63.5 ± 10.2 years, 125 males). In the late phase, 68 sessions of treatment were performed for 54 patients (mean age: 66.4 ± 13.3 years, 45 males) (Table 1). In the early phase, the treatment procedures consisted of balloon angioplasty for 157 patients (83.5%) and stenting for 31 (16.5%). In the late phase, the former was selected for 33 patients (48.5%) and the latter for 35 (51.5%); the number of patients treated by stenting increased. In the early phase, the internal carotid, middle cerebral, basilar, and vertebral arteries were treated in 46, 77, 19 and 21 patients, respectively. In the late phase, they were treated in 19, 18, 5, and 11 patients, respectively.

The initial success rates of balloon angioplasty and stenting were 96% and 100%, respectively. Patients with a percent stenosis of $\leq 50\%$ were regarded as achieving successful results. In the late phase, Wingspan stents were used in 14 patients with internal carotid artery stenosis, in eight with middle cerebral artery stenosis, in three with basilar artery stenosis, and in 12 with vertebral artery stenosis.

Perioperative complications related to treatment within 30 days consisted of minor stroke in six patients (3.2%) (peripheral embolism: three patients, penetrating vessel infarction: two patients and cerebral infarction related to vascular dissociation: one patient) and major stroke in three

Table 1 Comparison of patient characteristics between early and late phases

	Early-phase	Late-phase	Total
<i>N</i>	163	54	217
Procedures	188	68	256
Balloon angioplasty	157	33	190
Stenting	31	35	66
Age, mean \pm SD, years	63.5 ± 10.2	66.4 ± 13.3	
M/F	125/38	45/9	
Artery, <i>N</i> (procedures)			
ICA	46 (53)	19 (24)	65 (77)
MCA	77 (88)	18 (23)	95 (111)
BA	19 (23)	5 (6)	24 (29)
VA	21 (24)	11 (15)	32 (39)

Table 2 Comparison of complications within 30 days after the procedure between early and late phases

	Early-phase	Late-phase	Total
Complications within 30 days			
Minor stroke/TIA	6 (3.2%)	2 (2.9%)	8 (3.1%)
Major stroke	3 (1.6%)	1 (1.5%)	4 (1.8%)
Total	9 (4.8%)	3 (4.4%)	12 (4.7%)

(1.6%) (cerebral hemorrhage related to hyperperfusion disorder: two patients and cerebral infarction related to vascular dissection: one patient) in the early phase. In the late phase, minor stroke was observed in two patients (2.9%) (peripheral embolism: one patient and guidewire-perforation-related subarachnoid hemorrhage: two patients), and major stroke in one (in-stent thrombosis) (Table 2).

In the late phase, $\geq 50\%$ restenosis was noted in 11 patients during the follow-up period: eight patients (24.2%) who underwent balloon angioplasty and three (8.5%) who underwent stenting. Recurrent cerebral infarction was observed in one patient and TIAs in two. In 8 of the 11 patients, additional treatment was performed (Wingspan stent insertion: six patients and balloon angioplasty: two patients).

Discussion

In Japan, a balloon catheter for stenotic intracranial blood vessels was approved in 1991, earlier than in Europe and the United States. However, the catheter initially had a single lumen, and the incidence of perioperative complications was high. The results of treatment were not always favorable. In 2002, a double-lumen balloon catheter for intracranial blood vessels was approved, and stent-free balloon angioplasty has since been primarily selected in Japan. The reported incidence of perioperative complications related to minimally invasive procedures is relatively low, whereas that of restenosis is high [5, 6]. However, there are no data to prove the efficacy of endovascular treatment for patients with symptomatic intracranial stenosis so far.

In the United States, the Wingspan stent for intracranial stenosis was approved by the FDA in 2005. In 2011, a randomized, controlled study (SAMMPRIS) of vasodilation with a self-expandable-type stent for intracranial blood vessels, the Wingspan stent (Stryker, U.S.A.), which was newly developed to treat symptomatic intracranial artery stenosis, reported positive medical outcomes [7]. The subjects were 451 patients with $\geq 70\%$ stenosis with an interval of ≤ 1 month from the onset of TIA or mild cerebral infarction. Primary endpoints were stroke and death within 30 days. In the medical treatment and stenting groups, their incidences were

5.8% and 14.7%, respectively, demonstrating a significant difference. Regarding perioperative complications, the incidence of ischemic stroke was 10.2% and that of hemorrhagic stroke was 4.5%. Among ischemic complications, penetrating-vessel-infarction-associated complications were observed in 15 patients (6.7%), embolic-infarction-associated complications in six (2.7%), and stent thrombosis in two (0.9%) [8]. As etiological factors for the complications, the use of a thick, hard delivery system was indicated, and patients treated in the acute to subacute phases after the onset of cerebral infarction were included. On the other hand, the recurrence rate ≥ 30 days after treatment in the two groups was approximately 5.8%, demonstrating no difference. In addition, the long-term results of the SAMMPRIS trial suggested no significant difference in the incidence of new ischemic events after the perioperative period between the stenting and medical treatment groups [9].

In the United States, the Wingspan stent was initially indicated for drug-therapy-resistant patients with $\geq 50\%$ stenosis and ischemic cerebrovascular disorder, including TIA, related to intracranial artery stenosis. However, after 2008, the indication criteria were strictly modified based on the results of the SAMMPRIS trial: $\geq 70\%$ stenosis, resistance to drug therapy, a history of ≥ 2 strokes, excluding TIA, and an interval of ≥ 8 days from onset. Regarding stenting with a Wingspan stent for stenosis of the middle cerebral artery, the reported incidence of complications was high in the learning stage, whereas there was a 50% decrease in the incidence in the acquired stage [10, 11].

Intracranial angioplasty with stenting initially started using the coronary balloon-mounted stents. A recent multicenter registry study recruiting 300 patients demonstrated that the 30-day rate of stroke, TIA, and death after intracranial stenting with a balloon-mounted coronary stent or the Wingspan stent was 4.3%. Patients treated with a balloon-mounted stent were less likely to have MCA stenosis and had a lower degree of residual stenosis than the Wingspan stent. However, a randomized clinical trial (the Vitesse intracranial stent study for ischemic stroke therapy: VISSIT), which compared balloon-expandable stent treatment with medical therapy in symptomatic intracranial stenosis, indicated that the 30-day primary safety end point occurred in more patients in the stent group (24.1%) than in the medical group (9.4%) [12].

Both SAMMPRIS and VISSIT trials were not able to establish the efficacy of intracranial artery stenting compared with medical treatment. A SAMMPRIS post hoc analysis failed to show any subgroup of patients with intracranial artery stenosis who significantly benefited from stenting, even those at particularly high risk of stroke on aggressive medical therapy. Further clinical trials may consider selection of patients demonstrating hemodynamic compromise as the mechanism of their ischemic stroke related to intracranial artery stenosis.

In addition, balloon angioplasty without stenting technique may be another effective option for the treatment.

Our study has several limitations. This is a small retrospective study in which bias may have been introduced in the selection of patients and lack of medical arm. Other limitations are the single-center design of study, insufficient follow-up data, and only Japanese population data. Angiographic follow-up was usually performed once at 6 months after the procedure and MRA was performed mainly after that. Finally, this study consists of the experience of operators in an academic hospital, which may limit the generalizability of our results.

Balloon angioplasty and stenting for patients who have symptomatic intracranial atherosclerotic stenosis may have the potential of better clinical outcome if patients are properly selected and treated by an experienced operator at a high-volume center. However, prospective studies with a large population and long follow-up should be done to evaluate the conclusion. Furthermore, well-designed randomized controlled trials will be necessary to show the value of endovascular treatment (when compared to medical treatment) for patients with symptomatic intracranial atherosclerotic stenosis.

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Part III

**Arteriovenous Malformations and Dural
Arteriovenous Fistulas**



Living with a Brain AVM: A Quality of Life Assessment

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Introduction

Arteriovenous malformations (AVM) are considered to be sporadic congenital vascular lesions, consisting of abnormal blood vessels forming direct connections between arteries and veins without capillary network. Brain AVMs affect 0.1% of the population [1] with an incidence of 1.3 per 100,000 persons a year [2]. Cerebral AVMs can be asymptomatic, but when they are symptomatic, patients can present with intracranial hemorrhage (ICH), seizures, neurological deficits, and headache [3, 4]. The most frequent presenting symptom is ICH, detected in 50% of cases [4]. Hemorrhages are usually intraparenchymal, but subarachnoid location is also common: brain AVMs are responsible for 9% of subarachnoid hemorrhages [5] and represents the leading cause of ICH in young adults [4]. The overall annual rupture risk was reported to be 2.3–3%, 1.3–2.2% for unruptured, and 4.5–4.8% for ruptured cases respectively [4, 6]. Patients with a history of ruptured AVM are at higher risk of hemorrhage than those without it. Seizures are present in 11–33% of cases [7]. The 5-year seizure risk for asymptomatic patients with AVM is 8%, although when presenting with ICH or focal neurologic deficits the same risk rises to 23% [8]. Headache was reported to be associated with cerebral AVM in 17–50% of cases [9], while neurological deficits may be present in 3–10% [10]. Mortality rates range between 0.7% and 2.9% per year [11].

Treatment options include conservative therapy, neurosurgical elimination, radiosurgery, endovascular techniques, and combinations of these options. The therapeutic approach

to AVMs is controversial. Only one randomized controlled trial was published in the literature on the management of unruptured AVMs. According to the findings of the ARUBA trial it is suggested not to perform interventional treatment in such cases due to worse clinical outcome compared to those cases with medical treatment alone [12]. Many authors are arguing with these results due to their professional experience, controversial results of other reports, and the main limitations of the trial: application of a variety of treatment modalities without specifying the selection strategy, inclusion of a variety of different size and type of AMVs, and the short follow-up period [13, 14]. Nevertheless, the results of the non-randomized Scottish Audit of Intracranial Vascular Malformation with a follow-up of 12 years also supports the findings of the ARUBA trial [15]. Altogether because of the lack of evidence-based guidelines for management options, the therapeutic approach is highly individual, should be multidisciplinary, and has to be based on as much information as possible. According to the ARUBA trial, as well as in clinical practice, the primary consideration for decision-making in cases with untreated AVMs is the risk of hemorrhage, disability and mortality [13, 15, 16]. The impact of an untreated AVM on the quality of life (QOL) is generally not considered. Reports on outcome regarding QOL are uncommon in the literature, with most of the publications not focusing on cases with untreated AVM [17, 18], although disability doesn't always correlate with the QOL. Therefore, its assessment can provide important additional information for therapeutic decisions. The application of QOL assessment is increasingly accepted as a major endpoint in clinical trials and has a more important role in decision-making in neurosurgical practice as well [19, 20]. Hereby we report our observational results of patients with brain AVM without interventional treatment based on their QOL.

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Methods and Materials

Twenty female and 16 male patients were enrolled in our study with a mean age of 45 ± 16 years. Subjects were identified retrospectively from the AVM database of our hospital. Patients with unruptured cerebral AVM without interventional treatment over the age of 18 met our inclusion criteria. We excluded patients with other intracranial pathology potentially responsible for the symptoms. The AVMs were detected between 2000 and 2018. All patients have visited either the outpatient or the inpatient ward of the National Institute of Clinical Neurosciences in Budapest, where the diagnosis of AVM was either made or confirmed. After physical examination, AVM was detected by either contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Digital subtraction angiography (DSA) was performed for precise characterization of the AVM in each case. Treatment decision (conservative or invasive) was made by the patient or chosen individually by the treatment team.

We used the standardized EQ-5D-5L questionnaire for measuring the QOL [21]. It was designed by the EuroQol Group to estimate the patient's health-related state with the help of a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L descriptive system consists of a 5-level scale (according to the severity of symptoms) in five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression). The VAS registers the patient's actual level of general health on a scale from 0 to 100, assuming 0 as the worst and 100 as the best imaginable health state. Our subjects were interviewed by telephone in 2018 retrospectively. No previous QOL tests were performed in their cases prior to our study.

As a control group we used the results of the Research Report (RR) of the National Health Survey from 2002 [22]. This Hungarian nationwide report used the EQ-5D-3L questionnaire [23] to measure the QOL on a cohort of 5534 healthy subjects. This questionnaire was also designed by the EuroQol Group as a less sensitive tool than the EQ-5D-5L version; it uses a 3-level scale instead of 5 in case of every dimension of the descriptive system. Level 1 is chosen if the subject doesn't have any problem in the designated dimension, Level 2 if there is some trouble regarding the category, and Level 3 if severe impairment is present. The EQ-5D-3L descriptive system results of the RR were categorized in two groups for statistical analysis in every dimension: the first group contained the answers of Level 1, while Levels 2 and 3 represented the second group. To facilitate an adequate comparison we categorized our results likewise: the first group represented patients with no complaint (Level 1) and subjects with any complaint (Level 2–5) became the members of the second group. The aforementioned RR discussed

their findings in three age groups (18–34, 35–64 and older than 65) and considered females and males separately. We, therefore, made the same subdivisions. The RR summarized their findings on VAS as well, though they were not reported by age groups; therefore, we lacked data for adequate comparison.

We compared the results of the descriptive system of the RR with our findings, but statistical analysis wasn't made due to the small number of our subjects. For illustrating our results, we prepared diagrams to demonstrate the numeric differences between the two groups. Our observations on the VAS were also provided in details and demonstrated visually, but we missed data for comparison.

The study was approved by the Institutional Committee of Science and Research Ethics of the National Institute of Clinical Neurosciences. All participants gave written informed consent of participation.

Results

Thirty-six patients ($n = 20$ female and $n = 16$ male) met our inclusion criteria with a mean age of 45 ± 16 years. Their average follow-up time was 57.4 ± 49 months. Headache was present in 15 patients with a female predominance ($n = 12$ female and $n = 3$ male), thus proving to be the most common AVM-related sign in our cohort (41.6%). Epileptic seizures occurred in nine cases (25%), more commonly affecting male subjects ($n = 7$ male and $n = 2$ female). Neurological deficit was detected in 33% of our cohort ($n = 12$; $n = 8$ female and $n = 4$ male). Table 1 shows the patient characteristics.

Results of the EQ-5D-5L Descriptive System

Mobility

We observed a tendency toward decrease in the mobility of our female subjects by age, which occurred also in the control population, but less frequently. Although we expected the same tendency for men, older male subjects proved not to

Table 1 Patient characteristics. Division by the sex of the patients

	Female (<i>n</i>)	Male (<i>n</i>)	All (<i>n</i> , %)
Age			
18–34	6	5	11 (30.5%)
35–64	10	8	18 (50%)
>65	4	3	7 (19.5%)
Symptoms			
headache	12	3	41.6 (40%)
epileptic seizures	2	7	9 (25%)
neurological deficit	8	4	12 (33%)

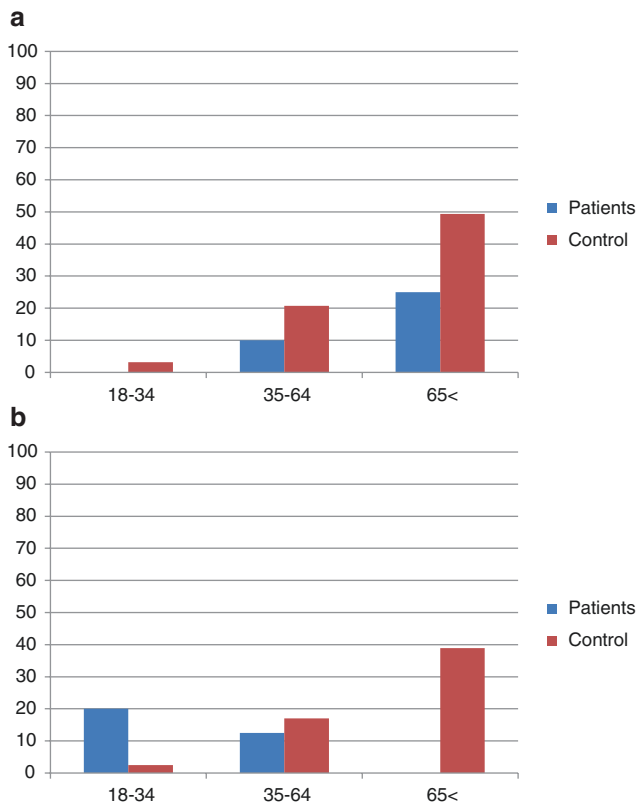


Fig. 1 (a) Female mobility impairment according to age groups in our patients (blue columns) compared to the control cohort (red columns). (b). Male mobility impairment according to age groups in our patients (blue columns) compared to the control cohort (red columns)

have any problem in this regard, middle-aged patients had less complaint than the subjects of the RR, and young males showed significantly more severe impairment in their mobility compared with the control group (we observed an eight-fold difference) (Fig. 1).

Self-Care

Although the results of the RR show an increasing impairment by age in the question of self-care, our female subjects and younger male patients proved not to be limited by this factor. In case of our male subjects older than 65 years of age, we observed a severe impairment in comparison with the control group (twofold difference) (Fig. 2).

Usual Activity

Decline in usual activity showed a male dominance in our cohort. The most significant difference between the control group and our patients was seen in the case of young (22-fold difference) and middle-aged males (2.8-fold difference). Only middle-aged female subjects exceeded their healthy controls. *Altogether usual activity impairment seems to be a more limiting factor in male patients under the age of 65 years* (Fig. 3).

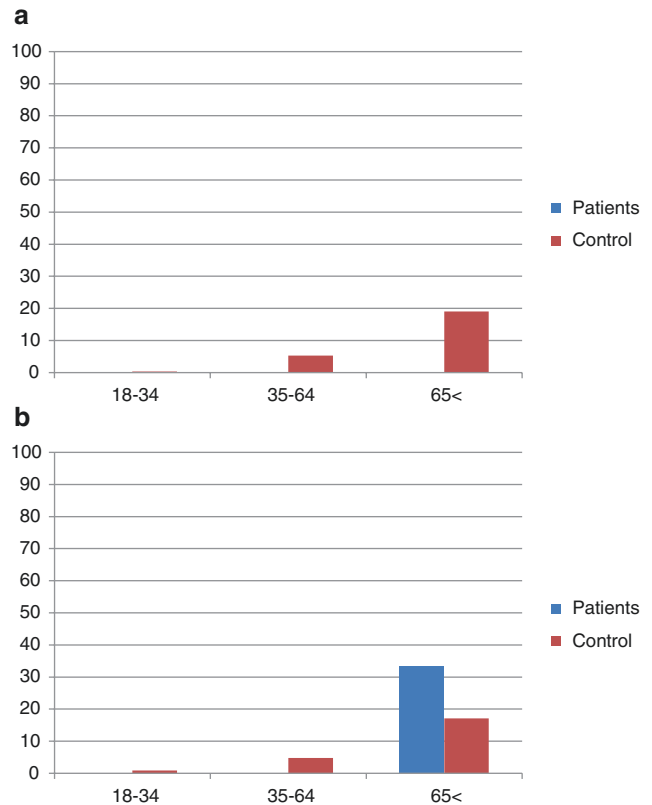


Fig. 2 (a) Female self-care impairment according to age groups in our patients (blue columns) compared to the control cohort (red columns). (b) Male self-care impairment according to age groups in our patients (blue columns) compared to the control cohort (red columns)

Pain and Discomfort

Pain and discomfort have an increasing impact on the QOL of the general population by age according to the results of the RR. Women are affected more frequently in all age groups compared with male subjects. Our patients demonstrated a different behavior. Young women (18–34 years) exceeded by 3.6-fold the level of their healthy controls, while female subjects older than 35 years of age stayed below the level of the control group. Middle-aged male patients also surpassed the control males by 1.4. The greatest difference (fourfold) was seen in case of young male subjects (18–34 years). *In conclusion, cerebral AVM has the most remarkable effect on pain and discomfort in case of young patients, especially in male subjects* (Fig. 4).

Anxiety and Depression

Very similarly to the pain and discomfort results we found anxiety and depression to affect young patients (18–34 years) the most, surpassing the RR population. Eighty percent of men and 50% of women of the youngest age group answered that anxiety and depression were important factors in their lives due to their diagnosed AVM. Different sex ratios, however, were found: 2 for female and 5.3 for male patients.

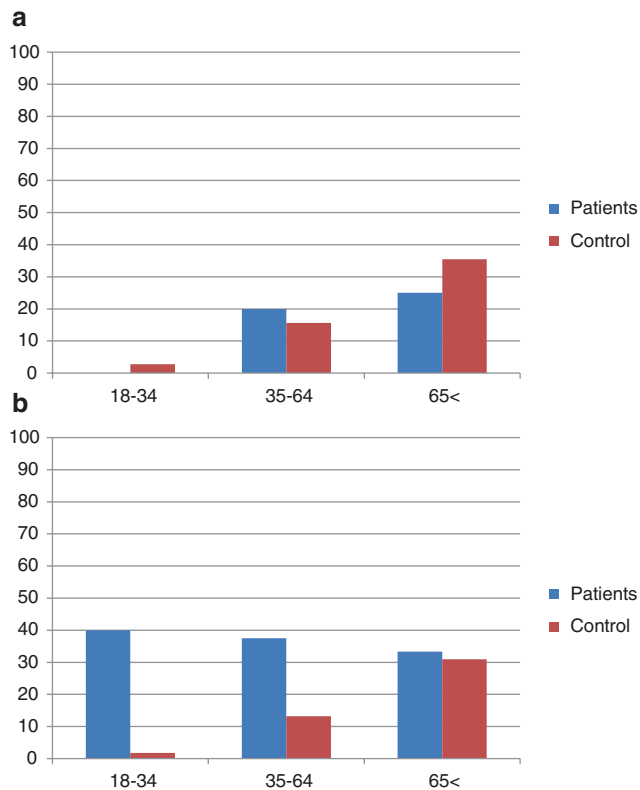


Fig. 3 (a) Female usual activity decline according to age groups in our patients (blue columns) compared to the control cohort (red columns). (b) Male usual activity decline according to age groups in our patients (blue columns) compared to the control cohort (red columns)

Middle-aged males also surpassed the control group, but only with a 1.25-fold difference. *In conclusion, brain AVM also has a significant effect on anxiety and depression with a male predominance in case of younger patients* (Fig. 5).

Impact of the Different Factors on QOL

We found that anxiety/depression and pain/discomfort are the most significant factors influencing the QOL in our cohort (47.2% and 41.6% respectively). Twenty-five percent of our patients responded that they had troubles in performing their usual activities, while mobility and self-care were affected less frequently (11% and 2.7% respectively) (Fig. 6).

Results of the EQ-5D-5L VAS

The mean result of the VAS in our cohort was proved to be 84.6 ± 22 points. According to age groups, the youngest and middle-aged patients were found similar (83% and 86%), while older subjects rated themselves to a lower level (70%). Forty-four percent of our cases rated themselves above 95 points, while 30.5% of them considered their actual level of general health less than 80 points. The RR findings on VAS

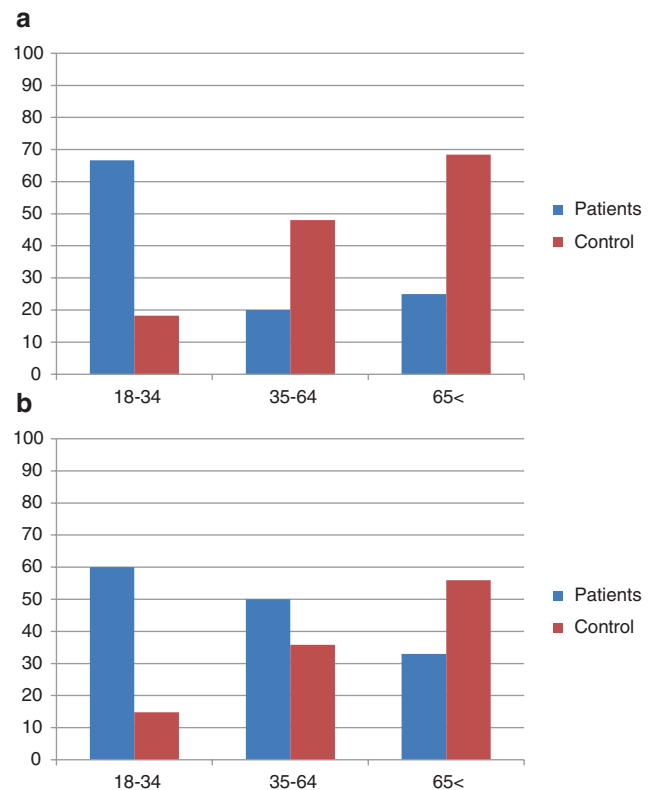


Fig. 4 (a) Female frequency of pain and discomfort according to age groups in our patients (blue columns) compared to the control cohort (red columns). (b) Male frequency of pain and discomfort according to age groups in our patients (blue columns) compared to the control cohort (red columns)

were not reported by age group; therefore we lack data for comparison (Table 2).

Discussion

Untreated unruptured brain AVMs do have an impact on the QOL. Due to the judgement of more than 30% of our subjects, living with cerebral AVM represents a significant limitation in their QOL. Multiple conditions are responsible for the decreased level of health, but anxiety, depression, pain, and discomfort seem to be the most common influencing factors, especially in young male subjects. Female patients with untreated AVMs demonstrate a greater dependence than men in all age groups. Males with a predominance of young age have a more significant impairment in their usual activities when compared to women. Older patients are affected more significantly in their self-care, while the impact of discomfort and anxiety is more severe in the younger population. The impairment of mobility was seen to surpass significantly the healthy controls in case of young men.

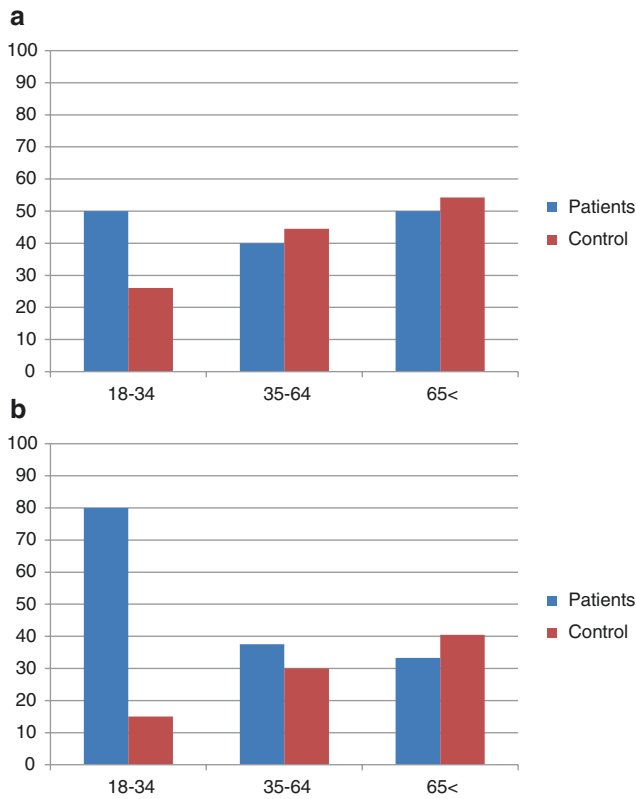


Fig. 5 (a) Female frequency of anxiety and depression according to age groups in our patients (blue columns) compared to the control cohort (red columns). (b) Male frequency of anxiety and depression according to age groups in our patients (blue columns) compared to the control cohort (red columns)

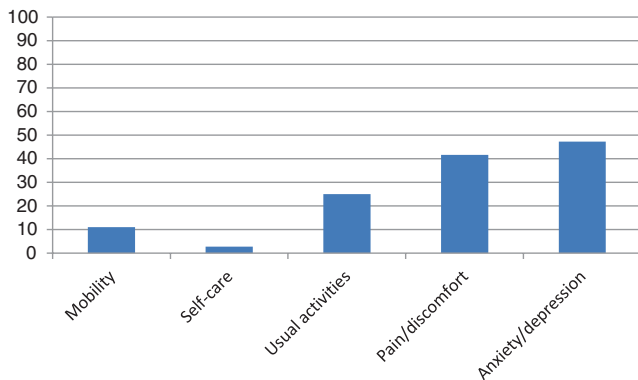


Fig. 6 Impact of the different factors on the QOL in our cohort

Table 2 The VAS results of our cohort by age groups. Male and female subjects are discussed separately

Age	Female (%)	Male (%)
18–34	86.7	78.8
35–64	88.5	84.6
65<	78.8	58

In summary, untreated cerebral AVMs seem to have the most demonstrative impact on young male patients, although the limiting factors are highly individual. QOL assessment is, therefore, an important tool and needs to be considered in the therapeutic decision-making in patients with brain AVM. Future studies are necessary to confirm our findings.

The main limitation of our study is the low number of cases, especially in the subgroup calculations, so compelling statistical analysis could not be done when comparing with the control group. Another weakness is the high scatter in the follow-up time and the time between the diagnosis and QOL assessment. Further investigations are needed with larger cohorts and longer follow-up times, though the rarity of the disease represents a great limiting factor.

The strength of our study is the demonstration of the outcome of QOL in the natural course of the disease focusing on purely untreated cases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no financial or other conflicts of interest.

Ethical Approval The study was approved by the Institutional Committee of Science and Research Ethics of the National Institute of Clinical Neurosciences and it have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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Complications in AVM Surgery

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Surgery of cerebral arteriovenous malformations (AVM) is considered to be high-risk. This means that the risk of having complications during or soon after surgery is substantially elevated. This article describes the possible peri-operative complications for surgery of arteriovenous malformations and some suggestions to avoid their onset.

Brain malformation surgery has predominantly three kinds of complications that may result in possible neurological deficits for the patient:

1. Direct lesion of eloquent areas.
2. Postoperative bleeding due to the presence of a residual that has not been removed during surgery.
3. Postoperative hyperemia.

Direct Lesion of an Eloquent Area

Defining the limits between what is eloquent and what is not eloquent is not always so simple. Traditionally, eloquence has been referred to the cortical areas assigned to a specific function, essentially the motor areas, the areas of language and visual function, in addition, of course, to the brain stem and the deep structures. Magnetic resonance imaging with its high definition allows us to accurately understand the cortical areas affected by the arteriovenous malformation and the contiguous ones that may be damaged by surgery.

Functional resonance in arteriovenous malformations is questionable [1] and probably not reliable, because the excessive flow surrounding the AVM can alter the BOLD

effect. Transcranial magnetic stimulation may be a more precise method to identify the eloquent function. [2].

A malformation that affects eloquent cortical areas is hardly indicated as susceptible to surgical treatment. In these cases, the use of the Gamma Knife is the preferred alternative to surgery [3, 4].

Concerning eloquence, until a decade ago, white matter did not deserve great attention from neurosurgeons. Over the last decade the study of magnetic resonance with tractography allowed a more precise definition of the deep tracts of white matter [5, 6] and how eloquent they are. Before the introduction of the non-stick bipolar, one of the biggest problems to deal with, during arteriovenous malformations surgery, was to control the bleeding from the deep medullary vessels. That typically comes from the deep of the white matter [7]. These deep medullary vessels were extremely challenging to coagulate and required a meticulous and patient coagulation technique that was often laborious and difficult to obtain. Managing these fragile vessels was difficult because of the disproportion between the size of the vessel and the thickness of the protein wall. These vessels must often be pursued in the depth of the white substance to obtain a secure hemostasis. This often caused a damage of eloquent white matter tracts. Conventional bipolar forceps were effective only within a narrow range of humidity obtained by the irrigation of the surgical field. An excessive washing made the coagulation ineffective, while an insufficient washing led to an adhesion of the vessel to the tips of the bipolar forceps with subsequent rupture.

Today the hemostasis techniques are significantly improved. The introduction of the non-stick bipolar permits a more effective coagulation and does not require irrigation (dry coagulation). This allows the surgeon to be more effective at lower-current intensities without sticking the wall of the fragile deep vessels to the tip of the bipolar.

The use of non-stick dry coagulation, possibly in association with the “dirty coagulation” described by Hernesniemi, now makes coagulation of these medullary vessel easier and

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more effective. Dirty coagulation is a technique that, when the vessel wall is very thin, uses a small part of brain tissue adjacent to the vessel to increase the amount of protein to be subjected to coagulation [8]. This changed the risk of damaging eloquent deep white matter and permits more selective excision of the arteriovenous malformation within the interface malformation-brain tissue. We have found also that Thulium laser proved to be very useful in coagulating these very fragile deep vessels. It is a very versatile tool that allows a coagulation of the vessels without direct contact [9]. We prefer to avoid the use of contact hemostatic agents in AVM surgery, as often postoperative bleeds are related to residues and cannot be avoided with overlying hemostatic agents that can actually cause the spread of the bleeding into the parenchyma instead of the subarachnoid space. If a vessel has to bleed, it is preferable for the blood to spill in the cavity rather than within the brain.

Moreover, in the last few years the strict interaction with neuroradiologists promoted the selective use of presurgical embolization to close specific deep vessels that we anticipate will be difficult to reach during the excision of the AVM, instead of a massive nidus embolization. The previous strategy of embolizing the nidus with Onyx through the large feeders keeps the deep feeders open, often with an increased flow, complicating the control of bleeding [10]. Selectively embolizing the deep feeders reduces the need to follow a bleeding vessel in the deep white matter. Difficulty controlling hemostasis of these vessels was one of the main causes of postoperative neurological damage. The introduction of non-stick bipolar dramatically improved the outcome of AVM surgery by allowing a more selective resection with a faster and safer surgery.

Obtaining a good hemostasis of the deep vessels is essential to avoid direct damage to the white substance but is also the key to avoiding postoperative hemorrhages. A last detail can be suggested regarding arteriovenous malformations with deep feeders involving branches from the choroidal arteries: When safe, try to reach the ventricle, where the medullary vessels coming from the choroidal arteries are more easily identifiable and controllable.

Postoperative Hematoma

Postoperative bleeding usually occurs very early, in the first postoperative hours after surgery for arteriovenous malformation. Out of 214 AVM treated in the last 7 years, we had only two episodes of postoperative bleeding that occurred after 24 h.

The main causes of postoperative bleeding are:

- An inaccurate hemostasis of the aforementioned deep feeding vessels.
- A bleeding from a large-sized vessel where coagulation ceases after a while. We experienced re-bleeding from

vessels that appeared to be well coagulated and then caused postoperative hematomas. We observed that relevant-sized collateral originated a few millimeters before the previously coagulated end of the cut vessel. The collateral therefore maintained high pressure near a too-short coagulated tract of the vessel. We therefore recommend in these cases to use a micro clip to control the bleeding. It is important to keep a long-coagulated tract of the vessel where the blood can stagnate and then stabilize the clot. If this is not possible, and if the vessel has a significant caliber, it is advisable to use micro clips for AVM to ensure a better seal of the clot.

- A third element that can lead to postoperative bleeding is the presence of a residual of the malformation that has not been removed during surgery because it is hidden by brain tissue. In our experience this has happened close to eloquent areas that we want to preserve, or has been caused by lack of awareness of the full extent of the malformation. The presence of a residual in the postoperative angiography has a high risk of bleeding, so our *modus operandi* is to return to the operating room and complete the removal of the malformation in the same setting, if this is possible. It is important to reduce intraoperatively the chances that this will occur. Tools that allow us to detect the presence of a hidden residual at the end of the surgical procedure are:

- Intraoperative Fluorangiography (FA) with Indocyanine green is useful to check the flow in the vessels in real time. A recognized limit of FA is that it shows only what is on the surface. What is beyond the surface remains hidden. Nevertheless, the key sign to look for in the presence of a hidden residual of AVM is the early filling of a visible vein in the surgical field [11].
- Intraoperative Ultrasound doppler and enhanced Ultrasound imaging with microbubbles contrast. High definition ultrasound is a new, valuable instrument in the OR. It is cheap and in real time. It can be of valuable in AVM surgery. Doppler ultrasound can show a high flow beyond the surface. The use of contrast with microbubbles allows us to identify beyond the visible surface the possible presence of a small residue. It is a technique that requires training and confidence with the instrument, but can be a precious help [12].
- The intraoperative micro-Doppler can be used to explore the entire surgical cavity. If high flow is identified, it can indicate a residual malformation that is worthwhile to explore [13].
- Obviously the most suitable instrument to identify AVM residuals is a catheter angiography; therefore, a hybrid surgical room equipped with intraoperative angiography represents the best solution. They are rare and only few centers have the luxury of an integrated operating room. If the hybrid O.R. is not available, we suggest obtaining an angiographic

examination immediately at the end of the surgical procedure even if this may prove time-consuming. The last element that can favor a postoperative bleeding is an increase in the arterial pressure during the postoperative awakening or transport of the patient. During the awakening phase, the patient can feel pain and the arterial pressure can increase, or the patient may cough and increase the venous pressure. Both situations are dangerous when you must rely on fragile vessels just coagulated. For this reason, it is preferable to maintain the patient asleep for at least 12 h in intensive care, especially in complex malformations and those where intraoperative hemostasis has been more difficult. This allows for the stabilization of the clot in the closed vessels.

Postoperative Hyperemia

This complication typically occurs 3 or 4 days after the intervention. It is a hemorrhagic infarction of the surrounding brain that progressively evolves and that may require reoperation or even bone-flap removal for brain decompression.

The underlying process is explained by three different theories:

- Normal perfusion pressure breakthrough [14, 15]
- Occlusive hyperemia [16]
- Venous engorgement [17–19]

The Normal perfusion pressure breakthrough theory is a term coined by Spetzler in 1978. He used it to indicate a postoperative hyperemia responsible for hemorrhagic infarction. According to the theory developed by Spetzler, the brain tissue around an arteriovenous malformation has lost the ability of self-regulating based on CO₂. The chronic dilatation in the presence of chronic ischemia prevents an increase in the resistance of the capillaries once the malformation has been removed. The chronically dilated low-resistance vessels are therefore unable to resist the suddenly increased flow once the flow is redirected in the surrounding tissue after the AVM is removed.

The second theory is the occlusive hyperemia theory, proposed by al-Rodhan in 1993. It is based on two interrelated mechanisms: the first refers to stagnation of the arterial flow in the vessels that previously supplied the malformation and its collaterals; the second refers to an obstruction of the venous drainage in the adjacent brain tissue, resulting in a venous engorgement.

The theory on venous engorgement refers to stagnation only into the venous compartment. This theory was proposed in 1993 by Wilson and sustained by Schaller in 2002 and by D'Aliberti in 2013. If the malformation has

one or more large venous outflows, these veins tend to thrombose when the AVM is removed. If these veins drain the venous outflow of the surrounding cerebral parenchyma, thrombosis may extend so as to cause venous outflow obstruction, and therefore venous infarction of the surrounding brain tissue.

In our experience, postoperative hyperemia is a rare phenomenon. Out of 266 cases it occurred only three times. In these three cases there was a large venous pattern that suggested that the third hypothesis may reflect the underlying mechanism best.

We consider it extremely important to pay attention to the venous drainage of arteriovenous malformations. When the cerebral venous discharge involves the large draining veins of the malformation, the surgical risk of having postoperative infarction is relevant. A direct surgical access to the malformation must therefore be evaluated and eventually postponed (Fig. 1). Our strategy, depending on the characteristic of the malformation, is to treat the malformation with an embolization in order to reduce the flow through the vein, and then wait a few months, if possible, to reduce the caliber of the main drainage vein. The second alternative is to treat the malformation with Gamma Knife to reduce the flow, allowing the venous outflow to redistribute. The possible residual can be operated after a few years.

Finally, in a few cases where there was a single large draining vein that collected also normal brain vein drainage and where we were worried that the thrombus can spread to functionally useful veins, we used a technique to reduce the caliber of the main draining vein of the malformation. On four occasions we treated the vein intraoperatively with Tullium laser, shrinking the vein and obtaining a reduction in the caliber to almost half of the diameter. The goal of this procedure was to increase the flow velocity and therefore prevent stagnation and thrombosis in the postoperative period (Fig. 2).

Conclusions

Surgically related complications in AVM treatment, in many cases, can be avoided by paying attention to details:

1. Careful selection of the patient:
 - (a) addressing a patient with eloquent AVM to Gamma Knife treatment
 - (b) preoperative treatment with selective embolization of the accessible deep feeders
 - (c) preoperative gamma knife or embolize those patient with an over-expressed venous pattern
2. Meticulous coagulation of deep medullary feeders:
 - (a) Using dirty coagulation
 - (b) Using dry non-stick coagulation

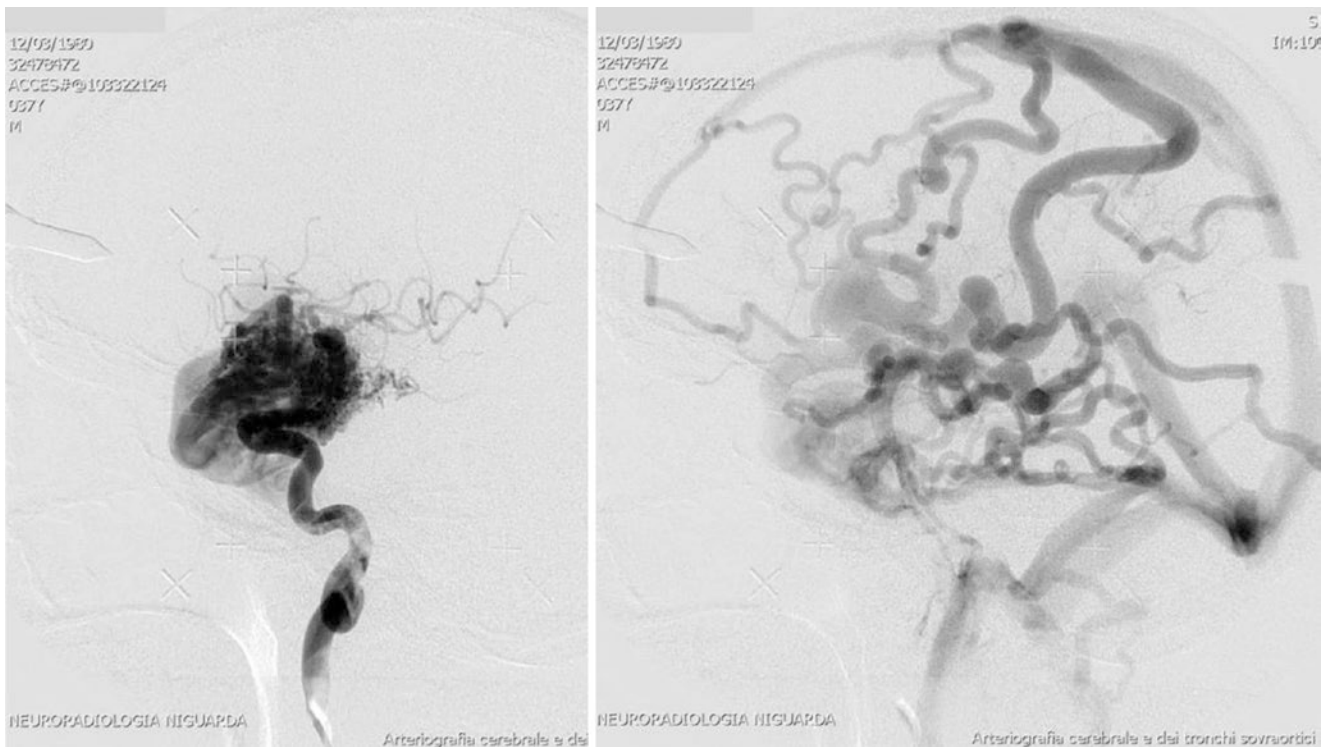
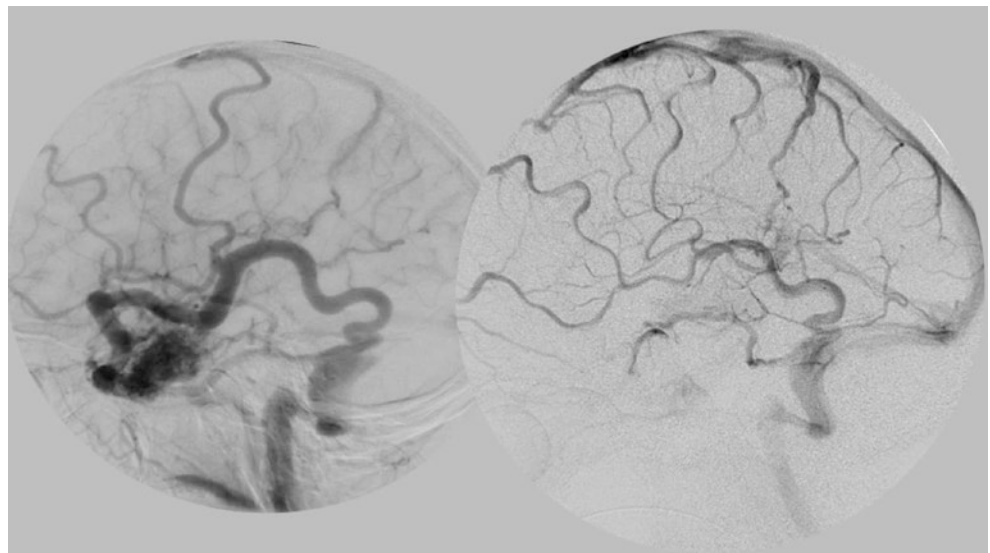


Fig. 1 An overexpressed venous pattern of a small temporal AVM. Resecting the AVM in this case, although technically feasible, is very dangerous due to the high risk of extensive thrombosis of the venous network

Fig. 2 Laser shrinkage of the main draining vein to prevent spreading of the thrombus through useful draining veins



- (c) Using micro clips
 - (d) Using laser
 - (e) Reaching the choroidal vessel in the ventricle when possible
 - (f) Avoiding occlusive coagulation with hemostatic agents
3. Check and avoiding any residual of the AVM

4. Keep the patient under pressure control during postoperative period

Fulfilling these steps contributed over time to reduced complications in this difficult surgery, leading to a safer treatment that compares favorably with natural history of brain arteriovenous malformations [20].

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Surgical Simulation with Three-Dimensional Fusion Images in Patients with Arteriovenous Malformation

Takayuki Hara and Masanori Yoshino

Introduction

In AVM surgery, evaluation of angiostructure is essential to make a good surgical strategy. With conventional two-dimensional digital subtraction angiography (DSA), it is sometimes difficult to understand AVM structure stereoscopically. Three-dimensional rotational angiography (3D-RA) gives us much more precise information about the relationships of each feeder, drainer, and nidus, but when the AVM is supplied by a multiple vascular territory (e.g., middle cerebral artery and posterior cerebral artery), all the details cannot be seen in one image. For the surgical simulation, the location of the nidus in the brain is also important so as to decide the surgical approach. Recent image fusion technologies have helped surgeons create virtual surgical fields, especially in brain tumors [1–3]. In this article the authors introduced 3D fusion images in AVM surgeries and evaluated their clinical use.

Methods

Image data, including 3D-RA, 3D-rotational venography (RV), computed tomography (CT), and magnetic resonance imaging (MRI), was obtained from AVM patients. Three-dimensional-RA and RV were performed with a C-arm angiography unit (Allura XperFD 20/10; Philips Medical Systems, Best, the Netherlands). The C-arm rotated through 240° at 55°/s and obtained 120 images on a 17-in. FOV during contrast injection. MRI was performed with a 3.0-T system for the head (Ingenia 3.0T; Philips Healthcare, Andover, MA.). Fluid-attenuated inversion recovery (FLAIR) in MRI was acquired with an eight-channel head coil. CT was done

with a 64-section CT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). The slice thickness was 1 mm.

Image data was coded in digital imaging and communication in medicine (DICOM) format and was imported to the two different imaging applications. In this study, we used iPLAN cranial (BrainLab, Germany) and Avizo (Visualization Science Group, Bordeaux, France) for 3D image reconstruction using a previously reported method [1, 2]. In iPLAN, the 3D model was constructed with a volume rendering method with autosegmentation, whereas Avizo used a hybrid method combining surface- and volume-rendering methods, and manual segmentation was used to distinguish the small anatomical structures, such as the feeding arteries, from surrounding noise.

Results

The 3D fusion images of the right parietal lobe AVM for a representative patient are illustrated in Fig. 1. The fusion image with iPLAN has lower resolution and the feeders, nidus, and drainers are not distinguishable because these three vasculatures are visualized in the same time phase in case of arterio-venous shunting disease. Avizo created higher resolution images, and feeders, drainers, and normal vessels are visualized clearly with different colors. Also, each feeder and its supplying territory in the nidus are distinguished, and surgical simulation becomes possible after adding the MRI (FLAIR) and CT images (Fig. 2). On the other hand, the time required for creation is much shorter in iPLAN (approximately 1 h) than Avizo (more than 3 h).

Discussion

In AVM surgery, understanding the angiostructure is essential for planning good surgical strategy. In principle, feeders should be occluded before the dissection and obliteration

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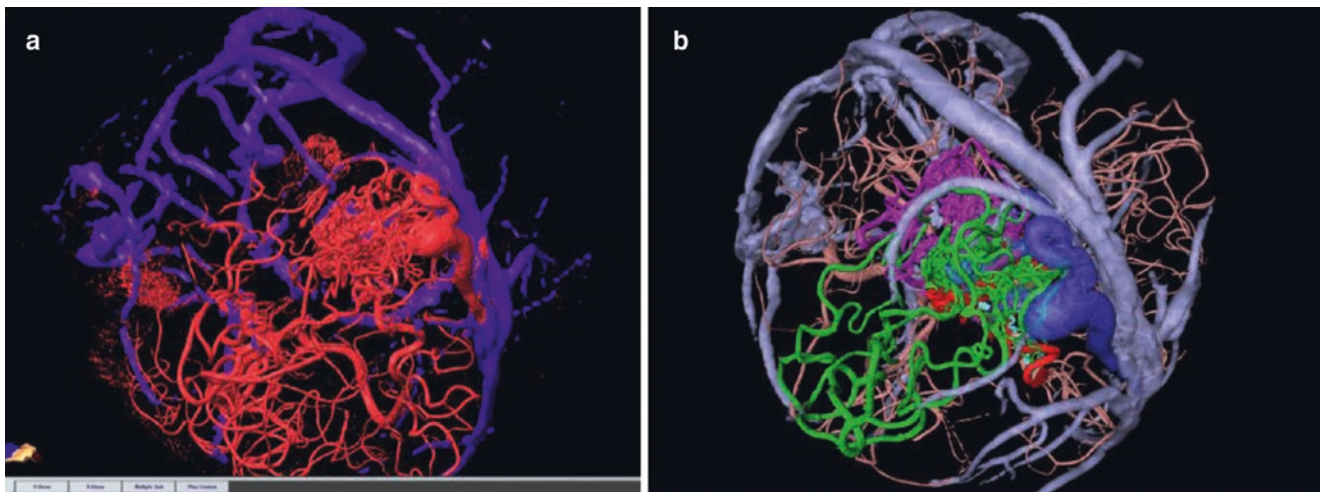


Fig. 1 Three-dimensional fusion images in an 18-year-old female with right parietal AVM. (a) Fusion image by iPLAN. Feeder, nidus, and drainer are visualized in the same color. (b) Fusion image by Avizo.

Each feeder, drainer, and surrounding normal vein is identified separately with high resolution

of the gliotic tissue around the nidus. However, in conventional angiography, and especially with high-flow AVMs, it is sometimes difficult to identify each feeder and its anatomical relationship with the nidus and drainers. Three dimensional-RA images give us much more precise information about the angiostructure of AVMs, and have become prerequisites for the surgery. However, in the real surgical field, we have to dissect the nidus from the brain, and the feeders may be found on the brain surface or in the sulci or fissures; therefore it is also necessary to evaluate the anatomical relationship between the AVM and the brain. Surgeons must currently use their experience and knowledge to mentally reconstruct 3D fusion images from different modalities for this purpose. In this study, we created two types of 3D fusion images in AVM patients with different imaging software and compared their efficacy in the surgical simulations. Images by iPLAN were easily created without much time or AVM surgery experience, because this software enables the automatic segmentation of DICOM data. The resultant 3D fusion image is highly versatile, the quality is similar between creators, and it can be introduced to the navigation system (BrainLab), all of which make surgical simulation easier for less experienced surgeons. On the other hand, the resolution is not so high and each feeder and its supplying territory in the nidus are not distinguishable. Moreover, it is difficult to find “hidden feeders” existing just behind the drainer, which we sometimes encounter in a clinical setting, because feeders and drainers are recognized in the same color. In contrast, 3D fusion images by Avizo are created by both surface and volume rendering methods, so that they have a much higher resolution and the contrast between feeders, nidus, and drainers are much better than with the images by

iPLAN. Therefore, we can identify all feeders even if they are close to the drainers or “en passage” arteries (Fig. 2). Avizo can also discriminate not only each feeder but also its supplying territory in the nidus with different colors, helping us to understand which feeders impinge more on the nidus (Fig. 2). According to these data, we can then decide which feeders have priority for surgical or endovascular occlusion. Adding MRI data to the Avizo images produces a virtual surgical field and surgical simulation (positioning, craniotomy, exposure of the brain, and the dissection of the nidus) becomes easy.

AVM surgical simulation with other virtual reality technologies has also been published [4, 5]. In these articles, the authors created 3D fusion images with a virtual reality simulator (Dextroscope), but they used only MR-angiography (MRA) and MR-venography (MRV) as vessel images, so the resolution of each vessel was not as high and classification of each feeder and its supplying territory in the nidus was impossible. To our knowledge, only Avizo provides adequate detail to distinguish individual feeder territories, so it may have an advantage especially in the surgical simulation of large, complex AVMs. On the other hand, the limitation of the Avizo imaging technique is that it is time-consuming because the segmentation of DICOM data and extraction of each feeder must be done manually and requires some knowledge of AVM surgery.

Conclusions

To make the surgical simulation of AVM easier, it is important to visualize all vasculatures sterically. Recent technologies have made this level of detail possible with 3D fusion

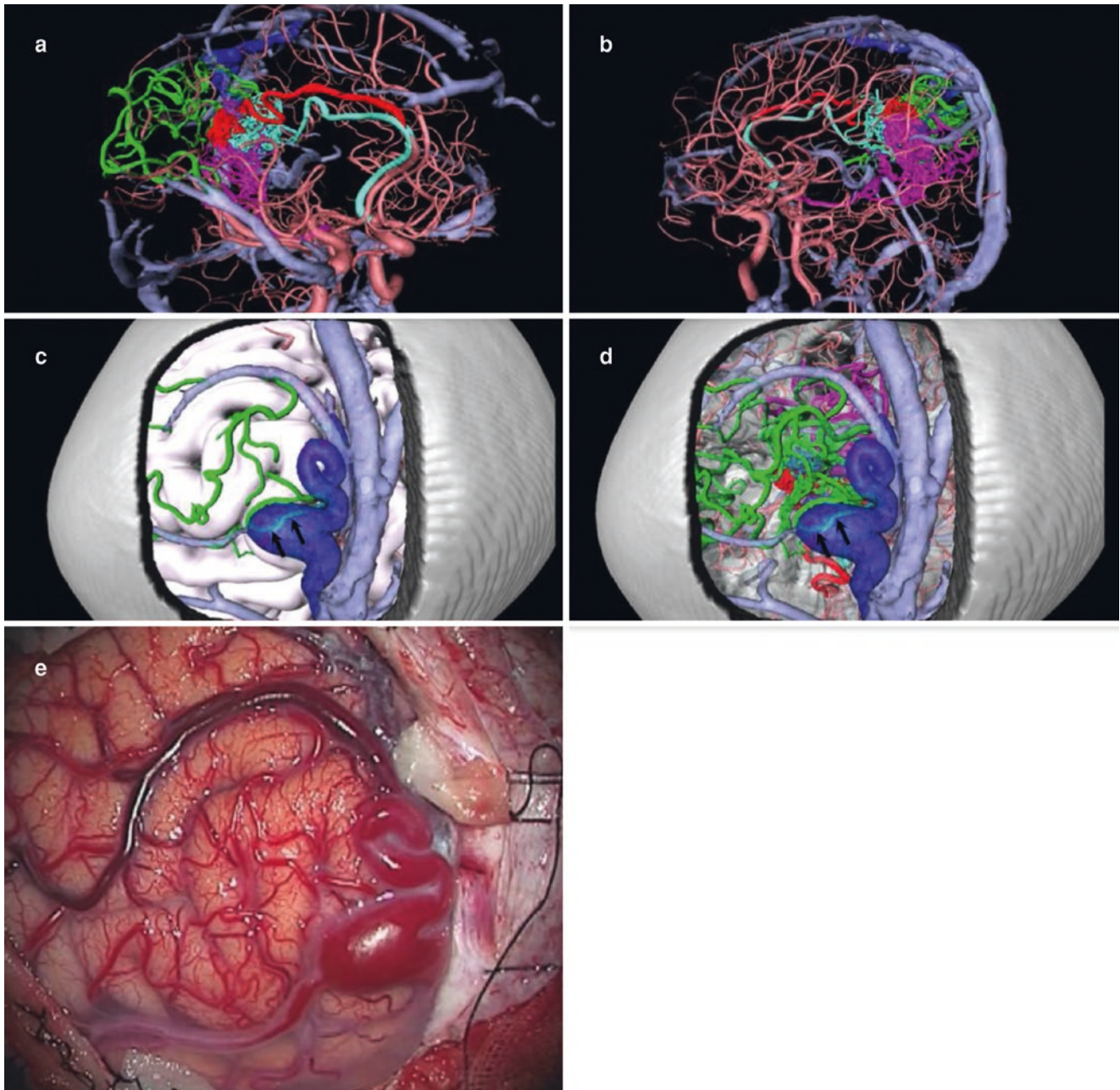


Fig. 2 Three-dimensional fusion images of the same patient by Avizo and comparison to the surgical field. (a, b) Not only each feeder but also its supplying territory in the nidus is well demarcated. Feeders from anterior cerebral arteries are colored red and cyan, those from middle cerebral arteries are green, and those from posterior cerebral arteries are

pink. (c, d) Surgical simulation using fusion images. The feeder existing just behind the main drainer (arrows) is well recognized. (e) Real surgical field in the same patient. The cortical artery feeders were quite similar to fusion image (c)

images. Our study demonstrates that the Avizo 3D fusion images may be especially useful in surgical simulations for large, complex AVMs, and adoption of this technology may contribute to safer AVM surgeries.

Conflict of Interest The authors declare that they have no conflict of interest.

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Surgical Treatment of Unruptured Brain AVMs: Short- and Long-Term Results

Shalva Eliava, Vadim Gorozhanin, Oleg Shekhtman, Yuri Pilipenko, and Olga Kuchina

Introduction

Brain arteriovenous malformations (bAVM) are one of the most common congenital vascular brain malformations, which frequently manifests at young age [1]. Besides hemorrhages, patients may exhibit seizures (17–40%) and chronic headaches (9.8–46%) that decrease the quality of life [2]. Growing access to high-quality imaging has increased the number of patients with unruptured bAVM. The annual risk of bAVM hemorrhage reported previously is 1.7–3.1% [3–7]. Mortality after rupture reaches 29% and permanent morbidity occurs in more than one-third of cases [8].

Microsurgery remains the most effective treatment option and is considered a first-line treatment for ruptured bAVMs [9–11]. However, the clinical approach to unruptured AVMs remains under discussion. ARUBA randomized trial and the following SAIMS showed that conservative management is more beneficial than invasive modalities. Trial results were followed by a wave of criticism from neurosurgeons across the globe. Many specialists emphasized numerous biases that could have affected its results. Further surgical series for unruptured bAVMs published in the “post-Aruba era” mostly overruled ARUBA conclusions. The presented work reflects our experience with unruptured AVM patients operated upon in Burdenko National Research Center for Neurosurgery.

Materials and Methods

The retrospective study included 160 adult patients (>18 years old) with unruptured bAVMs admitted for microsurgery in 2009–2017. Of these, 93 (58.1%) were males and

67 (41.9%) were females. Mean age was 33.4 ± 10 years (range 18–67 years). No signs of hemorrhage were found on brain MRI or CT in all cases. Seizures were the most common clinical sign, found in 99 patients (61.9%), and 49 patients (30.6%) had chronic headaches, four (2.5%) had transient ischemic symptoms, and in eight (5%) the AVMs were asymptomatic. Most patients with seizures (86%) had generalized seizures and only three patients had secondarily generalized seizures.

The decision for surgical treatment was based on Spetzler-Martin score (Grade I–III), clinical signs (permanent decrease of quality of life), AVM location (eloquence, supply, angiomatosis, etc.), and age (in terms of cumulative hemorrhage risk). In addition, a small group of patients with AVM Spetzler-Martin Grade IV (high risk) who had severe, disabling symptoms (pharmacoresistant seizures, persistent headache ineffectively controlled with medications) was included. Patient data were extracted from the electronic medical records (e-med). Before and after surgery patients were examined by a neurologist and ophthalmologist and electroencephalography (EEG) was done for seizure patients. AVM morphology was evaluated with cerebral angiography (CA) or spiral CT angiography (CTA). All patients had a control angiography postoperatively. Outcomes were assessed with modified Rankin scale (mRS) at discharge (10–14 days). Follow-up exams were carried in the outpatient department or over the phone.

Results

The distribution of patients by Spetzler-Martin score, AVM size, and location is presented in Table 1. Mean AVM size was 3.3 ± 1.07 cm (1.5–10 cm). Patients with AVM in the temporal (72%) and frontal (70%) lobes had a higher tendency for seizures. Of all patients with occipital AVMs, 13 manifested with headaches and five had photopsias (all AVMs were < 4 cm). In six patients with occipital AVM,

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Table 1 Distribution of AVMs by Spetzler-Martin score, size, and location

Spetzler-Martin score and AVM size, <i>n</i> (%)			
I	18 (11.3%)	Small (1–3 cm)	55 (34.4%)
II	71 (44.4%)	Medium (3.5–5.5 cm)	87 (54.4%)
III	60 (37.5%)	Large (≥ 6 cm)	18 (11.2%)
IV	11 (6.8%)		
Location, <i>n</i> (%)			
Frontal lobe	60 (37.5%)	Parietal lobe	10 (6.2%)
Temporal lobe	42 (26.3%)	Occipitotemporal	8 (5%)
Occipital lobe	22 (13.8%)	Cerebellum	4 (2.5%)
Occipitoparietal	13 (8.1%)	Temporoparietal	1 (0.6%)

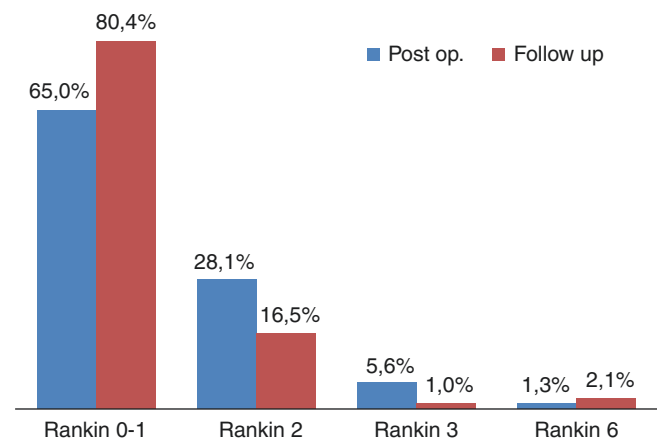
visual field defects that could not be associated with hemorrhages were found before surgery (homonymous hemianopia—five, quadrant hemianopia—one). These defects may have been congenital or due to asymptomatic ischemic changes).

Surgery. Microsurgical resection of AVM was performed in 128 (80%) patients, resection with preoperative embolization in 31 (19.4%). In one case, surgery was limited to AVM afferent clipping due to critical M-response decrease. In three cases simultaneous epilepsy resection using ECoG monitoring (amygdalohippocampectomy or temporal lobectomy) was performed. AVMs were located in the mediobasal temporal lobe in two patients and in the hippocampus in one patient.

In 33 cases (20.6%) minor hemorrhage signs (“silent” hemorrhage) were identified during surgery. Commonly, these included local hemosiderin deposits limited to the one or two sides of the lesions. No typical parenchymal hemorrhages in the form of hematomas residuals or post-hemorrhagic cysts were identified. Results of surgical treatment are summarized in Fig. 1. Favorable outcomes (mRS = 0–2) at discharge were achieved in 149 patients (93.1%), and satisfactory outcomes (mRS = 3) in 9 (5.6%) patients. Two patients died (1.25%), one due to the severe air embolism, the other from the complicated pre-surgical embolization (glue migration).

The long-term treatment outcomes were evaluated in 97 (60.6%) patients. Mean duration of follow-up was 59.3 months (13–108 months). At follow-up, the number of patients with excellent outcomes (mRS = 0–1) increased to 80.4%, and the total number of favorable outcomes (mRS = 0–2) reached 94.8%. Two (2%) patients died of causes unrelated to surgery.

The long-term outcomes were followed in 59 of 99 patients (55.6%) with seizures. Engel class I was achieved in 50 patients (84.8%) (complete regression—64.4%, improvement—30.5%); Engel class IIA was achieved in two (3.4%), Engel class IIIA in four (6.8%), and Engel class IV in three patients (5.1%). The headache intensity over the time was evaluated in 65 of 87 patients (74.7%). Headache intensity

**Fig. 1** Surgical outcomes for unruptured bAVM at discharge and follow-up

decreased after surgery in 41 patients (63%), frequency decreased in two (3.1%), headache worsened in twelve (18.5%), and remained unchanged in ten (15.4%).

Complications. Hemianopia was the most common post-surgical neurological deficit (in some a combination with central scotomas were observed) and was reported in 55 cases (64.7%) (homonymous hemianopia—39, quadrant hemianopia—16). Visual field defects occurred in 100% of AVMs found in the mediobasal temporal lobe ($n = 6$) and in the occipital-temporal area ($n = 8$); in 92.3% of AVMs found in the occipitoparietal area ($n = 12$), and in 86.3% ($n = 19$) of those found in the occipital lobe AVMs. In 13.7% of patients with occipital AVM, visual fields after surgery remained unchanged. Postoperative visual field defects were followed in 22 of 55 patients (40%) (mean follow-up duration was 61.7 months), including ophthalmologist examination and perimetry. Complete recovery of visual defects was reported in six patients (27%), partial recovery in eight (36%), vision was unchanged in seven (32%), and in one patient visual field defects worsened.

Other postoperative neurological complications included motor deficit in nine patients, aphasia in six patients, cognitive disorders including behavior changes in six patients, and cerebellar or vestibular dysfunctions in two patients. In two cases hemorrhages occurred after AVM embolization. Hematomas and AVMs were successfully removed with a good outcome in both cases.

Discussion

Generally, surgical treatment for unruptured bAVMs is recommended for young patients with high life expectancy (in this study, 77% of patients were aged <40 years) and low surgical risks (S-M I–III). A separate category, not analyzed in our work, is young women planning a pregnancy. As

K. Fukuda showed, the first AVM hemorrhage may be fatal to 28% of women and 14% of fetuses, as well as causing early miscarriage [12, 13]. Although the influence of labor on the AVM rupture is still under discussion, some studies have identified a higher risk of rupture compared to the general population [13, 14].

In most patients, symptomatic epilepsy was an indication for surgery. According to our data, favorable outcomes were achieved in 84.8% of patients (Engel class I) with complete seizures relieved (Engel class IA) in 64%. AVM resection does not ensure full seizure resolution; therefore, we recommend continuation of anticonvulsants for 6–12 months. According to the published reports, AVM resection is a quite effective treatment and results in seizure control (Engel class I) in 52–100% of patients [15–18].

Correlation between bAVMs and chronic headaches is unclear and remains a subject of further investigation. Of all bAVM patients, those with headaches comprise a significant percentage, but it is difficult to establish relevant association between headache and AVM [19–21]. According to the published reports, surgical resection of AVM led to headache intensity decrease or complete resolution in 33–83% of patients [22–24]. In our series, 66% of patients demonstrated various degrees of improvement.

Visual cortex and tracts are the most sensitive areas in terms of postoperative neurological defects. High risk factors for visual compromise are AVM size >3 cm and proximity to temporal, temporo-occipital or parieto-occipital cortex. It is also important to consider AVM angiomatosis that may require extended resection that exceeds initially planned boundaries. Although the group with follow-up ophthalmological examination was small ($n = 22$), field defects improvement was confirmed in more than half (63%) of the patients. Further study with more patients is obviously needed.

Endovascular embolization reduces the AVM volume and thus facilitates subsequent resection. To minimize hemorrhage risks between surgical steps it is an established practice in our department to focus an endovascular session on occlusion of hemodynamic aneurysms, embolization of deep afferents and AVM parts that are difficult for excision or excess during open surgery. A coordinated schedule of patient treatment and transportation may reduce time between both stages. In future, hybrid operating rooms may become a solution to such cases.

Functional outcomes in our study are consistent with the published data confirming that surgery for “low-grade” AVMs is reasonably safe and not associated with major neurological complications. Indications for surgery for unruptured bAVMs Spetzler-Martin Grade III–IV are individual and justified only when better quality of life is expected (e.g., improvement of the symptomatic epilepsy) rather than hemorrhage prevention. Patients with AVM Spetzler-Martin

Grade V should be managed conservatively regardless of the clinical signs. The effectiveness of the chronic headaches (migraine) treatment in patients with AVM is questionable and further studies are warranted.

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Conflict of interest. Authors declare that they have no conflict of interest.

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Maximum Nidus Depth as a Risk Factor of Surgical Morbidity in Eloquent Brain Arteriovenous Malformations

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Abbreviations

AUC	Areas under the receiver-operator characteristic curves
BAVM	Brain arteriovenous malformations
CI	Confidence interval
CST	Corticospinal tract
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
DTI	Diffusion tensor imaging
fMRI	Functional magnetic resonance imaging
GKS	Gamma knife surgery
LAD	Lesion-to-activation area distance
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
OR	Odds ratio
RCT	Randomized control trial
ROC	Receiver-operator characteristic

S-M Spetzler-Martin

Introduction

Surgical treatment of brain arteriovenous malformations (BAVMs) is a radical treatment modality. Safe and radical removal is expected to help prevent future hemorrhage and symptomatic deterioration. However, there are BAVMs that are unsuitable for surgical intervention and an eloquently located BAVM is known to increase the surgical risk [1–4]. In particular, in the Rolandic area, i.e., the motor and sensory areas, surgical morbidity is directly linked to the independence of the patient. Hence, it is still challenging to surgically treat these entities. Indicators for safe removal of Rolandic BAVMs are necessary but have not been determined thus far.

In addition to factors such as well-known hemorrhagic onset, unruptured BAVM, size, and deep venous drainage that are included in the Spetzler-Martin (S-M) grading scale [1–4], several surgical risk factors for eloquent BAVM have been reported in recent years, such as cortical reorganization and plasticity of motor area visualized via functional magnetic resonance imaging (fMRI) [5], BAVM lesion-to-corticospinal tract (CST) distance assessed by diffusion tensor imaging (DTI) [6, 7], and BAVM lesion-to-activation area distance (LAD) assessed by fMRI [8]. They can help predict postoperative neurological outcomes in the eloquent area and these factors contributed to acceptable long-term outcomes [6, 9], along with transient but finally reversible surgical morbidity. Thus, there is a possibility of plasticity and cortical reorganization of the cortical region. Impairment of the CST and deep white fibers may be more critical and irreversible in the Rolandic area. However, production of a uniform image is sometimes difficult with DTI and fMRI because of various methodological limitations [10]. The imaging results may differ between institutions and the type

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of imaging method. Therefore, predictors of surgical risk that can be evaluated easily with general imaging modalities are necessary. In this regard, we focused on the maximum nidus depth as a new indicator, which is a factor measurable on general imaging.

The aim of this study was to determine the surgical risk factors in patients with eloquent BAVMs, especially in the Rolandic area. Furthermore, we analyzed maximum nidus depth as a novel indicator and predictor of the surgical outcome in patients with this challenging entity.

Material and Methods

The institutional review board of Tokyo Women's Medical University approved this retrospective study. All patients provided written informed consent for the surgical procedures.

Patient Selection

This retrospective study included 297 consecutive patients with diagnosed BAVMs who underwent treatment at Tokyo Women's Medical University between January 2002 and August 2017. Of these, 202 patients were diagnosed with BAVM localized in an eloquent area. Furthermore, of these, 128 patients underwent gamma knife surgery (GKS) alone and 74 patients underwent surgical nidus removal. In these 74 patients who underwent surgical treatment, there were 29 patients who had BAVMs in the Rolandic motor or sensory area, or both. Data of these 29 patients were finally analyzed in this study.

Diagnosis and Treatment Strategy

The diagnoses and locations of BAVMs were established based on digital subtraction angiography (DSA) combined with magnetic resonance imaging (MRI) and computed tomography angiography (CTA) by a board-certified neurosurgeon of the Japan Neurosurgical Society. Data were collected from the medical records. The characteristics of BAVM included the size, depth, diffuseness, anatomic location, and venous drainage. These parameters were evaluated with a combination of imaging modalities. The size and depth of the nidus were also measured using the imaging modalities mentioned above. The maximum diameter was defined as the maximum nidus size measured from various angles. The maximum depth was defined as the distance from the brain surface to the deepest part of the nidus vertically. The nidus depth, if wider than other measurements, can be the same as the maximum diameter as well. BAVMs were further classified based on the S-M grading scale [1].

Uncontrollable symptoms, including hemorrhage, epilepsy, and severe headache, were considered as the indications for surgical nidus removal of the BAVM. However, asymptomatic BAVMs were also surgically removed if the patients strongly requested it after they were fully informed of the natural history and treatment options, including observation. The same surgical team performed the microsurgical nidus removal and managed the patients postoperatively. Preoperative endovascular interventions were performed as necessary. Each BAVM resection was completed while taking special care to preserve the functional reaction that was assessed using motor-evoked potentials, somatosensory-evoked potentials, and cortical/subcortical electrical stimulation.

Postoperatively, the patients were maintained in a hypotensive state under sedation. In principle, DSA was performed before and after the surgeries and complete removal was evaluated by postoperative DSA.

Outcome Parameters

Postoperative follow-ups were performed at our institution, and the degree of excision and the presence or absence of complications were evaluated. In this study, morbidity was defined as deterioration in the neurological findings related to the surgery and its associated complications. The final morbidity was assessed at 3 months postoperatively to evaluate whether the morbidity was a transient or permanent symptom. Furthermore, the modified Rankin Scale (mRS) score was assessed at 3 months postoperatively to evaluate whether it was intact or had worsened postoperatively. Permanent morbidity was defined as persistent neurological deterioration, and we classified it into two groups: "mRS change < 2" and "2 ≤ mRS change" compared with preoperative mRS. Transient morbidity was defined as neurological deterioration that occurred postoperatively and resolved within 3 months. Any death was determined as mortality.

Statistical Analysis

All statistical analyses were performed using JMP Pro13 (SAS Institute, NC, USA). Continuous variables were expressed as mean ± standard deviation. Univariate analysis was performed to identify the risk factors associated with postoperative surgical morbidity at 3 months in Rolandic eloquent BAVM. When comparing two groups, categorical variables were evaluated by Fisher's exact test and continuous variables were evaluated by Student's *t*-test. Significant risk factors and variables that were associated with morbidity, defined as $p < 0.20$ in univariate analysis, were included in multivariate logistic regression analysis. Since nidus size, eloquent location, deep venous drainage, age, ruptured presentation and diffuseness were already included as univariate

factors in statistical analysis, S-M grade and Lawton-Young supplementary grading system containing these factors were excluded because they were confounding factors.

Odds ratio (OR) for surgical morbidity was estimated from logistic regression analysis, and receiver-operator characteristic (ROC) curves were constructed to obtain the optimal cutoff values for the maximum nidus size and depth in predicting surgical morbidity. To confirm the predictive and diagnostic ability of the ROC curves, areas under the ROC curves (AUCs) were also determined. The significance level was set at $p < 0.05$ and all p values reported in this study are two-sided.

Results

Patient Demographics and BAVM Characteristics

A total of 29 patients with BAVMs in the Rolandic area who underwent surgical nidus removal at our institution were analyzed in this study. The patient demographics and BAVM characteristics are summarized in Table 1. With respect to clinical presentation, uncontrollable symptomatic BAVM was seen in 22 patients (75.9%) and hemorrhagic onset was seen in 11 (37.3%). Four patients (13.8%) underwent pre-surgical embolization and six patients (20.7%) pre-surgical GKS. The overall median S-M grading scale score was 3 (2–4), and the most frequent SM grade was grade III (51.7%). All BAVMs were in the eloquent location; in 12 patients (41.4%) they were related to the motor area, while in 11 patients (37.9%), they were related to the sensory area, and in six patients (20.7%), they were related to both. The mean maximum nidus size was 33 ± 17 mm, and the mean maximum nidus depth was 37 ± 17 mm. BAVMs with deep venous drainage were seen in only a few (13.8%).

Outcomes

The outcomes after surgical nidus removal are summarized in Table 2. Complete removal was achieved in 28 patients (96.6%). Partial removal was achieved in one patient; the patient suffered from perioperative hemorrhage and required reoperation. Postoperative hemorrhage due to normal perfusion pressure breakthrough visualized by cold-Xenon computed tomography was recognized in two patients. There was no incidence of hemorrhage after the perioperative period. Overall, 14 patients (48.3%) suffered from postoperative morbidity, including transient morbidity in nine patients (31.0%) and permanent morbidity in five patients (17.2%). The deterioration in neurological findings related to the surgery was often resolved during

Table 1 Characteristics of patients with Rolandic BAVM

Variable	Total Rolandic BAVM
No. of patients	29
Age	35.0 \pm 13.1
Male/female	15 (51.7%)/14 (48.3%)
Clinical presentation	
Seizures	5 (17.2%)
Headache	4 (13.8%)
Asymptomatic	7 (24.1%)
Hemorrhagic onset	11 (37.3%)
Preoperative mRS	
0–2	25 (86.1%)
3	1 (3.6%)
4–5	3 (10.3%)
BAVM characteristics	
Spetzler-Martin grade	
II	11 (37.3%)
III	15 (51.7%)
IV	3 (10.3%)
Maximum nidus size (cm)	3.3 \pm 1.7
Maximum nidus depth (cm)	3.7 \pm 1.7
Deep venous drainage	4 (13.8%)
Diffuseness	4 (13.8%)
Eloquent location	
Motor area	12 (41.4%)
Sensory area	11 (37.9%)
Motor and sensory area	6 (20.7%)
Laterality (right/left hemisphere)	16 (55.2%)/13 (44.8%)
Treatment	
Surgical removal alone	19 (65.5%)
Presurgical embolization	4 (13.8%)
Preoperative gamma knife	6 (20.7%)

mRS modified Rankin Scale, *BAVM* brain arteriovenous malformation
Values are expressed as mean \pm standard deviation for quantitative variables or as absolute number (percentage) for qualitative variables

the follow-up after a few weeks. Motor and sensory disorders, dysarthria, and higher brain dysfunction were recognized as neurological complications. Although renal failure occurred in one patient, there were no major systemic complications leading to mRS deterioration. There was no mortality. Deterioration of two or more on mRS was observed in two patients.

Univariate and Multivariate Analyses of Predictors of Surgical Morbidity for Rolandic BAVM

To identify the risk factor for surgical morbidity in Rolandic area BAVMs, several variables were analyzed between the total morbidity group and no morbidity group using univariate analysis (Table 3). The patients in both groups were well-matched with respect to age, sex, and preoperative mRS. Asymptomatic BAVM was a significant risk factor for surgical morbidity ($p = 0.0229$), but hemorrhagic onset was

Table 2 Surgical outcomes after nidus removal

Outcome	Total	Morbidity ^a (+)	Morbidity ^a (-)
No. of patients	29	14	15
mRS at 3 months after the surgery			
0–2	23 (79.3%)	12 (85.7%)	11 (73.3%)
3	2 (6.9%)	0 (0%)	2 (13.3%)
4–5	4 (13.8%)	2 (14.2%)	2 (13.3%)
Partial removal	1 (3.4%)	1 (7.1%)	0 (0%)
Complete removal	28 (96.6%)	13 (92.8%)	15 (100%)
Postoperative hemorrhage	3 (10.3%)	3 (21.4%)	0 (0%)
Perioperative period	3 (10.3%)	3 (21.4%)	0 (0%)
Postoperative follow-up period	0 (0%)	0 (0%)	0 (0%)
Morbidity ^a	14 (48.3%)	–	–
None	15 (51.7%)	0 (0%)	15 (100%)
Transient ^b	9 (31.0%)	9 (64.2%)	–
Permanent ^c ; mRS change <2	3 (10.3%)	3 (21.4%)	–
Permanent ^c ; mRS change ≥2	2 (6.9%)	2 (14.2%)	–
Mortality	0 (0%)	0 (0%)	–

mRS modified Rankin Scale

Values are expressed as percentages for qualitative variables

^aMorbidity was defined as deterioration in the neurological findings related to the surgery

^bTransient morbidity was defined as neurological deterioration that was transient after the surgery and resolved within 3 months after the surgery

^cPermanent morbidity was defined as neurological deterioration that was present at 3 months after the surgery

not ($p = 0.3156$). Of the BAVM characteristics, the maximum nidus size, deep venous drainage, diffuseness, and laterality were not significant risk factors, but maximum nidus depth was a significant risk factor for surgical morbidity ($p = 0.0204$).

For multivariate analysis (Table 4), significant variables and two variables that were associated with morbidity based on p value <0.20 in univariate analysis (preoperative mRS, laterality) were included in the multivariate logistic regression analysis. As mentioned in the methods section, S-M grade and Lawton-Young supplementary grading systems were excluded because they were confounding factors. The maximum nidus depth was the only risk factor of surgical morbidity in this analysis (OR = 2.78598, 95% confidence interval [CI]: 0.8866–8.7535, $p = 0.0357$).

Table 3 Univariate analysis of surgical risk factors for morbidity

Variable	Morbidity ^a (+)	Morbidity ^a (-)	p Value
No. of patients	14	15	
Age	37.9 ± 3.5	32.3 ± 3.4	0.2513
Male/female	8 / 6	7 / 8	0.5726
Asymptomatic (%)	6 (42.7%)	1 (6.67%)	0.0229
Hemorrhagic onset (%)	4 (28.6%)	7 (46.7%)	0.3156
Preoperative mRS	–	–	0.1358
0–2	14 (100%)	11 (73.3%)	
3	0 (0%)	1 (6.8%)	
4–5	0 (0%)	3 (20.0%)	
Maximum nidus size (mm)	36 ± 3	31 ± 3	0.2903
Maximum nidus depth (mm)	41 ± 3	32 ± 3	0.0204
Deep venous drainage	3 (21.4%)	1 (6.7%)	0.2493
Diffuseness	3 (21.4%)	1 (6.7%)	0.2493
Location	–	–	0.5717
Motor area	7 (41.4%)	4 (33.3%)	
Sensory area	4 (28.6%)	7 (46.7%)	
Motor and sensory area	3 (21.4%)	3 (20.0%)	
Laterality (right/left hemisphere)	6 (42.9%)/8 (57.1%)	10 (66.7%)/5 (33.3%)	0.1976
Presurgical embolization	2 (14.3%)	2 (13.3%)	0.9408
Preoperative gamma knife	3 (21.4%)	3 (20.0%)	0.9244

mRS modified Rankin Scale

Values are expressed as mean ± standard deviation for quantitative variables or percentage for qualitative variables

^aMorbidity was defined as deterioration in the neurological findings related to the surgery

Optimal Cut-off Values for Surgical Morbidity

From the results of logistic regression analysis (Table 5, Fig. 1a, b), maximum nidus depth was identified as a predictor of total morbidity (OR = 2.82190, $p = 0.015$) and permanent morbidity (OR = 8.34984, $p = 0.002$), and maximum nidus size was identified as a predictor of permanent morbidity (OR = 2.46749, $p = 0.027$). The optimal cutoff values identified from the ROC curve analysis included maximum nidus size of 30 mm for permanent morbidity, maximum nidus depth of 36 mm for total morbidity, and 41 mm for permanent morbidity (Table 5). AUC of total morbidity, indicating the predictive accuracy of the ROC curve, was 0.7428 for maximum nidus depth and 0.5785 for maximum nidus size. AUC for permanent morbidity was 0.8833 for maximum nidus depth and 0.7625 for maximum nidus size. AUC was higher for the maximum nidus depth compared with that for the maximum nidus size, for both total and permanent morbidities (Table 5, Fig. 1c, d). As illustrative cases, the patient (case 1) with sensory and motor area BAVM (S-M grade II) presented with headache, with maximum nidus size of 21 mm

Table 4 Multivariate analysis of surgical risk factors for morbidity

Variable	Multivariate analysis		
	OR	95% CI	p Value
Asymptomatic	4.70294	0.2782–79.4948	0.2610
Preoperative mRS	1.30196	0.1167–14.5154	0.3624
Maximum nidus depth (mm)	2.78598	0.8866–8.7535	0.0357
Laterality	2.82367	0.3786–21.0554	0.2971

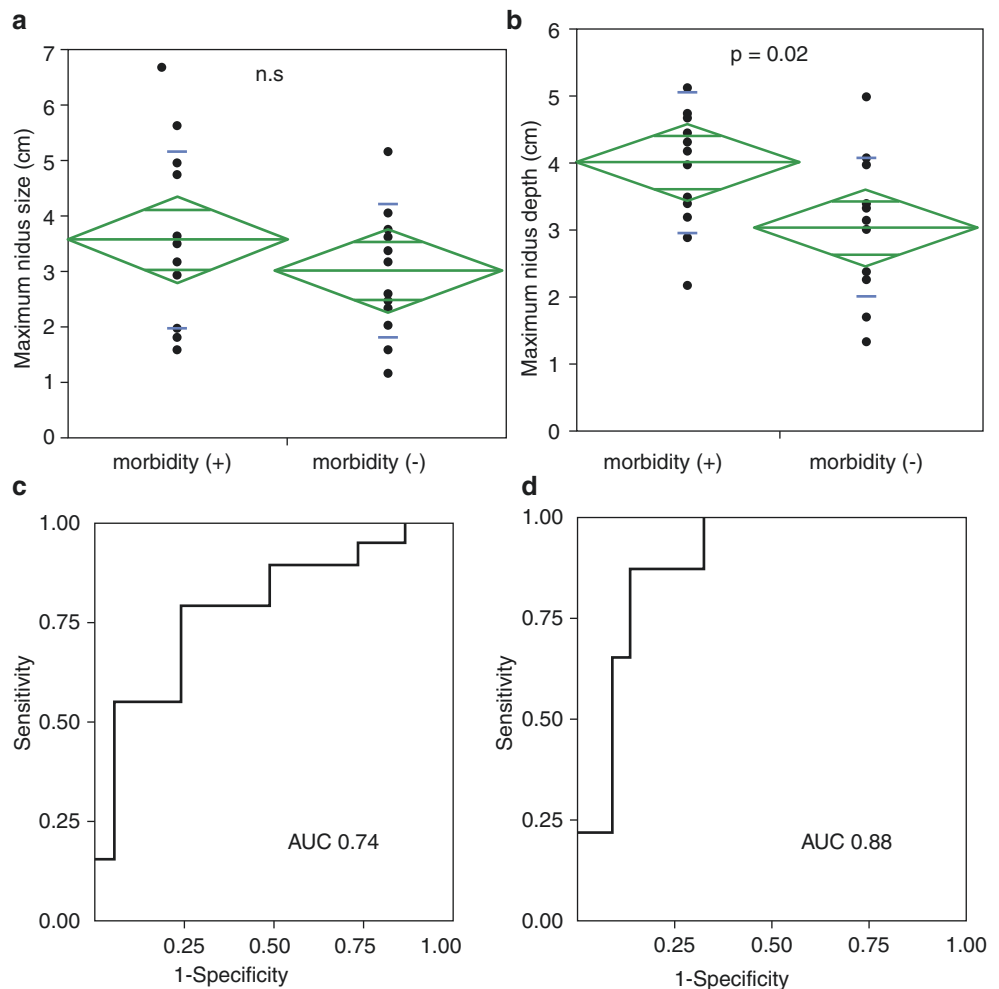
mRS modified Rankin Scale, OR odds ratio, CI confidence interval

Table 5 Cut-off values

Variable	Morbidity	Logistic regression analysis			ROC curve analysis	
		OR	95% CI	p Value	Cut-off value (mm)	AUC
Maximum nidus size	Total	1.40708	0.7531–2.62873	0.269	30	0.5785
	Permanent	2.46749	1.0031–6.069696	0.027	30	0.7625
Maximum nidus depth	Total	2.82190	1.0632–7.489138	0.015	36	0.7428
	Permanent	8.34984	1.2308–56.64248	0.002	41	0.8833

ROC receiver operating characteristic, OR odds ratio, CI confidence interval, AUC area under the curve

Fig. 1 Surgical risk factor and cutoff values in Rolandic brain arteriovenous malformations (BAVMs). (a and b) Maximum nidus depth was significantly correlated with surgical morbidity ($p = 0.02$), but maximum nidus size was not a significant factor. The distribution charts demonstrate the relationship between the maximum nidus size and surgical morbidity (a), and the maximum nidus depth and surgical morbidity (b). Green rhomboids indicate the mean and 95% confident intervals. (c and d) Receiver operating characteristic curve analyses for maximum nidus depth and surgical morbidity; total morbidity (c) and permanent morbidity (d). The area under the curve was 0.74 and the cutoff value was 36 mm (c). The area under the curve was 0.88 and the cutoff value was 41 mm (d)



and maximum nidus depth of 35 mm (Fig. 2a, b). Activation was found adjacent to the nidus on fMRI (Fig. 2c, d). Transient morbidity was observed after the surgery. In the patient (case 2) with asymptomatic sensory area BAVM (S-M grade III), maximum nidus size was 36 mm and maximum nidus depth was 44 mm (Fig. 3a, b). Permanent morbidity was observed after the surgery.

Discussion

In this series of 29 patients with BAVM who underwent surgical nidus removal, we found that nidus depth may be more useful than nidus size as a predictor of the surgical risk for postoperative surgery-related morbidity in eloquent BAVM, especially with BAVMs in the motor and sensory areas. As the maximum nidus depth from the brain surface increased, the morbidity rate elevated, suggesting that the morbidity was permanent.

Many grading scales and scores to indicate the surgical risk associated with BAVM removal, on behalf of S-M grading scale, have been previously reported [1–4, 11–13]. From these reports, it is well known that the surgical risk is higher with eloquent BAVM. Most of the grading scores include nidus size as a surgical risk factor, and its importance has been previously reported [1–4, 11–13]. There is no doubt that the surgical risk increases with increasing size of the BAVM nidus. However, regardless of the nidus size, there are reports of morbidity due to surgery even with a smaller nidus. Thus, in BAVMs in eloquent areas, the surgical risk is higher from the very beginning [1, 2]. Furthermore, there are no reports that have evaluated the assessment of eloquence in detail. Therefore, certain problems still remain, such as the lack of inclusion of white matter eloquent fibers in the grading systems, lack of definition of the width and depth of the eloquent area, and lack of quantitative variables to describe the relationship between the nidus and eloquence [14].

Following the findings of a randomized control trial (RCT) for unruptured BAVM [15], the treatment for eloquent BAVM is still considered challenging. However, there are also some cases wherein BAVM resulted in hemorrhage with high morbidity and presented with uncontrollable symptoms, suggesting that surgical treatment should be considered for eloquent BAVM. As was reported previously, although symptoms appear transiently after surgical removal, they often resolve during follow-up [5, 8, 16, 17]. It appears that there may be risk factors other than nidus size. If there is a factor that can predict whether eloquent BAVM is treatable or not, then the decision for surgical intervention can be better judged.

Nidus Depth as a New Indicator of Surgical Risk for Eloquent BAVM

In previous reports, the following variables have been reported as risk factors for surgical removal in BAVM: BAVM size, eloquence, deep venous drainage, diffuseness, perforating artery supply, and unruptured presentation [1–4, 11–13]. It is also known that relatively good outcomes are obtained with surgical treatment of BAVM with hemorrhagic onset [5, 18]. Particularly with regard to the nidus size, it is easy to predict that BAVM localization will dominate the critical area as it gets bigger, and it will lead to an increase in the risk. However, in measuring the size, the obtained values and implications vary depending on the direction used to measure on the image since the size can be measured in all directions. There are no uniform guidelines on assessing this measurement. Therefore, we focused on the nidus depth and performed the analyses for surgical morbidity for eloquent BAVM in this study. Although it seems like common sense that more extensive and deeper AVMs in eloquent locations will be associated with more surgical morbidity, to the best of our knowledge there are no reports in the literature that investigated and mentioned BAVM depth. Various factors that were previously reported to be significantly correlated with postoperative morbidity were not found to be significantly correlated in this study; the p values of the factors, though relatively low, were not significant. It is suggested that the maximum nidus depth may be more useful as a predictor in the surgical treatment of BAVM in the Rolandic area (Table 3 and Fig. 2).

Optimal Cutoff Value of Maximum Nidus Depth for Surgical Morbidity

To determine the optimal cutoff values for the maximum nidus depth and size in relationship with surgical morbidity, ROC curves were generated. The cutoff value for the maximum nidus depth was 36 mm for total morbidity and 41 mm for permanent morbidity (Table 4). Therefore, the deeper the maximum nidus depth, the higher the surgical risk. The cutoff value for the maximum nidus size for permanent morbidity was 30 mm. The AUC of the maximum depth (total morbidity: 0.74, permanent morbidity: 0.88) was larger than that of the maximum size (total morbidity: 0.58, permanent morbidity: 0.76); therefore, maximum nidus depth is a more useful predictor than the maximum nidus size (Table 4, Fig. 2).

These findings raise the question of the underlying mechanism that can explain how the nidus depth affects the surgical risk. Frequently this is due to small arterioles arriving at the deep part of the AVM nidus, or due to small draining

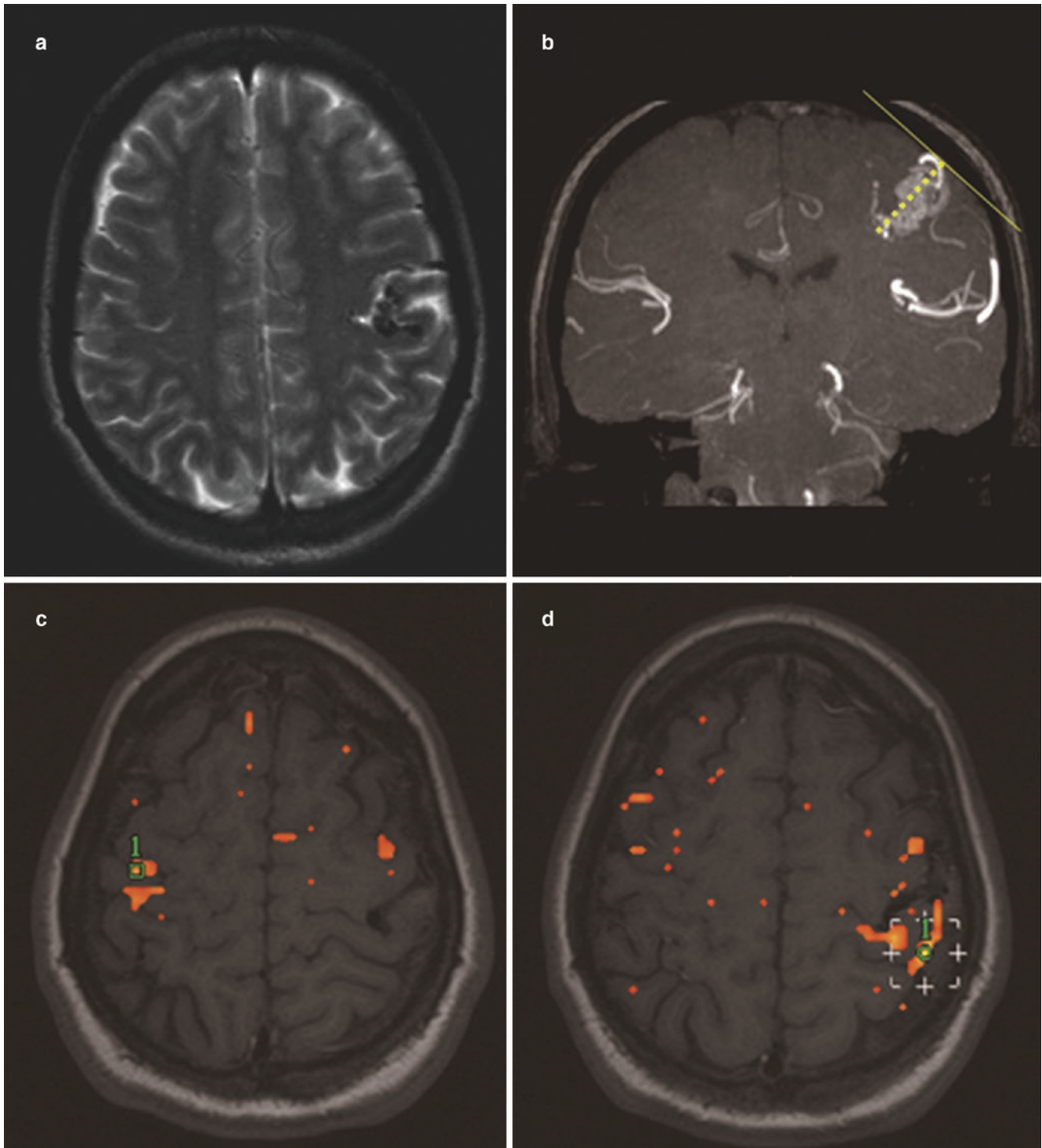


Fig. 2 Illustrative case 1. Axial T2-weighted image (a) and coronal maximum intensity projection image of time of flight magnetic resonance angiography (b) showing sensory motor area brain arteriovenous malformation (Spetzler-Martin grade II). The maximum nidus depth

was 35 mm. The yellow dotted line indicates the maximum nidus depth relative to the tangential line of the brain's surface. The activations related to left-hand gripping (c) and right-hand gripping were found adjacent to the nidus (d) on fMRI

venules, which are bleeding notoriously and are difficult to coagulate at the same time. It is also already known that the deeper a BAVM is, the more the nidus involves the CST [9] and is closer to the perforating supply area. In previous

reports, lesion-to-CST distance measured by DTI [6, 7] and LAD measured by fMRI [8] have been reported as surgical risk factors for vascular malformations of the eloquent area. Furthermore, the plasticity and cortical reorganization of the

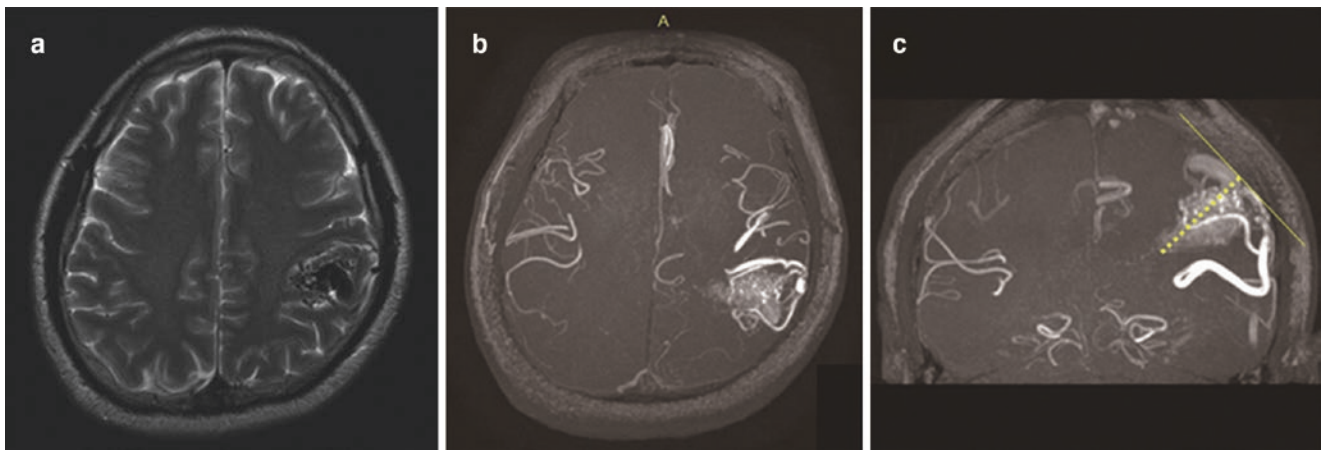


Fig. 3 Illustrative case 2. Axial T2-weighted image (a) and axial and coronal maximum intensity projection image of time of flight magnetic resonance angiography (b and c) showing brain arteriovenous malfor-

mation (Spetzler-Martin grade III) in the sensory area. The maximum nidus depth was 44 mm. The yellow dotted line indicates the maximum nidus depth relative to the tangential line of the brain's surface

eloquent cortical area were also reported [5, 16, 17], and it was suggested, based on fMRI, that significant activation did not lie within the nidus of BAVM [16]. The anatomic location alone of a BAVM may not provide any information on the functional reorganization. In fact, we have encountered cases where translocation of the eloquent area was found on intraoperative direct stimulation. Thus, the plasticity may contribute to the transient deterioration in the cortical regions after the surgery. On the other hand, impairment of CST and deep white fibers may be more critical and irreversible, resulting in permanent deterioration. Therefore, the nidus depth can be a risk factor as it reflects the association between a BAVM and the deep white fibers.

Although DTI and fMRI are useful for the prediction of the surgical outcomes, they are often complicated. It is often difficult to perform imaging accurately because of methodological limitations and technical difficulties like different stepwise procedures between institutions, false-positives and false-negatives, and hemorrhage and edema that can affect the results [10]. On the other hand, nidus depth, as proposed in this study, is an easily measurable parameter that does not require special images. It can be measured with routine images that do not vary significantly between institutions.

ARUBA trial was the only RCT in unruptured BAVMs with a negative stance on interventions [15], and it suggested that interventions for unruptured BAVM should be cautious; however, there have been objections to that report [19, 20]. In this study, asymptomatic presentation was a significant risk factor in univariate analysis but not in multivariate analysis. Maximum nidus depth was the only significant factor in multivariate analysis. Its cutoff value obtained in this study does not strongly recommend the surgical removal of elo-

quent BAVMs; however, it can be one of the indicators of the surgical risk in cases that require treatment. This study does not deny the importance of the size of the nidus as a risk factor since there were cases wherein the measured maximum size was in the same direction as the depth. Therefore, the direction in which the maximum size is measured is also important.

Many outstanding questions and issues pertinent to this study remain. The results obtained in this study are from limited locations of eloquent BAVMs, specifically the Rolandic area. However, it is unclear as to which area is better—the motor or sensory area. The significance of the depth in other eloquent areas like the language area remains unknown. Furthermore, we do not discuss the relations between DTI tractography and closeness of the nidus. Although the effectiveness of GKS and multimodal treatment for high-grade BAVM has been reported in recent years [21–23], the current study is not a comparative one between the modalities of treatment. The question remains whether surgical removal is superior to GKS or another multimodal strategy. As another limitation, this study was a retrospective one and the sample size was small. Further analyses and experiments are needed in this regard. This small subset of patients may overestimate the value of nidus depth compared with other variables that are well known to be factors in development of perioperative morbidity, including hemorrhagic status and size, primarily, and others. However, this is an interesting case series of an uncommon entity: surgically operated motorsensory cortex. We think that it is a meaningful report derived from rare cases.

From our results, the radicality of surgical removal was extremely high and the requirement for surgery cannot be

completely ruled out. In the future, downgrading using multimodal treatment may also be promising as a new strategy to prevent surgical morbidities in such challenging entities. Thus, critical deep lesions or eloquent locations should first be eliminated with relatively noninvasive treatment modalities with higher priority [24], resulting in downgrading by decreasing the maximum nidus depth and affected eloquent area followed by surgical treatment. It is necessary to consider new treatment strategies for safe and highly radical BAVM treatment. Maximum nidus depth is more likely to be associated with surgical morbidity in BAVMs in the eloquent Rolandic areas. Although surgical treatment should be carefully considered, the maximum nidus depth is a simpler and stronger predictor of the outcome than maximum nidus size in patients with this challenging entity.

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Conflict of interest: The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Tokyo Women's Medical University) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: The requirement for written informed consent was waived because of the retrospective design.

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Brain Arteriovenous Malformations Classifications: A Surgical Point of View

Giovanni Marco Sicuri, Nicola Galante,
and Roberto Stefani

Introduction

Brain arteriovenous malformations are complex developmental malformations that primarily affect the leptomeningeal vessels. AVMs are subject to a dynamic process that leads to dilation of arteries and veins and to the pathological modification of their elastic and muscular laminae. Involvement of perforating vessels may add damage of the adjacent neural tissue. In typical plexiform AVMs, the nidus of the malformation is composed of a network of abnormal vessels interposed between the feeding arteries and the draining veins [1].

Hemorrhage is the most frequent onset symptom, although AVM can also occur with epileptic seizures, progressive focal neurological deficits, and neurocognitive deficits. Surgery is still considered the most effective and definitive treatment; endovascular occlusion and radiosurgery can be considered as alternatives in specific cases. However, each treatment might carry potential transient or permanent postoperative sequelae. Patient selection should therefore weigh the natural history of AVMs against treatment-related risks. It is a difficult process complicated by the variety of angioarchitecture, size, location, and clinical features of AVMs. It is, however, the key to achieving a good outcome.

A good classification system should assess therapeutic risks, surgical challenges, and operative morbidity. After validation, its first purpose is to guide the physician to present to the patient the optimal treatment option. At the same time, it may facilitate communication among researchers on the best care. An ideal scheme should be assessed at bedside and contemplate few variables; otherwise it may be cumbersome. However, even oversimplification has some drawbacks and does not exclude the risk of over-grading or

under-grading for the interobserver variability. For instance, it is common experience that neuroradiologists tend to under-grade, whereas the neurosurgeons tend to over-grade a brain AVM classified by Spetzler-Martin (S-M) grading [2]. Furthermore, agreement on the overall grade differed depending on imaging modalities; the best agreement came from using Computer Tomographic Angiography and Magnetic Resonance Imaging rather than Digital Subtraction Angiography [3].

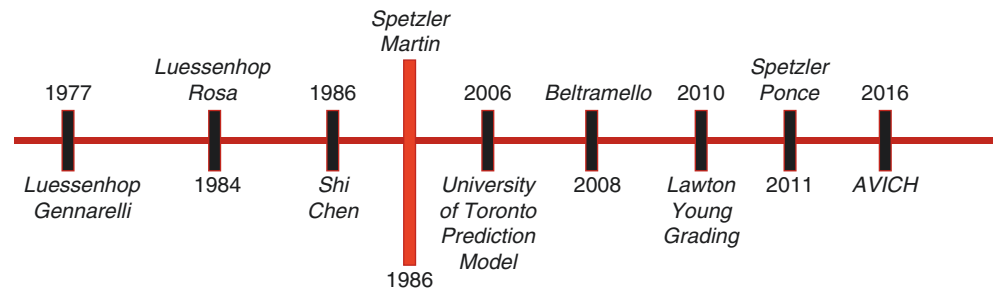
Classification Schemes on AVM Operability

The first and most common classification systems are those that assess AVMs' operability by balancing the risks of surgical treatment (Fig. 1). These schemes are based on predictive factors extrapolated from the neuroradiological exams and the clinical features of the patient. The most important anatomical factors appear to be the size and the location of the AVM's nidus. An arterial supply prevalent from perforating arteries and the location in an eloquent area can complicate surgery. A deep venous drainage is used as an indicator of deep-seated extension of AVMs and of the presence of small choroidal vessels around the vein in the white matter that can cause some technical difficulties and promote postoperative focal neurological deficit [4–7].

In addition, the more compact the AVM's nidus, the easier the surgical resection. Hemodynamic predictive factors have been related to the onset of hyperemic complications, represented by the formation of vasogenic edema or bleeding in the territories surrounding the AVM after its removal. The onset of these events is related to a venous hyperemia resulting from the occlusion of venous drainage and an arterial hyperemia related to the reperfusion of previously hypoperfused brain areas due to blood steal phenomena. D'Aliberti et al. correlated the onset of hyperemic complications with venous times measured in angiography. The "early venous time" was defined as the time of appearance of the nidus and

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Fig. 1 Timeline of brain arteriovenous malformations classifications



of the veins directly draining the AVM, while the “intermediate venous time” was defined as the time of appearance of the recruited veins, namely the veins draining the brain parenchyma afferent to a drainage of the AVM. These venous times were considered altered when very short or when there was a prolonged interval with the “late venous time,” namely the time of appearance of normal brain veins. The altered times were closely correlated with the incidence of hyperemic complications, which accounted for about 50% of adverse events in the series [8].

Furthermore, clinical factors negatively correlated with the outcome are the advanced age, the presence of neurological deficits or an alteration of the state of consciousness at the time of treatment, and the presence of a previous bleeding [7].

Pre-Spetzler-Martin (S-M) Classifications

The first relevant classification was developed by **Luessenhop and Gennarelli** in 1977 [9]. Data were exclusively related to supratentorial AVM. AVMs were divided into four degrees according to the number of arterial pedicles in a single vascular territory. Lenticulostriate arteries and Heubner’s recurrent artery were considered separate feeders. The greater the number of peduncles involved, the greater the difficulty of resection. Grade IV AVMs were considered inoperable. The presence of subarachnoid hemorrhage was managed as an unfavorable factor, and an eloquent area was considered relevant for morbidity. In 1984, **Luessenhop and Rosa** simplified the grading of the previous classification [10]. Assuming that the size of the AVM’s nidus is related to the number of arterial pedicles, the grade was defined according to the diameter of the nidus: > 2 cm was grade I, 2–4 cm grade II, 4–6 cm grade III, and >6 cm grade IV. Cerebellar AVMs were included. Surgical results indicated that in grade I and II the mortality and morbidity of surgical treatment were probably lower than the natural risk of the disease. In 1986 **Shi and Chen** presented an alternative classification [11]. More factors were included in the classification: *dimension, location, complexity of arterial supply, and venous drainage*. Each of the four factors was subclassified in grade I–

IV. When all the criteria matched, the AVM was of that grade. When only one of the criteria was of a higher degree, the AVM was of intermediate grade. However, when at least two criteria were of the same highest grade, the AVM would have been of the latter degree. Therefore, three intermediate degrees were possible in addition to the four main degrees. The authors demonstrated an increased risk with increasing AVM grade with a 20% mortality in grade III-IV AVMs.

Spetzler-Martin Classification and Following Edits

In 1986, **Spetzler and Martin** published a new classification with the aim of simplifying the analysis and reducing the variables while maintaining a good predictive value [12]. The basis for simplification was the concept that many of the predictive factors are interrelated. This scheme has become the predominant pattern in the classification of cerebral AVMs. The only criteria included in scoring were the nidus size, the venous drainage pattern, and the AVM location. Each factor had an independent score that was added to the others. The dimensions of the nidus were separated into three grades: when <3 cm, one point was assigned; if between 3 to 6 cm, two points; over 6 cm, three points. The authors implied that the greater the size of the nidus, the greater the brain tissue exposed at risk during surgery. Size was also directly related to the number of vascular afferent peduncles, to the flow and to the degree of blood steal. When the venous drainage pattern included only the cortical veins, it was regarded as superficial, and no points were therefore assigned. Conversely, when it involved the deep venous system (internal cerebral veins, basal veins, precentral cerebellar vein), one point was assigned. A deep venous drainage was related to the surgical accessibility to the AVM because deep veins are difficult to coagulate and can retract into the adjacent cerebral parenchyma and into the ventricle. Lastly, one point was assigned to AVMs located in eloquent areas. Elective areas were considered the sensory motor cortex, the area of language, the visual cortex, the hypothalamus and the thalamus, the internal capsule, the brain stem, the cerebellar peduncles, and the deep cerebellar nuclei.

The grade of the AVM was derived from the sum of the scores assigned for each category. Therefore, AVMs of grade I–V were identified. The simplicity of application of this classification system certainly contributed to its diffusion. Moreover, a low number of variables increased the statistical power of scientific studies, enlarging the number of subjects assigned to each category. Some drawbacks, however, have been identified: The compactness of the nidus and the involvement of deep arterial afferents, although important to define the surgical complexity, were not considered. Furthermore, the definition of eloquence of a brain area cannot be always accurate. It is known that, especially for higher-level cognitive functions, structural anatomy often does not fully correspond to functional anatomy. Eventually, S-M grading did not take into account the patient's clinical and neurological status.

The weakest point of this classification consisted in its lower power to define an accurate outcome in Grade III patients. Indeed, grade III AVMs were not a homogeneous group, with varying risks of morbidity and mortality. For these reasons, in 1998 **de Oliveira et al** tried to subclass the grade III AVMs by defining a grade IIIa and a grade IIIb [13]. In grade IIIa, the score was given by the large size of the nidus (>6 cm), while in grade IIIb the score was determined by the deep drainage and/or the eloquent area. The authors advised against surgical treatment for grade IIIb AVMs, albeit with some exceptions. In 2003, **Lawton** further subdivided grade three AVMs into four subtypes [14]. According to his classification, AVMs <3 cm with deep drainage and located in an eloquent area (grade III-) had a low surgical risk, similar to that of low-grade AVMs. The 3–6 cm AVMs with deep drainage (plain grade III) had an intermediate risk, while the 3–6 cm AVMs in an eloquent area had a high surgical risk, similar to that of high-grade AVM. AVMs >6 cm with superficial drainage in a non-eloquent area were absent in the surgical series described (grade III *). The authors recommended surgical resection in Grade III and III-AVMs.

Since experience showed that the AVMs of Grade I and II and IV and V of the score of Spetzler and Martin perform similarly, in 2011 **Spetzler and Ponce** condensed the original classification into only three degrees [15]. Grade I and II AVMs were merged into grade A, Grade III AVMs were assigned grade B, Grade IV and V grades were condensed into grade C. The predictive power on surgical outcome was identical to the original classification. The authors generally recommended surgical treatment for grade A AVMs, multimodal treatment for grade B, and observation for grade C, reserving treatment for cases of recurrent hemorrhages or progressive neurological deficits due to blood steal phenomena. This scheme offered the advantage of increased samples for statistical analysis, but it did not dissolve the lack of homogeneity of Grade III AVMs.

Two alternative schemes were developed after the Spetzler-Martin classification: the **University of Toronto Prediction Model** and the **Lawton-Young Grading System**. Both contested the excessive simplicity of the classification of Spetzler-Martin in an effort to increase the discriminative power on the outcome of AVM patients after surgery.

The former model was published in 2006 after a retrospective analysis of 175 patients [16]. The authors added nidus morphology to significant predictors of short- and long-term neurological outcomes in addition to the eloquent area and deep venous drainage. A diffuse nidus morphology was defined as a nidus including normal brain parenchyma, with no defined margins, as opposed to a compact nidus. On the other side, the size of the nidus >3 cm, the deep arterial supply, and the presence of associated aneurysms were not significant in the retrospective analysis and were excluded from the model. The model assigned a relative weight to the three factors considered: the eloquent area was assigned four points, the diffusivity of the nidus three points, the deep venous drainage two points. Low-risk patients (0–2 points), medium-risk (3–5 points) and high-risk patients (6–7 points) were stratified. The authors showed in the series that the proposed scheme had a superior discriminative power with respect to the grading of S-M in predicting permanent neurological deficits, especially in low-grade AVMs.

In 2010 **Lawton and Young** analyzed 300 patients undergoing AVM surgical resection and developed a new grading system [17]. Three variables were included in the scheme: age, hemorrhagic presentation, and nidus compactness. Similarly to the S-M scale the scoring ranged from one to five points: one point was assigned for age <20 years, two points for 20–40 years, three points for >40 years; one point was assigned for AVMs with diffuse nidus and one point for hemorrhagic presentation. The predictive accuracy of the neurological outcome of the proposed model was higher than the S-M scale and was even higher by adding the scores obtained with the S-M grading and their grading [18]. Lawton et al. concluded that the risk of a surgical resection was acceptable in patients with grades ≤ 3 according to the Lawton-Young grading system and grades ≤ 6 according to the score obtained from the sum of the their grading and S-M scale. Like the Toronto Prediction Model, the study did not confirm a predictive value of deep arterial support.

Other Operative AVM Classification Schemes

Classifications described above are useful for defining the risk of microsurgical resection of an AVM according to the clinical and angioarchitectural features. However, over the past few decades, alternative or combined treatments have been developed and refined. Radiosurgery and endovascular

surgery are effective on AVM exclusion by the administration of ionizing radiations and by the obliteration with embolic liquids, respectively. Since the techniques mentioned obviously use methods other than microsurgery, risk assessment criteria used for surgical treatment cannot be as valid. For both techniques, specific classifications for predicting the complication rate and treatment success were developed over time [19–26].

All these schemes have shown some limitations. First, since treatment is often multimodal, an exact definition of the risk is difficult and the comparison between the series is complex. In addition, the ARUBA study recently showed that the risk of death and stroke in unruptured AVM was higher with interventional treatment than with medical therapy. Although this study has been severely criticized for its design, conduct, analysis, and interpretation, it has brought out the importance of weighing the natural history of the disease and its most frequent and feared complication, hemorrhage, with treatment-related risks. A mere risk stratification for a type of treatment may miss that goal. Interestingly, Beltramello et al. drew up a score that considers the psychosocial aspects of the patient and that is valid for all modalities of AVM treatment [27]. The authors proposed an AVM Cumulative Score that summed the Intention to Treat Score (ITS) and the Treatment Risk Score (TRS). The former was composed of the sum of patient clinical features and morphological features of the AVM: age (<50 years: 0 point; 50–65 years: 1; >65 years: 2); previous bleeding (yes: 0 points; no: 2); neurological deficit unrelated to previous bleeding (yes: 0 points; no: 1); patient's firm purpose to be treated (yes: 0 point; no: 1); AVM size <10 cm³ (yes: 0 points; no: 1); deep location (yes: 0 points; no: 1); deep venous drainage only (yes: 0 points; no: 2); varices or associated aneurysms (yes: 0 points; no: 2). The ITS therefore ranged from 0 to 12. The TRS was instead calculated differently according to the chosen treatment and ranged from 0 to 5. When a surgical treatment was indicated, the S-M scales that divides patients into five categories was used, with the difference that the grade III AVM with vascular supply from the lenticulostriate arteries marked 4 points instead of 3. The authors based the radiosurgical risk prediction exclusively on the size of the nidus (<5 cm³: 1 point; 5–10 cm³: 2; 10–20 cm³: 3; 20–30 cm³: 4; >30 cm³: 5); however, they subtracted one point in low-flow AVMs, as they believed that this aspect was associated with a higher rate of obliteration in shorter time. Eventually, factors considered in the endovascular risk prediction were the AVM volume (<10 cm³: 1 point; >10 cm³: 2); the eloquent area (yes: 1 point; no: 0); the presence of perforating feeders (yes: 1 point; no: 0); and an unfavorable AVM angioarchitecture (yes: 1 point; no: 0). The Cumulative Score was formed by the sum of ITS and TRS. The authors recommended treatment when ≤ 10 ,

offered it with substantial risk if 11 or 12, advised against it when between 13 and 17. The same group then validated this classification on 104 treated patients, with only a slight change to the points assigned to age (<40 years: 0 point; 40–60 years: 1; >60 years: 2) [28].

All classifications described so far are useful in elective cases. In 2016 Neidert et al. proposed a new grading system to predict the outcome of patients with intracerebral hemorrhage (ICH) due to AVM rupture [29]. Scoring systems that predict outcome in spontaneous ICH may not be reliable in AVM patients because the pathophysiology of bleeding is different. Indeed, outcome in spontaneous ICH has been shown to be worse than in AVM-related ICH. Prognosis may then be more linked to the angioarchitectural features of the AVM than to the ICH itself. The proposed score included the sum of the scores obtained from factors derived from the S-M scale and the Lawton-Young grading system (size, deep drainage, eloquent area, age, compactness of the nidus) and from factors derived from the ICH Score [30], namely the GCS score (13–15: 0 points, 5–12: 1; 3–4: 2); volume of intracerebral hemorrhage (<30 cm³: 0 points; >30 cm³: 1); presence of intraventricular hemorrhage (no: 0 points, yes: 1). The score therefore ranged from 2 to 13. In a recent validation it was confirmed that with a score ≥ 9 there was a favorable outcome in only 5.7% of cases, while in 1.4% with a score ≥ 10 [31].

Topographic AVM Classifications

Anatomical classifications have been devised for AVM located in specific anatomical areas of the brain, highlighting some peculiarities that may be useful for the surgeon. AVMs of the sylvian fissure were classified by Sugita in 1987 [32] into four subtypes: pure sylvian AVMs, located in the subarachnoid space around the middle cerebral artery without a parenchymal base; sylvian lateral AVMs, located in the lateral part of the sylvian fissure and in the temporal lobe cortex; medial sylvian AVMs, located in the medial part of the sylvian fissure and in the frontal lobe; deep sylvian AVMs, located in the deepest part of the sylvian fissure and in the insular cortex. Lawton et al. in 2007 published an application of the Sugita classification on 28 surgical patients [33]. In both papers, the classification itself did not effect a significant change in the outcome but was useful to indicate some surgical tips. First, deep AVMs required a slight posterior extension of the craniotomy to allow a wider opening of the sylvian fissure to reach the nidus, since the trunks of the middle cerebral artery (ACM) normally lay on the surface of the nidus. In pure AVMs, branches of the ACM were instead under the nidus, while the venous drainage was superficial in the middle cerebral veins; in the latter the authors advised the

dissection of the sylvian fissure from distal to proximal to better preserve the *en passage* arteries. In medial AVMs, the greatest surgical challenge was generally the coagulation of the feeding branches from lenticulostriate arteries, while in lateral AVMs it was the control of the branches of the anterior choroidal artery.

The San Francisco Group described other specific locations of the AVMs. AVMs of the midline were classified into five subtypes according to location (anterior, middle, or posterior) and depth (superficial and deep) [34]. Compared to other AVMs of the convexity, which can be approached perpendicularly, surgical excision was judged to be more complex, because dissection of the nidus along the medial side in superficial parafalcine AVMs and along all four sides in deep parafalcine AVMs must be tangential, though requiring brain retraction and mobilization of the nidus. For each subtype, the authors described a peculiar strategy of patient positioning and operating table movements, in order to help the surgeon with gravity retraction to better expose the nidus and the afferent arterial branches. The highest risk was attributed to superficial-middle AVMs, probably due to the more extensive arterial supply (greater percentage of two or three vascular territories) and the adjacency to the sensory-motor cortex.

AVMs of the temporal lobe were subdivided into five subtypes [35]. Lateral AVMs were found immediately beneath the convexity and could be approached perpendicularly with a pterional approach. The other subtypes required more complex approaches (subtemporal for basal, orbytozygomatic for medial, transylvian for sylvian and transcortical for ventricular AVMs) and tangential dissections. The classification was not found useful for predicting the outcome, described as generally good.

For cerebellar AVMs, five anatomic subtypes were identified: three corresponded to the three cerebellar surfaces described by Rhoton (suboccipital, tentorial, petrosal), to which the vermian and tonsillar AVMs were added [36]. A torcular craniotomy with transverse sinus lift was generally performed for vermian and tentorial, a retrosigmoid craniotomy for the petrosal, a medial suboccipital craniotomy for tonsillar, a lateral suboccipital craniotomy for suboccipital AVMs. The outcome was better in the tentorial and tonsillar AVMs, worse for the petrosal and vermian ones.

Brainstem AVMs were classified into six subtypes: anterior and posterior midbrain, anterior or lateral pontine and anterior or lateral medullary [37]. Lateral AVMs could generally be resected, whereas AVMs with more anterior localization, or when it was difficult to distinguish between normal and feeding perforating branches, were treated with “occlusion in situ,” namely closing of the feeding arteries and of the drainage veins leaving the nidus in the brainstem. The authors recommended surgical treatment only in patients with AVMs at high risk of rupture.

Conclusions

Over the years, several classifications for AVMs have been proposed, some favoring simplification and others preferring accurateness, at the expense of a lower feasibility. So far, the Spetzler-Martin classification has been used most often to quickly assess the operability of AVMs. However, AVM treatment is increasingly multimodal and evolving, so parameters to consider are changing. Clinical and neuroradiological evaluation will in the near future be complemented by genetic and molecular factors; thus, clinical trials will assess the individual response to each therapeutic option. On the other hand, the increasing insights into the anatomic subtypes of AVMs in recent years has allowed surgeons to approach surgically, with acceptable risks, AVMs located in territories previously considered inoperable.

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The Preoperative Functional Downgrading of Brain AVMs

Sabino Luzzi, Mattia Del Maestro, and Renato Galzio

Introduction

Treatment options for brain arteriovenous malformations (AVMs) include microsurgical resection, transarterial or transvenous catheter-based embolization, radiosurgery, or a combination of these. From the surgical standpoint, Spetzler-Martin (SM) grade III AVMs pose more special challenges than doing grades I and II because of their frequent deep-seated location, common vascular supply from the lenticulostriate, or thalamostriate arteries, and a not unusual racemose nidal angioarchitecture. On the other hand, deeper arterial feeders have been reported to be pivotal in determining the morbidity and resectability of middle-sized AVMs [1–4]. In principle, the preoperative embolization of the deeper arterial feeders, as well as the increasing of the compactness of the nidus, may both lead to an easier dissection, helping the hemostasis and ultimately reducing intraoperative blood loss. Although the literature reports many studies about the utility of the preoperative embolization of brain AVMs, too few of them

stay focused on the technical details to be implemented to maximize the effectiveness and safety of the treatment.

Throughout a retrospective review of an institutional series, the present study is aimed to report the key technical aspects of the preoperative endovascular-based functional downgrading of SM grade III brain AVMs, as well as those factors underlying its effectiveness and safety.

Material and Methods

Data of 97 patients consecutively treated for a brain AVM were retrospectively reviewed. Only SM grade III malformations that underwent a combined endovascular-surgical treatment were selected, resulting in 31 overall treated cases. Table 1 summarizes patients' demographics, the prevalence according to the location, and the clinical onset of the analyzed surgical series (Table 1). By default, preoperative imaging included CT scan, T1-, T2-, and time-of-flight-weighted gadolinium contrast-enhanced MRI, and four-vessels, or six-vessels in case of cortical location, brain digital subtraction angiography (DSA). In cases of hemorrhagic onset characterized by the presence of an intracerebral hematoma, the indication for surgery was built upon a more general evidence-based management algorithm about intracerebral hemorrhages reported by our group [5]. Blood oxygenation level-dependent functional MRI was performed only in cases of elective AVMs involving eloquent areas. Based on size (S), involvement of eloquent area (E), and pattern of venous drainage (V), the selected grade III AVMs were further divided into four main types according to the parameters reported in Table 2. AVMs' volumes were calculated on DSA with the method reported by Pasqualin and colleagues [6]. As treatment strategy concerns, SM grade, angioarchitecture, evidence for flow-related or intranidal aneurysms, and stenosis of the straight sinus basically

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Table 1 Summary of patients' demographics, sites prevalence and clinical onset

Patients' demographics		N. (\pm SD)	
Average patients' age		36.9 (\pm 11.2) years	
Male/female ratio		2.8	
Prevalence according to site		N.	
Infratentorial		0	
Supratentorial		31	
Main supratentorial site involved			
Site		N. (%)	N. (%)
Frontal lobe	R	–	8
	L	8 (25.8%)	(25.8%)
Parietal lobe	R	2 (6.4%)	4
	L	2 (6.4%)	(12.9%)
Central lobe	R	–	6
	L	6 (19.3%)	(19.3%)
Occipital lobe	R	4 (12.9%)	6
	L	2 (6.4%)	(19.3%)
Temporal lobe	R	5 (16.1%)	6
	L	1 (3.2%)	(19.3%)
Insular cortex	R	–	–
	L	–	–
Central core	R	–	1 (3.3%)
	L	1 (thalamus) (3.2%)	
Clinical onset		N. (%)	
Seizure		6 (19.5%)	
Focal deficits		2 (6.5%)	
Hemorrhage		14 (45%)	
Ischemic stroke		–	
Incidental		9 (29%)	
Average Admission WFNS Grade		N. (\pm SD)	
Hemorrhagic onset		3.3 (\pm 1.2)	
Non-hemorrhagic onset		1.2 (\pm 0.5)	

SD standard deviation, WFNS World Federation of Neurosurgical Societies Grading System

dictated the decision-making process within a multidisciplinary team of neurosurgeons and interventional neuroradiologists. The timeframe between the embolization sessions was also discussed on a case-by-case basis and mainly decided upon DSA findings. The effectiveness of the staged embolization was reported as a percentage ratio between the initial and the final post-embolization volume of the nidus.

During surgery, image guidance was used in all cases for both planning and intraoperative navigation, while neurophysiological monitoring was employed in eloquent area AVMs. A rigid 0° or 30°, 4 mm length endoscope was employed in all deep-seated or mesial AVMs treated using an inter-hemispheric approach to check for residuals at the final steps of surgery. Flow assessment techniques involved micro-Doppler ultrasound (MDU) (20 MHz System, Mizuho Medical Co., Ltd., Tokyo, Japan) since 2007, indocyanine green (ICG) video angiography (Flow 800 Infrared Module, OPMI Pentero 800, Zeiss, Oberkochen, Germany) since 2009, and fluorescein angiography (Yellow 560 Fluorescence Module, Kinevo 900, Zeiss, Oberkochen, Germany) since 2018. Operation time, blood loss, and admission WFNS grade were evaluated as variables in a comparison between a good, modified Ranking Scale (mRS) score <3, versus a bad mRS score >2, and overall outcome. A Mann-Whitney test for nonparametric statistical analysis was performed by means of GraphPad Prism software (GraphPad Software, La Jolla, California, USA), where the *P*-value was set at <0.05. All the embolization-related complications were described to assess the safety of the technique. The Overall outcome was reported as mRS [7] at a 6-month follow-up. Modified Ranking Scale scores of 0–2, 3, and 4–6 were assumed as good, moderate, and bad outcomes, respectively. The Overall radiological outcome was assessed based on the 6-month DSA.

Table 2 Typing, prevalence and overall outcome of grade III AVMs according to Spetzler-Martin grading system

SM classification parameters			Grade III typing		Prevalence N. (%)	Overall outcome		
Size (cm)	Involvement of eloquent area	Type of venous drainage	Type	Class		mRS		
					N (%)	0–2 N (%)	3 N (%)	4–6 N (%)
<3	Yes	Deep	I (S1E1V1)	Small-eloquent	12 (38.7%)	11 (91.7%)	1 (8.3%)	–
3–6	No	Deep	II (S2E0V1)	Medium-deep	12 (38.7%)	9 (75%)	3 (25%)	
3–6	Yes	Superficial	III (S2E1V0)	Medium-eloquent	6 (19.4%)	1 (16.7%)	5 (83.3%)	
>6	No	Superficial	IV (S3E0V0)	Large	1 (3.2%)	–	–	1 (100%)

SM Spetzler-Martin, S AVM size, E eloquent area; V venous drainage, mRS modified Rankin Scale score

Results

Prevalence of Grade III Types

The prevalence of type I (small-eloquent), medium-deep (type II), medium-eloquent (type III) and large (type IV) SM grade III AVMs was 38.7%, 38.7%, 19.4% and 3.2%, respectively (Table 2).

Technical Caveats of the Preoperative Functional Downgrading of AVMs

Thirty-one AVMs were embolized in 51 endovascular procedures. Only low-density Onyx (Onyx 18, 6% EVOH; Micro Therapeutics, Inc., eV3, Irvine, CA) was used as the embolic agent in the present series. Through a transarterial transfemoral approach, a flow-directed microcatheter (Marathon; eV3A) and a tapered microguidewire (Mirage; eV3) were advanced until the nidus. After a superselective catheterization of the main arterial feeders, a microcatheter was moved throughout the target feeders inside the nidus. While preferring the deep-seated parts, Onyx was injected with a flow rate of 0.1 mL/s by means of the “plug and push” technique [8]. The first session was always aimed to achieve the widest obliteration possible volume, stopping, however, after having reached the safest final possible result.

Effectiveness of the Staged Embolization

Average AVM volume at diagnosis was 19.7 (± 3.8) mL versus a mean volume of 13.6 (± 3) at the end of the last preoperative embolization session; the average obliteration rate was 29.6 (± 14.6)%. The time window between the embolization sessions ranged between 10 and 15 days, whereas the mean number of the procedures performed per single patient was 1.6 (± 0.6). The Average time between the last embolization and surgery session was 3.7 (± 1.8) days. Intraoperatively, Onyx allowed for prompt identification of the nidus; also if initially racemose, it made it more compact and easier to dissect, and ultimately facilitated the hemostasis and the removal of the deepest parts of the malformation. No differences were found about operation time, blood loss, and WFNS grade comparing good versus bad outcome groups.

Safety of the Staged Embolization

Two mechanical and one hemodynamic endovascular complications were recorded during the embolization sessions; the mechanical ones both consisted of a catheter stuck, while

a hemiparesis occurred in a single patient 8 h after the procedure. The estimated embolization-related morbidity rate was 3.2% with zero mortality.

Neurological and Angiographic Overall Outcome

At the 6-month follow-up, the overall outcome was as follows: mRS 0–2, mRS 3, and mRS > 4 in 77.5%, 19.3%, and 3.2% of the patients, respectively. Two patients (6.4%) had a small remnant, which underwent radiosurgery. As grade III typing concerns, the best outcome was achieved in small and medium-deep AVMs (Table 2).

Table 3 summarizes the overall data about staged embolization and surgery.

Illustrative Case

Case #1: SM Grade III AVM Involving the Right Primary Visual Cortex Secondary to a mild traumatic brain injury, a 48-year-old male was diagnosed with an incidental right occipital SM grade III AVM (Fig. 1). The Visual field test was normal. DSA of the right ICA and VA revealed two main arterial feeders from the distal right pericallosal artery (a) and the P3 segment of the right posterior cerebral artery (b and c). Small feeders also came from the distal left pericallosal artery (d). The huge nidus involved the right primary visual cortex and the venous phase showed two cortical veins draining into the posterior third of the superior sagittal sinus (e). A first Onyx embolization session was aimed to exclude the feeders from the right posterior cerebral artery (f and g), whereas a second session, performed after 12 days, allowed to occlude the feeders from the right pericallosal artery (h). Post-embolization preoperative DSA showed a rearrangement of the venous outflow (i) and MRI documented no ischemic complications (j). The final nidal volume was 11.3 mL and the estimated overall post-embolization rate was 49.7%.

The patients underwent surgery which consisted of the nidus excision by a posterior-interhemispheric approach with the patient in a prone position. Intraoperatively, a compact and very easy to dissect nidus was found (k–m). Furthermore, the blood loss was insignificant. Final ICG videoangiography in arterial (n) and venous (o) phase documented a normal filling of both neighboring arterial vessels and previously arterialized veins. No remnants were detected. Postoperative DSA confirmed a complete exclusion of the AVM (p–t) and the patient was discharged with no deficits on the fifth postoperative day.

Table 3 Data about staged embolization and surgery

Clinical onset	Average admission nidal volume (mL)	Onyx embolization			Average days between embolization and surgery	Average mRS
		Average procedures (N.)	Average overall post-embolization nidal volume (mL)	Average obliteration rate (%)		
Hemorrhagic onset	19 (± 2.9)	1.5 (± 2.4)	13.2 (± 2.4)	29.1 (± 16.1)	3.4 (± 1.6)	0.7 (± 1.1)
Non-hemorrhagic onset	20.2 (± 4.3)	1.7 (± 0.6)	13.9 (± 3.3)	30.1 (± 13.6)	4.1 (± 1.9)	1.1 (± 1.4)

mRS modified Rankin Scale score

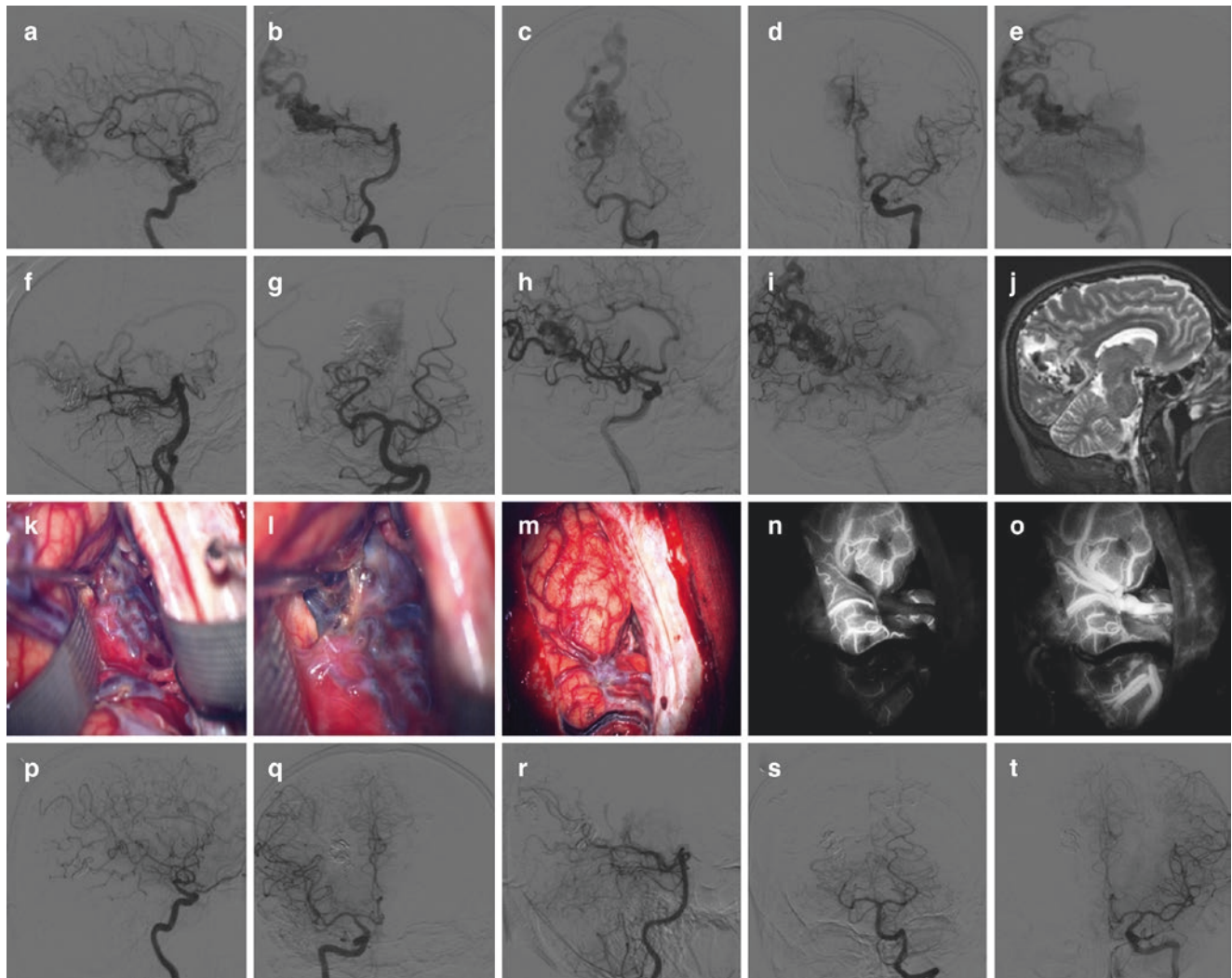


Fig. 1 DSA of the right ICA (**a**) and right VA in lateral (**b**) and anterior-posterior (**c**) projection revealing two main arterial feeders from the distal right pericallosal artery and the P3 segment of the right posterior cerebral artery. DSA of the left ICA (**d**). Right VA DSA in venous phase (**e**) showing the presence of two cortical veins draining into the posterior third of the superior sagittal sinus. DSA of the right VA in lateral (**f**) and anterior-posterior (**g**) projection after the first Onyx embolization session. DSA of the right ICA in lateral projection (**h**) after the second Onyx embolization session. (**i**) Right ICA DSA in venous phase showing the rearrangement and the slowing of the venous outflow. (**j**) Sagittal

T2 weighted MRI revealing no ischemic complications after the second embolization session. (**k, l**) Intraoperative pictures during the right posterior inter-hemispheric approach showing the compactness of the nidus. (**m**) Intraoperative picture confirming the complete exclusion of the nidus at the final stage of surgery. Intraoperative ICG videoangiography in arterial (**n**) and venous (**o**) phase. Postoperative DSA of right ICA in lateral (**p**) and anterior-posterior (**q**) projection confirming the complete exclusion of the AVM. Postoperative DSA of the left VA in lateral (**r**) and anterior-posterior (**s**) projection (**t**) Postoperative DSA of the left ICA in anterior-posterior projection

Discussion

SM Grade III represents a heterogeneous group of brain AVMs concerning size, the involvement of eloquent areas, venous drainage, and, ultimately, angioarchitecture. Surgery has been reported as the option of choice for grade I and grade II malformations, but also for grade III ones [9]. Nevertheless, a paramount role of preoperative embolization has been now recognized and commonly implemented for the latter, being the elimination of the deeper feeders at the base of easier hemostasis and, lastly, reduced morbidity [9–11].

The results of the reported retrospective series fully confirm the effectiveness of the Onyx preoperative embolization before surgery of grade III AVMs. The good outcome observed especially in small-eloquent type I and medium-deep type II AVMs led to delineate these types as the best candidate for a preoperative endovascular AVM occlusion. Additionally, the overall results of the further two types are to be considered as other than free from additional and intrinsic angioarchitectural factors, eloquence first, which is undoubtedly related to higher morbidity [3, 4, 9, 12, 13]. Technically, the superselective microcatheterization of the feeders is the key starting point to achieve an effective but also safe preoperative embolization of the AVM through a detailed study of the shunts inside the nidus. Equally important is the recognition of the eventual peri-nidal angiogenesis in the form of a peripheric tenuous blush since it ought to be excluded from the embolization targets. The goal of the first session of the embolization should consist of a functional vascular downgrading of the AVM, having to be instead the subsequent sessions targeted to the deeper portion.

In our experience, the major advantages of the preoperative embolization came from the exclusion of the deeper arterial feeders, these being of utmost importance for affecting the morbidity and resectability of the larger malformations [1, 2].

Nevertheless, any endovascular overtreatment of the nidus ought to be avoided both because it is dangerous and because an excessive amount of embolic agent inside the nidus has been reported to interfere with the shrinking and mobilization of the nidus itself during surgery [1–4, 14–17].

Regarding the timeframe between the embolization sessions, an interval greater than 2 or 3 weeks at maximum should be avoided because of the well-known potential for the recruitment of new feeders. For the same reasons, surgery should be performed no later than 7 days from the last embolization. Within the present series, the implemented neurophysiological monitoring protocol, already reported by our group for vascular neurosurgery [18–24], was particularly useful also for those malformations located within eloquent areas. Equally helpful for checking for residuals at the final steps of surgery was endoscopic assistance in all deep-

seated or mesial AVMs, the latter usually treated by means of an interhemispheric approach. The advantages of the endoscope-assisted technique for deep-seated AVMs are the same previously described by our group for the treatment of other pathologies characterized by the presence of blind spots [18, 25]. Lastly, an essential aspect of AVM surgery lies in constant microneurosurgical vascular training [26].

In conclusion, the results of the reported series confirm that preoperative staged embolization is a safe, feasible, and useful option in the treatment of both hemorrhagic and non-hemorrhagic SM Grade III AVMs.

A careful selection of patients as candidates for combined treatment, a detailed evaluation of the angioarchitecture, meticulous planning, and an effective and safe functional downgrading of the AVM, which should be based upon the key technical aspects reported in the present study, are all paramount factors that make surgery straightforward and, ultimately, to achieve the best outcome.

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Ethical Approval This study was approved by the Internal Advisory Board.

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Intracranial Dural Arteriovenous Fistulas: The Sinus and Non-Sinus Concept

Giuseppe D'Aliberti, Giuseppe Talamonti, Davide Boeris, Francesco M. Crisà, Alessia Fratianni, Roberto Stefini, Edoardo Boccardi, and Marco Cenzato

Introduction

Dural arteriovenous fistulas (dAVFs) represent 15% of all intracranial arteriovenous shunts. In particular, 7% of supratentorial and 35% of infratentorial shunts are dAVFs [1]. Dural arteriovenous fistulas are a group of acquired pathological vascular malformations, defined by an abnormal communication within the dural leaflets, between arteries and dural venous sinuses and/or subarachnoid veins. The feeding arteries are commonly branches of the external carotid artery, tentorial branches of the internal carotid artery, meningeal branches of the vertebral artery or, rarely, pial branches of the cerebral arteries [2]. Dural arteriovenous fistulas are more commonly supratentorial than infratentorial in location. The transverse-sigmoid sinus junction is the most common location for dAVFs, with a slight left-sided predominance. Through the years many classification systems have been proposed for intracranial dAVFs. These systems are based on the lesion's venous drainage patterns, as this factor dictates the behavior of the lesion itself. Djindjian and Merland first classified dAVFs according to their venous angioarchitecture in 1977 [3]. In 1995, Cognard further classified both cranial and spinal arteriovenous fistulas according to their venous outflow with prognostic and treatment impli-

cations [4]. Borden simplified the Cognard classification, emphasizing that the major factor in predicting an aggressive clinical course is the presence of cortical venous drainage. Unlike venous sinuses, cortical veins are not protected by the dura and cannot withstand arterial pressures. Therefore, dAVFs with cortical venous drainage (Borden types II and III) have a higher risk of rupture and hemorrhage [5, 6].

The Vascular Malformations Study Group of Toronto identified in 1997 the same rate of bleeding for dAVF and cerebral AVMs. Intracranial hemorrhage and neurologic deficit is likely in 2% of the Borden classification type I, 39% of type II, and 79% of type III dAVFs [7]. However, there is a 45% mortality rate over 4 years among patients with cortical venous drainage, a 19.2% intracranial hemorrhage rate per year, and 10.9% new neurologic deficit rate per year. For patients who present with hemorrhage, the rate of repeated hemorrhage is 35% within the first 2 weeks of the initial ictus [1, 6, 8–10]. According to our experience [11–13], we suggest a simplified classification of dAVFs: sinus and non-sinus. This classification guides the choice of surgical treatment. As previously observed by other authors, posterior fossa localization of the fistulas is not a real adjunctive risk-factor [14].

Our Experience

Sinus Fistula: We define as sinus dAVF all the fistulas having the dural arteries shunting directly into dural sinus. This direct communication between the artery and the sinus can subsequently recruit cerebral veins. The classification for this type of fistula, despite venous recruitment, does not change and still represents a sinus fistula (Fig. 1a).

Non-Sinus Fistula: In non-sinus fistula the sinus maintains functional for the venous discharge of the brain. The pathological shunt is embedded into the dural leaflet without communication with the sinus. Drainage of the fistula depends entirely upon cerebral veins (Fig. 1b).

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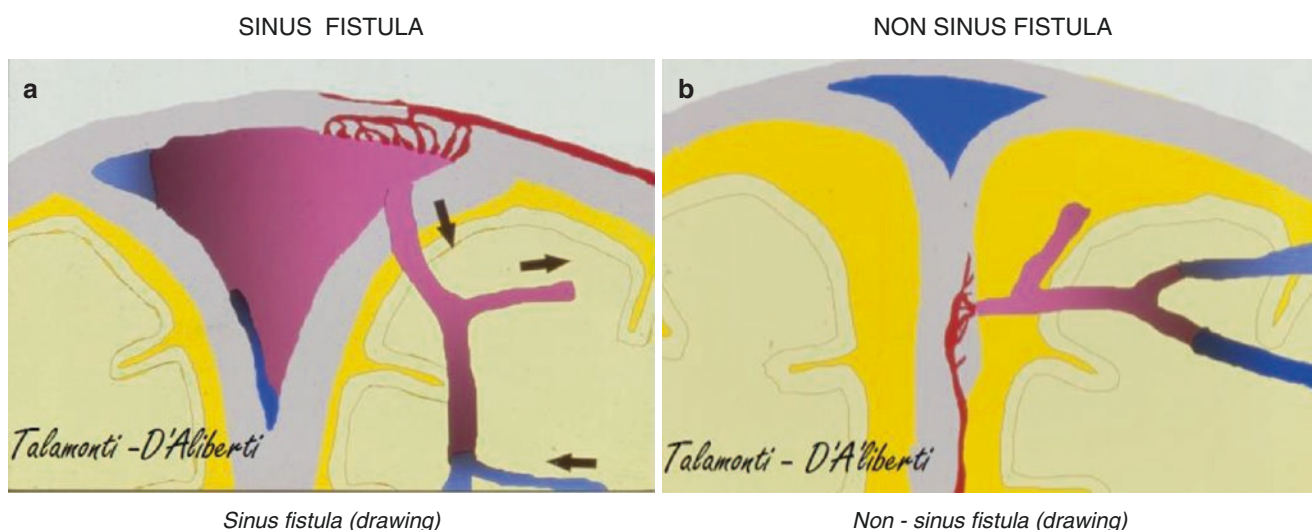


Fig. 1 (a) Sinus fistula (drawing). (b) Non-sinus fistula (drawing)

From 2006 to 2016, at our Neurosurgical Department and our Interventional Neuroradiology at Niguarda Hospital, Milan, Italy, 477 intracranial dural arteriovenous fistulas have been treated: 376 underwent endovascular treatment and 101 underwent surgical treatment. Cavernous sinus dAVFs and Galen ampulla malformations have been excluded from this series, as they represent a different pathology per se. Of the 376 dAVFs treated by the endovascular approach, 180 were sinus and 179 were non-sinus. Of the 101 dAVFs treated with the surgical approach: 15 were sinus and 86 were non-sinus.

This classification was found to be very useful in our daily practice. In a sinus fistula there is a direct communication between the arterious dural branch and one dural sinus, and cerebral veins can subsequently be recruited. These recruited veins, called by some authors “red veins” due to the inverted internal blood flow, are not functioning veins. Red veins must be excluded from the circulation together with the excision of the portion of sinus interested by the fistula. In non-sinus fistula, the shunt is embedded into the dural leaflet and it doesn't communicate with any sinus, whereas it drains itself into a cortical vein. Therefore, the sinus is functional for the brain. This draining vein—a red vein—has to be occluded proximally (“piè” of the vein) through a surgical or endovascular transvenous approach.

Correct individuation of the type of fistula, sinus or not sinus, is important in order to plan a proper surgical treatment, regardless of the presence of venous varices in the malformation. Those varices, in fact, do not represent an anatomopathological variant and do not require a different surgical approach [13].

The draining vein in a non-sinus fistula, with one or more associated varices on its course, so-called Type IV of some classification systems [4], does not configure a different type

of fistula in terms of another anatomopathological entity, so it is not an adjunctive surgical risk factor. Therefore, surgical treatment of both infratentorial and supratentorial fistulas is the same: clipping or occlusion of the vein at its emergence (See “Illustrative Cases”: Fig. 2, Cases 1 and 2)

Illustrative Cases

Case 1 A 65-year-old man come to observation for ictal onset of headache and coma. At admittance in ER, he presented with GCS 3 and anisocoria (> right), onset <1 h. A CT scan showed a left temporal ICH and a CT-Angio with 3D reconstruction showed a non-sinus dural fistula of pterional dura (a–c). The patient underwent an urgent surgery, with carotid exposure at neck. A wide craniotomy was performed, the hemorrhage was drained, and non-sinus fistula was excluded through multiple clipping of drainage vein, after temporary (7 min) occlusion of external carotid artery (d). The postoperative stay was good, a postoperative DSA showed the complete exclusion of dAVF, and a postoperative CT scan showed the results of previous hemorrhage (e–f). At 2 months follow-up the patient was able to walk alone and he had just a slight expressive dysphasia.

Case 2 A 45-year-old female came to our ED for progressive onset of nuchal headache and instability. A first CT scan showed a right, small intracerebellar hemorrhage (g). Six hours after admittance, the patient complained of a new headache attack and the onset of a coma. A new CT scan showed a new hemorrhage and a DSA showed a falco-tentorial non-sinus fistula with associated varix on the drainage vein (h, i, l). The patient underwent urgent surgery with drainage of

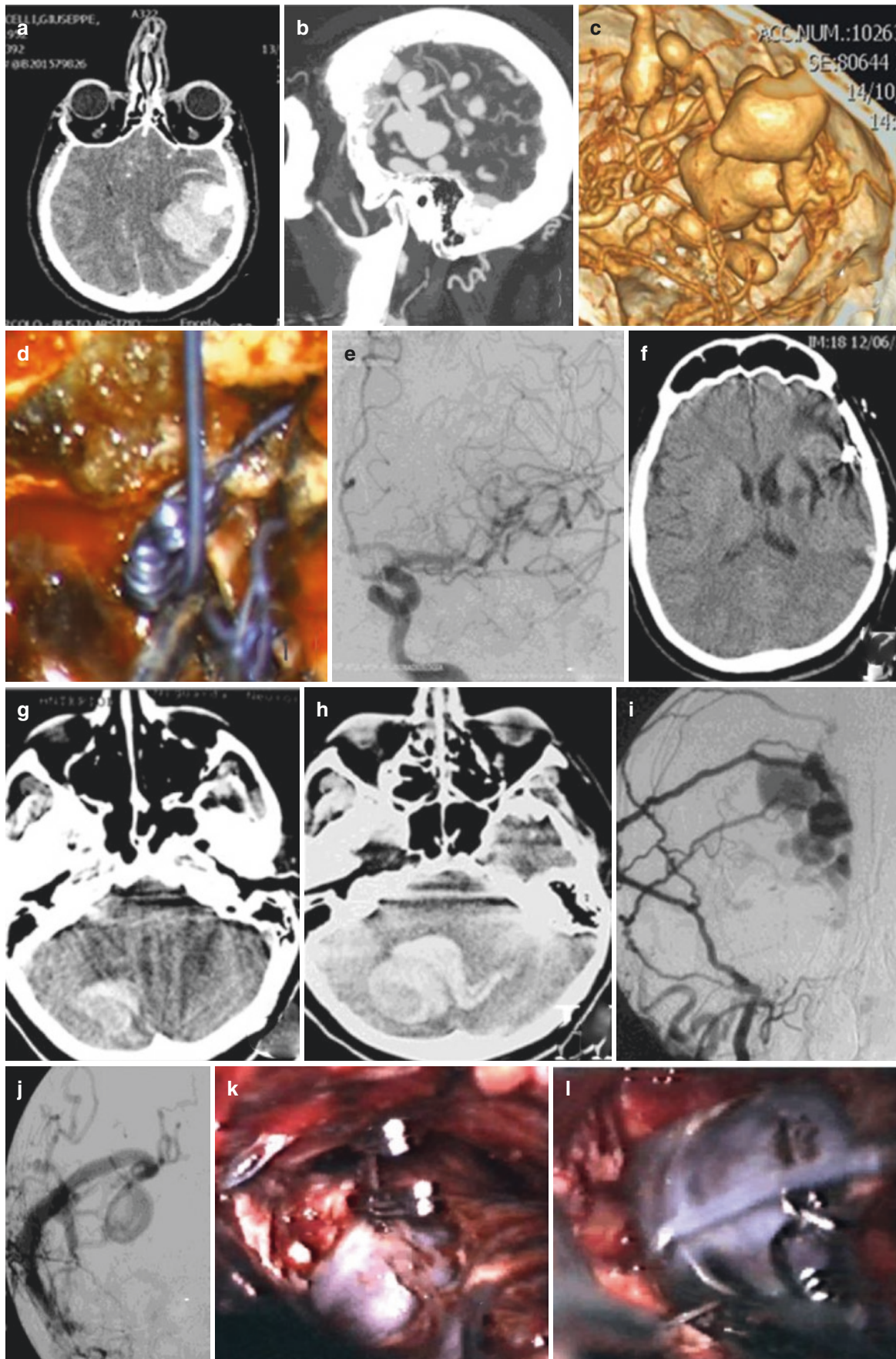


Fig. 2 Case 1. Supratentorial pterional non-sinus fistula (associated with varix) (a–f). Case 2. Infratentorial non-sinus fistula (associated with varix) (g–n)

hemorrhage and clipping of “piè” of the vein. Varix was excised with the hemorrhage (m, n). Postoperative stay was good with a prompt recovering of consciousness. The patient was discharged after 2 weeks with a slight instability.

The different surgical approach in FAVD next to a venous sinus depends on the type of the shunt and it doesn't depend on the localization but on type of drainage and on the recruited cerebral veins. In the case of a sinus fistula, therefore, it is possible the resection of the fistulous sinus tract and the occlusion of the recruited nonfunctional veins and the absolute preservation of the veins still functional to the brain (See “Illustrative Cases”: Fig. 3, Cases 3 and 4).

Case 3 A 48-year-old male came to our observation for an intracranial hypertension syndrome with slow onset (some months before), with headache and progressive cognitive impairment. Some days before the patient complained of a severe impairment of awareness and vomiting with associated visual impairment. A DSA showed a sinus fistula of the torcular with engorgement of straight sinus and severe recruitment of many cerebral veins, which seemed to persist long because of engorgement (a–c). The patient underwent a surgical resection of torcular with occlusion of recruited veins (red veins), both not functional for the brain. Postoperative DSE showed exclusion of the FAVD and the non-visualization of straight sinus in arterial phase, for the restoring of a normal situation (d, e).

Case 4 A 17-year-old male with a slow onset symptomatology (6 months) with headache and visual blurring. A DSA showed a sinus FAVD of the middle third of SSS with recruitment of cerebral veins (f–h). The anterior one is not functional; the posterior one, instead, remains normally visible in venous phases of angiography when dAVF is not visible. The patient underwent surgical resection of fistulous sinus tract with occlusion of anterior recruited vein (i, l, m) and avoidance of the posterior one, functional for the brain. The postoperative DSA shows a normal venous angiogram (n).

Different types of dAVFs (sinus or non-sinus) in posterior cranial fossa may localize in the same place, but they require different surgical treatment, in particular those located at the petrous bone apex (See “Illustrative Cases”: Fig. 4, Cases 5 and 6). Finally, non-sinus fistulas with associated varix and perimedullary drainage, so-called Type V of Cognard-Gobin Classification [4], are not a different type of fistula and they do not add an adjunctive surgical risk factor [15] (See “Illustrative Cases”: Fig. 5, Cases 7 and 8).

Case 5 A 44-year-old female fashion designer come to our observation for a progressive brainstem symptomatology. An MRI showed a right ischemic lesion in the pons. Three years before, she was treated in another institution with embolization of a sinus transverse-sigmoid dAVF with an initial recruitment of the superior petrous sinus (a–c). A new DSA showed sinus recanalization associated with an evident recruitment of the superior petrous sinus and reflux in engorged infratentorial veins (d, e). The postoperative angiography showed a disappearance of sinus fistula after sinus removal and clipping of main recruited vein (f). After 6 months of swallowing rehabilitation the patient was able to go back to her job.

Case 6 A 48-year-old male journalist come to our observation for a progressive tetraparesis with sphincter disorders. An MRI showed a severe cervical spine myelopathy, and because of the presence of a disk herniation at C4–C5, initial diagnosis was spondylotic cervical myelopathy. Because of the presence, in MRI, of vascular structures in cervical subarachnoid space (g), a second opinion suggested a complete angiographic study of the brain and medulla. The latter showed a non-sinus fistula of the apex of the right petrous bone, with feeder from the Bernasconi-Cassinari artery and drainage in a perimesencephalic vein with associated engorgement of perimedullary veins (h, i, l). The patient underwent surgical intervention through a suboccipital craniotomy and clipping of drainage vein at the apex of the petrous bone (m, n). Postoperative DSA showed the complete exclusion of the dAVF (o). After 6 months of rehabilitation, the patient went back to work with autonomous life and with slight sphincter impairment.

Case 7 A 52-year-old male presented with a progressive myelopathy, and MRI showed a cervical spine myelopathy without a cervical spondylosis and presence of vascular structures in posterior subarachnoid space (a). The patient underwent complete DSA of brain and medulla, which showed a non-sinus fistula on the dura close to the entrance into intracranial space of the left vertebral artery and engorgement of perimedullary veins of the cervical tract (b). Through a far lateral approach, the “piè” of the vein was exposed in the anterior part of the intracranial entry point of vertebral artery (c, d). The malformation was excluded through clipping of the drainage vein at its origin. Postoperative DSA showed the complete exclusion of the dAVF (e). At 5 months follow-up, the patient walked with aid and still had sphincter disorders.

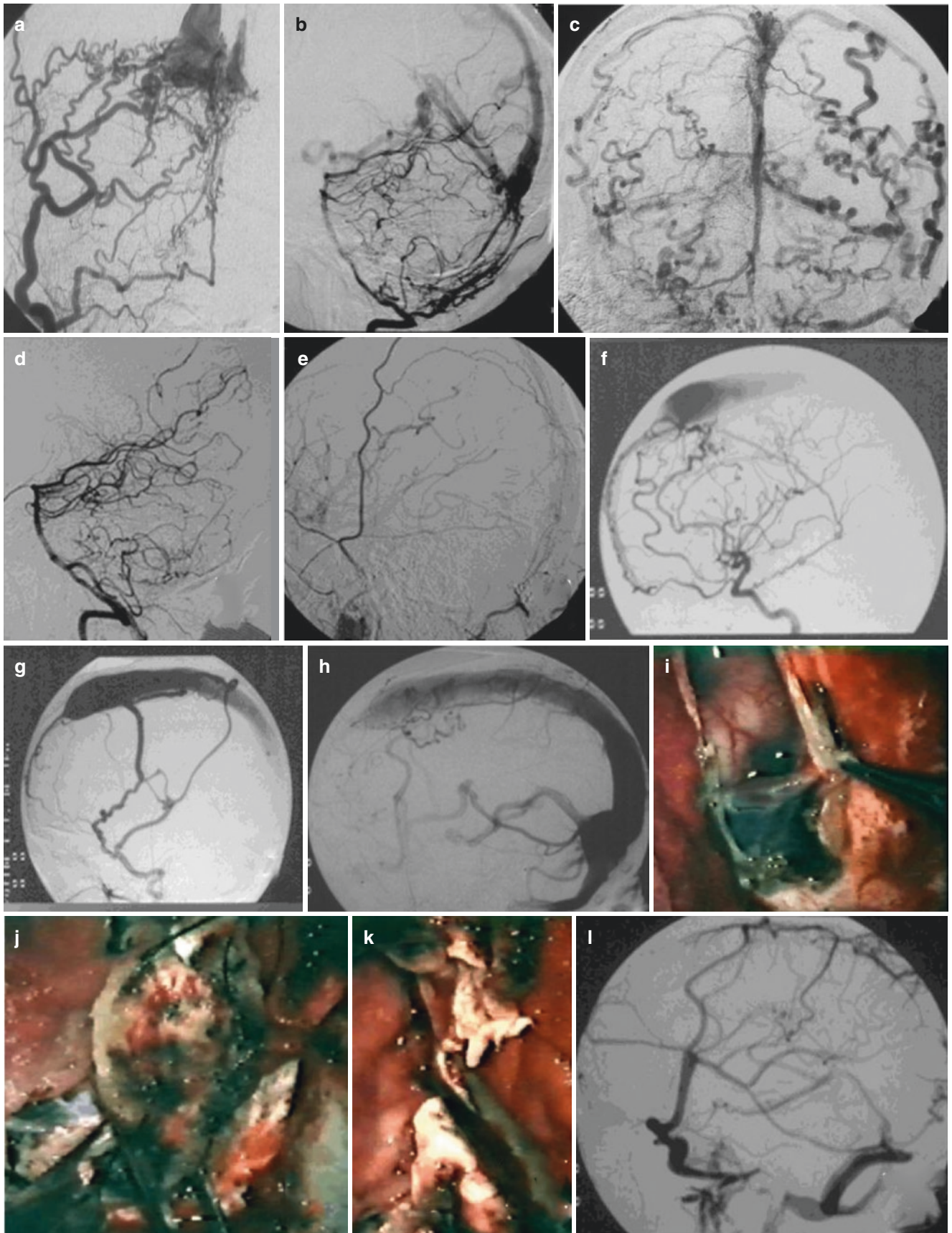


Fig. 3 Case 3. Sinus Fistula of Torcular (a–e). Case 4. Non sinus fistula SSS (f–n)

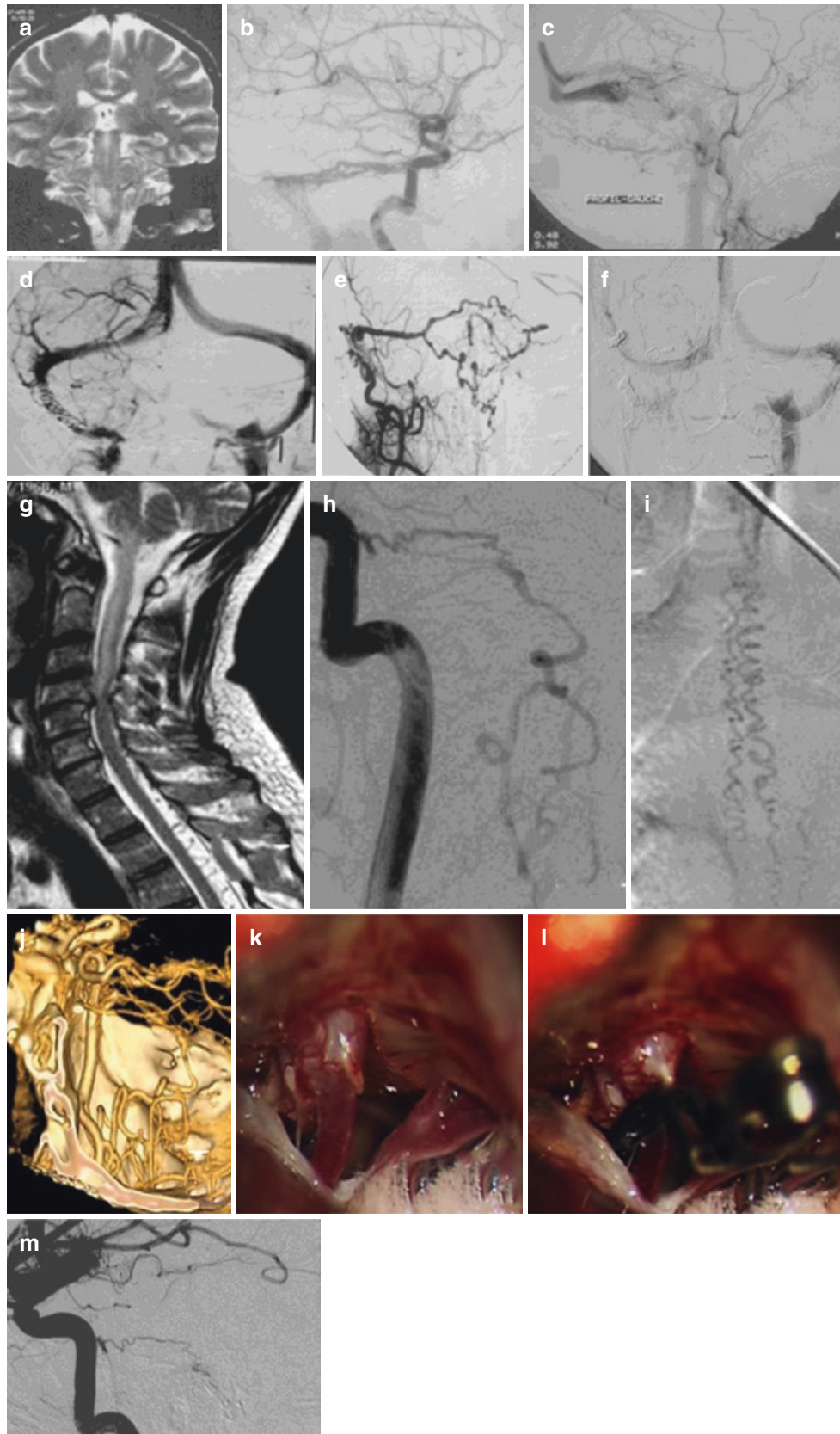


Fig. 4 Case 5. Sinus Fistula of Petrous bone apex (a–f). Case 6. Non-sinus fistula of Petrous bone apex (g–o)

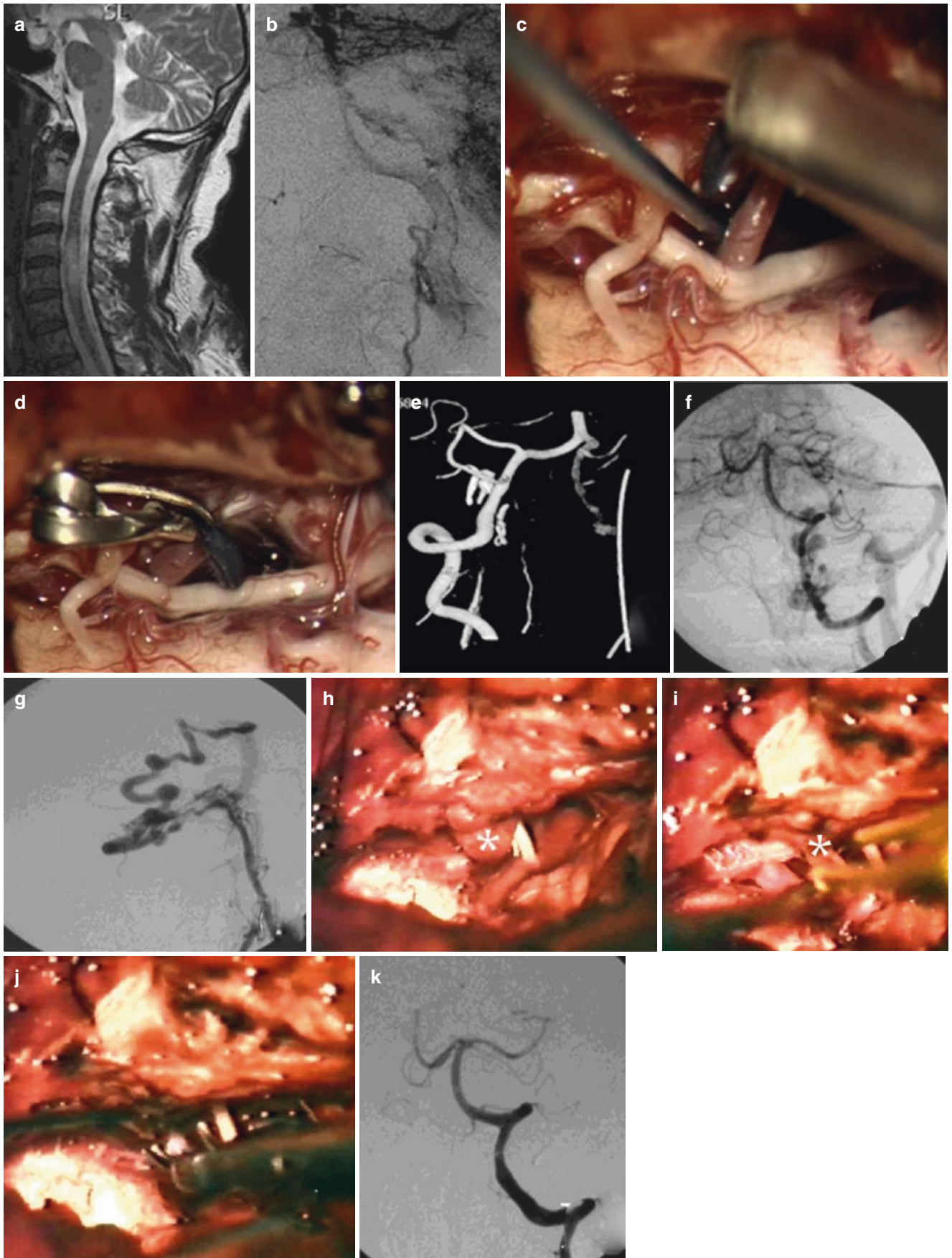


Fig. 5 Case 7 Non-sinus Fistula of Foramen Magnum (a–e). Case 8 Non-sinus fistula of Jugular Foramen (f–m)

Table 1 Surgical results

Mortality	2/101 (2%)
Severe morbidity	1/101 (1%)
Minor morbidity	4/101(4%)
Complete obliteration	101/101 (100%)
F.U 5 years: recurrence	1/101 (1%)

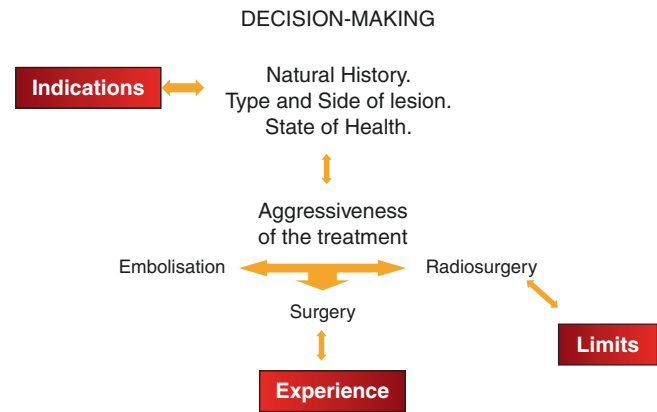
Case 8 A 58-year-old Italian politician come to our observation for a left tinnitus with onset 1 year previous. Some weeks before, the patient experienced onset of progressive motor impairment in walking with sensitive deficit. Angiography showed a non-sinus fistula close to the jugular foramen (f, g). The fistula was excluded through a surgical intervention with clipping of “piè” of the vein (h, i, l). Post-operative DSA showed the complete disappearance of the malformation (m).

Surgical Results

Surgical series results are described in Table 1. Mortality and severe disability was 3% and morbidity less than 4%. All patients underwent a postoperative DSA with nearly 100% of complete occlusion of the fistula. At a mean follow up of 5 years in one case there was a non-sinus fistula recurrence, due to the presence of a partial clipping of “the shunting foot.” Our surgical experience underlines the fact that posterior fossa localization, per se, does not represent and adjunctive risk factor for treatment. Moreover, based on shunt location, dAVFs can be classified in the same way as meningiomas: falcotentorial, straight sinus-vein of Galen-torcular, transverse and jugular sinus, CPA and foramen magnum (before or at the entrance of the vertebral artery).

Discussion

Dural arteriovenous fistulas (dAVFs) account for 10–15% of all intracranial arteriovenous lesions. Symptoms and prognosis are highly variable. Some dural AVFs produce neurological symptoms depending on the locations and the involved structures; others are associated with intracranial hemorrhage [1, 7, 16]. It is very important to have a good understanding of the natural history of dural AVFs when it comes to decision-making about treatment (See Fig. 6). This challenging and interesting topic has been reviewed since 1984, when Malik et al. [17] studied 223 previously reported cases and concluded that lesions related to large dural sinuses are less likely to bleed than lesions with restricted dural outflow. In this first review there were no angiographic features, in particular, the pattern of venous drainage taken into consideration. In 1986, Lasjaunias et al. [18] presented a meta-

**Fig. 6** Decision-making workflow

analysis of 191 cases. They analyzed the mechanism of neurologic manifestations and concluded that apart from the peripheral cranial nerve palsy due to arterial steal phenomena, central nervous system symptoms seem to be related to passive venous hypertension. In 1990, Awad et al. [19] reviewed 360 cases reported in the literature and 17 of their own cases to compare the angiographic features of 100 aggressive cases and 277 benign cases. They concluded that leptomeningeal venous drainage, variceal or aneurysmal venous dilatations, and galenic drainage were indicative of possible aggressive neurologic signs. In 1995 Cognard et al. [4] reviewed a series of 205 consecutive patients with dural AVFs over 18 years. The purpose was to complete and validate the classification of dural AVFs proposed in 1978 by Djindjian et al. [3]. In the same year Borden proposed his classification system [5], which stratifies lesions on the basis of the site of venous drainage and the presence or absence of cortical venous drainage. Borden type I lesions have the direct communication of meningeal arteries with a meningeal vein or dural venous sinus and exhibit normal antegrade flow. Type II lesions have shunts between the meningeal arteries and dural sinus, with retrograde flow into the subarachnoid veins, causing venous hypertension. Type III lesions have direct drainage of meningeal arteries into subarachnoid veins or an “isolated” sinus segment. The latter phenomenon is often the result of thrombosis on either side of the arterialized sinus segment, which directs retrograde flow into the subarachnoid venous system. The Borden classification scheme further subclassifies lesions as single-hole (a) or multiple-hole (b) fistulas. In our experience, the most useful classification for a merely surgical point of view is to distinguish intracranial dAVFs as sinus or non-sinus, because the simple understanding of this point leads to the correct treatment. On the basis of venous drainage, Borden [5] classified intracranial dAVFs into three main types: sinus, sinus with recruitment of one or more cerebral veins, and fistulas draining into cortical cerebral veins.

Commonly, type I fistulas have a benign behavior and are conservatively treated. If a disabling bruit is present, a palliative transarterial embolization can be indicated, while surgery is chosen in very selected cases.

However, Type II and III dAVFs usually show an aggressive behavior including hemorrhage and progressive neurological deficits. Davies [1, 7] report an intracranial hemorrhage rate of 19.2% lesion/year and non-hemorrhagic deficit of 10.7% lesion/year. The complete obliteration of Type II or Type III fistula by embolization can be obtained in less than 50% of cases via the transarterial route and in more than 80% of cases when the venous route is used.

Urtasun, Roy, Link and Lucas [20–23] reported rates of 72% complete obliteration and 28% partial obliteration in patients treated by radiosurgery at 1 and 3 years of follow-up. On the basis of shunt location, posterior cranial fossa dAVFs can be classified in the same way as meningiomas: falcotentorial, straight sinus/vein of Galen, torcular, transverse sinus, jugular sinus, CPA, and foramen magnum dAVFs (Fig. 7). From a practical surgical point of view we

suggest to simply classify dAVFs as “sinusal” or “non sinusal fistula.” In the former type there is a direct communication between the dural shunt and one sinus, and cortical veins can sometimes be recruited; in the latter type the shunt is embedded into the dura and the drainage always involves a cerebral vein. As for all diseases, the decision-making process must take into account surgeon experience, aggressiveness of the lesion, and limits of the treatment. Three different approaches can be indicated in dAVFs: surgical, endovascular (i.e., transarterial/transvenous embolization), and radio-surgical with Gamma Knife.

Surgical treatment is different in sinus and non-sinus fistulas and comprise involved sinus resection and clipping or endovascular occlusion of recruited cerebral veins. Recruited veins, the so-called “red veins,” are not functional and show an inverted internal blood flow. Distal to the involved sinus there could be functional blue veins that must be spared. On the other hand, treatment of non-sinusal fistula consists in clipping or endovascular occlusion of the draining red vein which, as mentioned before, is a non-functional vein.

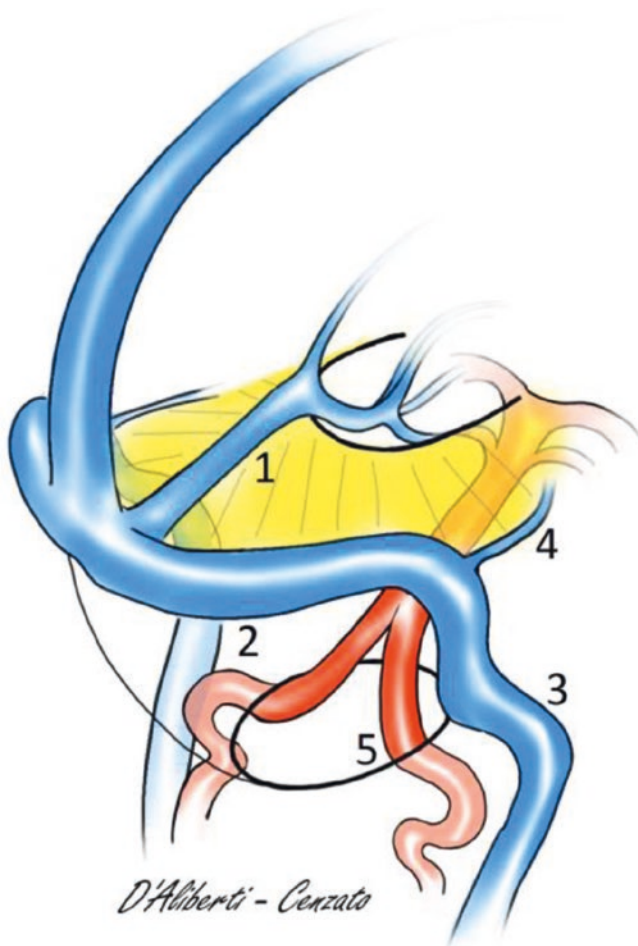


Fig. 7 Localization of posterior cranial fossa dAVFs (See Table 2 for description)

Conclusions

We want to underline the role of venous drainage in the management of dAVFs. Prioritization of treatment options is crucial to achieving a good result. As a consequence, identifying sinus vs non-sinus fistulas is crucial from a surgical point of view. Sinus fistulas require sinus excision and clipping and subsequent occlusion of recruited veins. Non-sinus fistulas require, on the other hand, clipping or endovascular venous embolization of the drainage vein. A posterior cranial fossa location does not represent an adjunctive risk factor in the treatment of dural fistulas. Type IV and V in Cognard and Gobin’s classification are not to be considered as independent entities: varices and perimedullary drainage can be seen in both sinus and non-sinus fistulas.

Table 2 Localization of posterior cranial fossa meningiomas and dAVFs

Localization of posterior cranial fossa meningioma (Castellano-Yasargil-AlMefty)	Localization of posterior cranial fossa non sinus-sinus DAVFs (D’Aliberti-Cenzato)
Tentorial-Falcotentorial	1. Straight sinus, Vein of Galen and Torcular
Petrous-Petroclival	2. Transverse Sinus
Jugular Foramen	3. Jugular Foramen
CPA	4. Petrous bone apex
Foramen Magnum	5. Foramen Magnum (Before or at the entrance of VA)

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Complications of Endovascular Treatment of Intracranial Dural Arteriovenous Fistulas

Naoya Kuwayama and Naoki Akioka

Dural arteriovenous fistulas (dAVF) are acquired lesions whose incidence is reported to be 0.3 per 100,000 per year [1]. The locations of the fistula include the cavernous sinus, transverse-sigmoid sinus, superior sagittal sinus, inferior and superior petrosal sinuses, anterior condylar confluence, tentorium, anterior skull base, craniocervical junction, convexity, and spinal cord. These lesions are divided into sinus type (the former six lesions) and non-sinus type (the latter five lesions).

The principle of dAVF therapy had been endovascular treatment for the sinus type and surgical treatment for the non-sinus type until Onyx was introduced as an embolic material. Nowadays the majority of non-sinus type dAVFs can be successfully treated with use of Onyx [2]. Current endovascular therapy includes transvenous coil embolization of the sinus type and transarterial glue or Onyx embolization of the non-sinus type. The aim of this study is to report complications that resulted from endovascular treatment of this disease.

Complication of Transarterial Embolization (TAE)

Migration Via the Arterial Anastomosis

One of the most important and critical complications is cerebral ischemia resulting from the migration of embolic materials via so-called dangerous anastomosis or the network between dural and pial arteries. Usually the dural branches of the external carotid artery have rich anastomosis with the dural and pial branches of the internal and vertebral arteries. Liquid embolic materials like NBCA (n-butyl cyanoacry-

late) and Onyx, as well as particulate materials smaller than 200 μm , are easily migrating to the pial arteries via the network. One must care about another dangerous behavior of the liquid materials; it tends to come back to the parent feeding pedicle via the arterial network arising from the feeding artery itself (Fig. 1).

Migration to the Venous Side

Onyx, particularly, tends to penetrate the arteriovenous fistula very easily and go to the venous side. This penetration is the essential phenomenon needed for the radical treatment and the most advantageous point of Onyx to the particulates. However, excessive penetration (migration) could occasionally result in the occlusion of the functioning cerebral veins (Fig. 2), causing potential venous infarction.

NBCA tends to make fragmentation in the venous side when arterial blood flow comes from the other feeding arteries. If the block of fragment occludes the distal side of the draining vein, venous bleeding may occur because of the remaining arterial inflow.

Ischemia of the Vasa Nervosum

NBCA, Onyx, and small particulates (<200 μm) migrating into the vasa nervosum will cause cranial nerve palsy. Many external carotid branches like the middle meningeal, accessory meningeal, deep temporal artery, and the artery of foramen rotundum give rise to branches feeding the cranial nerves around the middle fossa. The middle meningeal, ascending pharyngeal, occipital artery, and posterior meningeal branch of the vertebral artery also feed the cranial nerves inside and outside the posterior fossa. The inferolateral and meningohypophyseal trunk of the internal carotid artery feed many cranial nerves and have a rich collateral anastomosis between external carotid artery.

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Fig. 1 A case with dAVF in the craniocervical junction showing NBCA migration. (a) Preoperative vertebral angiogram indicating dAVF fed by C2 segmental artery of the vertebral artery and drained into the cerebral vein in the brain stem. (b) Microangiogram from the feeding artery. (c) Postoperative CT scan indicating migration of the fragmented pieces of NBCA. (d) Schematic drawing of the mechanism of NBCA migration; injected NBCA came back to the distal parent vertebral artery via the other feeding pedicle

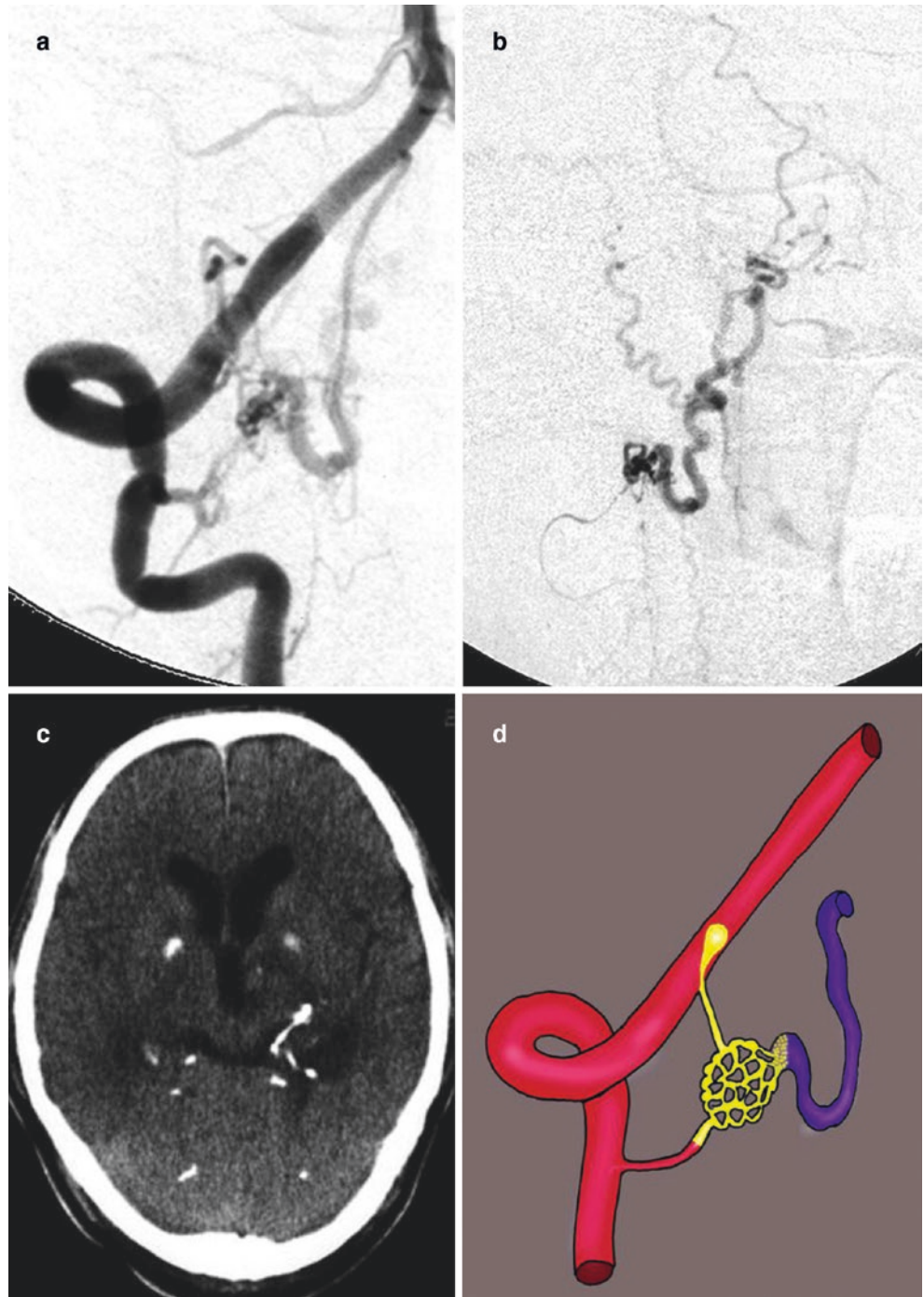
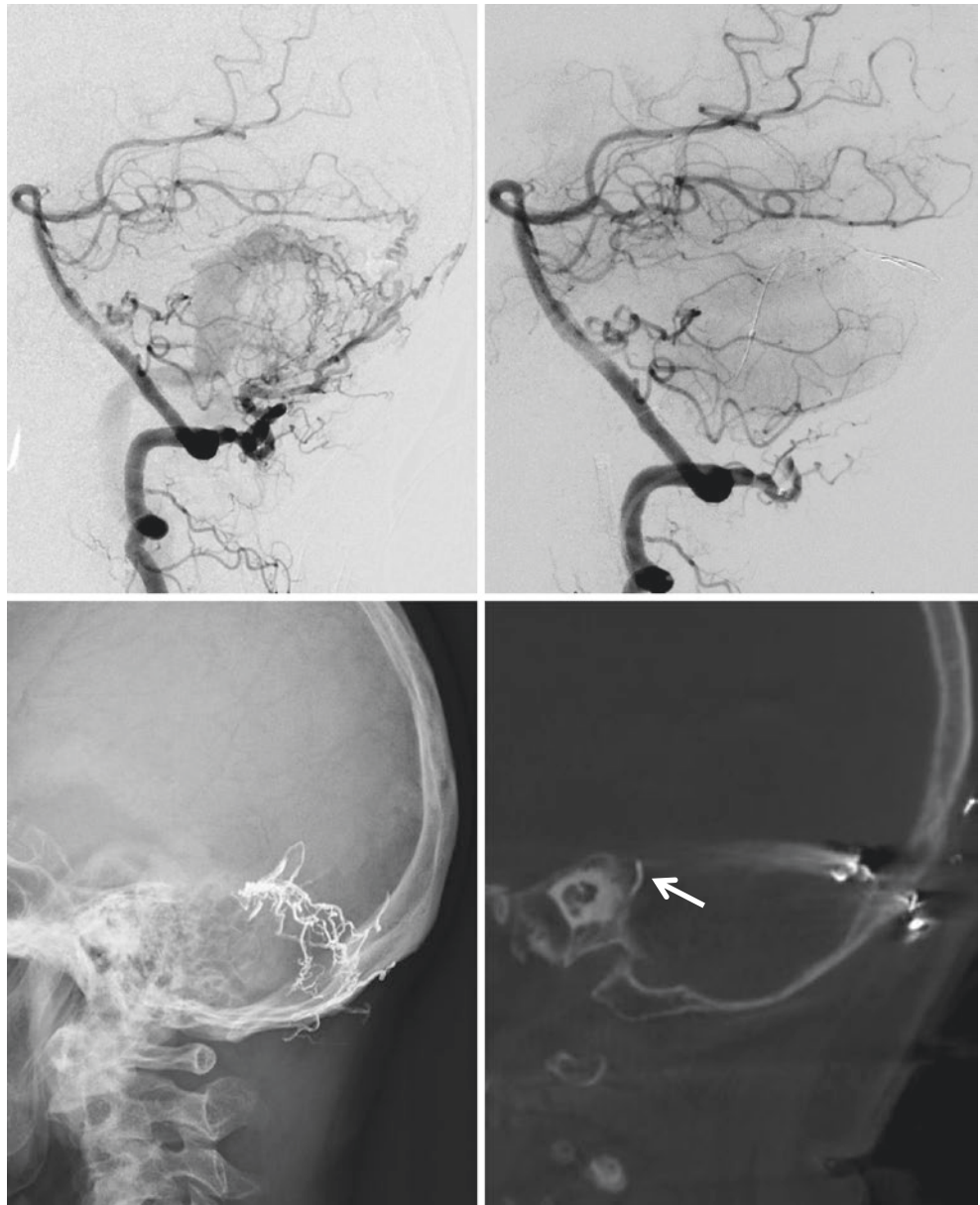


Fig. 2 A case with Borden type-I dAVF involving the transverse-sigmoid sinus. The shunt was obliterated with Onyx injection from the distal occipital artery arising from the vertebral artery. A balloon catheter was inflated in the involved sinus to prevent Onyx migration to the sinus side. (a) Preoperative vertebral angiogram. (b) Postoperative vertebral angiogram indicating complete obliteration of the shunt. (c) Postoperative craniogram showing the Onyx cast. (d) Postoperative cone beam CT indicating Onyx migration to the tinny petrosal vein (arrow) via the superior petrosal sinus



Complication of Transvenous Embolization (TVE)

Mass Effect to the Cranial Nerves

Excessive transvenous coil packing of the cavernous sinus and anterior condylar confluence causes III, IV, V cranial

nerve palsy and XII nerve palsy, respectively. Sometimes, the delayed ocular palsy will occur and never recover [3]. This mechanism still remains unknown but one should remind.

Venous Infarction and Bleeding

Normal cerebral veins sometimes drain into the involved sinus in an antegrade fashion. Venous infarction will occur after complete transvenous sinus packing by blocking the normal venous drainage (Fig. 3). Cortical venous drainage or retrograde leptomeningeal drainage in sinus type dAVFs is sometimes seen in Borden type II or III and Cognard type IIb. Transvenous sinus packing of these lesions have a potent

complication of venous bleeding from excessive residual drainage to the cortical vein if the packing is incomplete (Fig. 4). One must obliterate, at first, the dangerous small draining veins like the uncal vein, petrosal vein, and bridging veins to the brain stem (Fig. 5).

Conflict of Interest The authors do not have a financial relationship with any organization.

The authors declare that they have no conflict of interest.

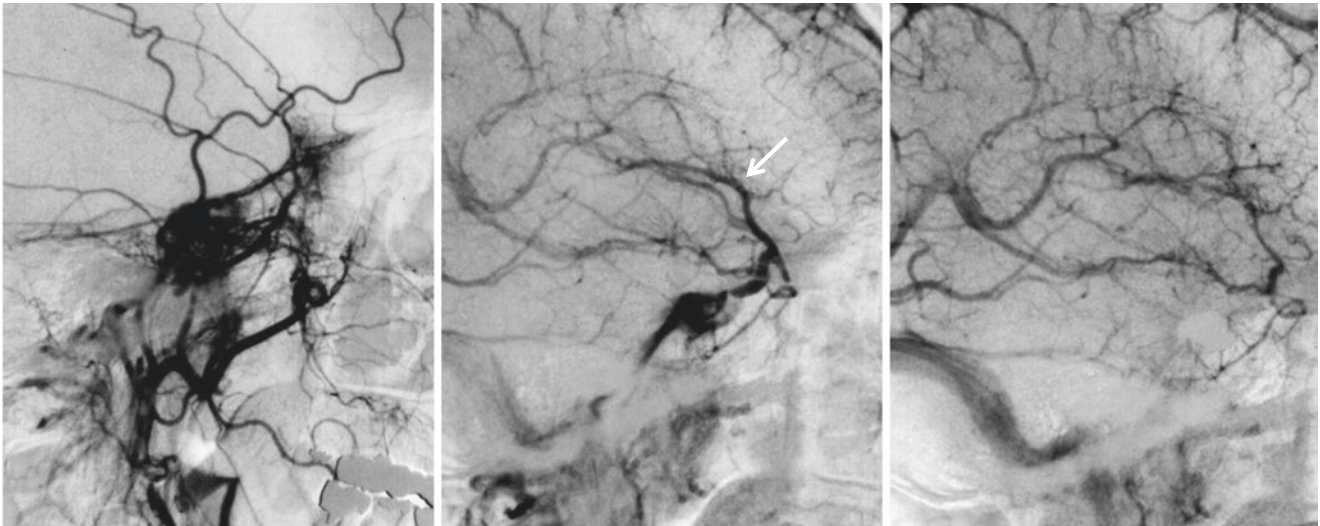


Fig. 3 A case with cavernous sinus dAVF treated with transvenous packing of the affected sinus. Left: Preoperative external carotid angiogram (lateral view) showing the shunt in the cavernous sinus. Center: Preoperative internal carotid angiogram (lateral view) showing the

superficial middle cerebral veins emptying into the affected cavernous sinus in an antegrade fashion. Right: Venous phase of the postoperative common carotid angiogram (lateral view). Note one of the superficial middle cerebral veins (arrow in the center figure) was missing

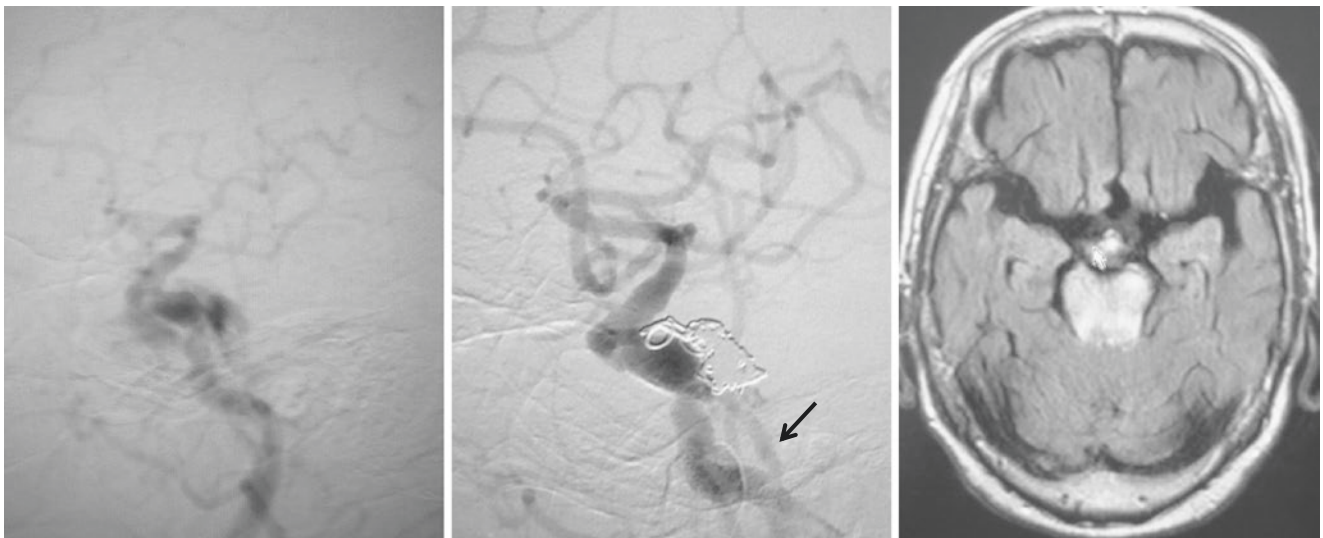


Fig. 4 A case with cavernous sinus dAVF treated by transvenous coil embolization. Left: Preoperative common carotid angiogram. Center: Postoperative common carotid angiogram showing incomplete obliteration of the affected cavernous sinus. Note the cavernous sinus was packed with coils but the inferior petrosal sinus was still opacified

(arrow). Right: MRI (FLAIR) examined in the next day showing (venous) infarction of the entire brain stem, suggesting the postoperative change of the draining route into the brain stem by incomplete transvenous occlusion of the cavernous sinus

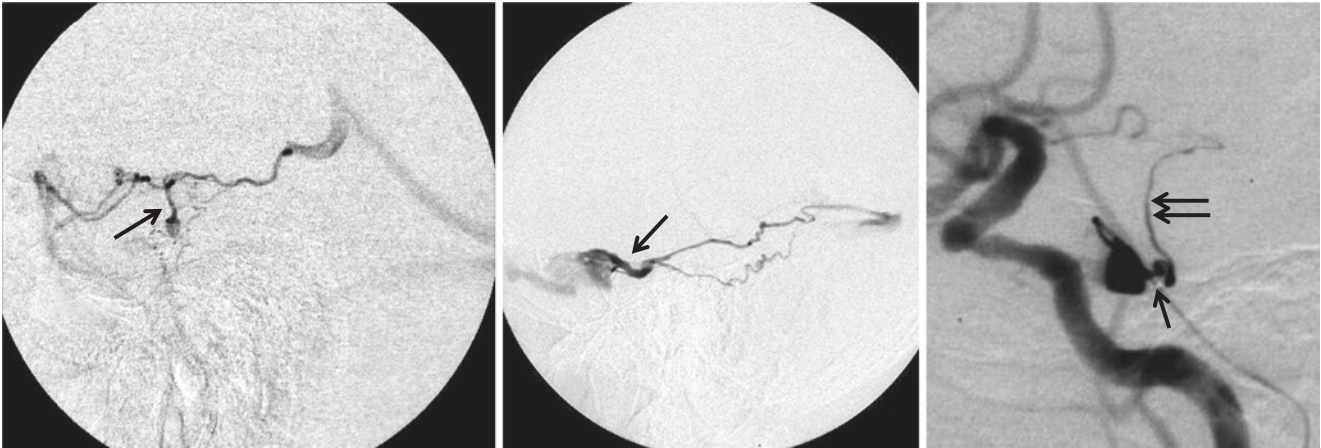


Fig. 5 Examples of the dangerous draining veins. Left: Cavernous sinus injection opacified the uncal vein (arrow) connecting with deep cerebral veins (vein of Rosenthal and vein of Galen). Center: Cavernous sinus injection opacified the petrosal vein (arrow). Right: Carotid

angiogram showing the cavernous sinus dAVF draining only into the tinny vein of the brain stem (double arrows) via the bridging vein (arrow)

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Spinal Dural AVFs: Classifications and Advanced Imaging

Michihiro Tanaka

Abbreviations

ASA	Anterior spinal artery
CBCT	High-resolution cone beam computed tomography
CE-MRA	Contrast-enhanced MR angiography
DSB	Dorsal somatic branch
DV	Initial segment of the draining vein
MRI	Magnetic resonance imaging
PSA	Posterior spinal artery
SDAVFs	Spinal dural arteriovenous fistulas
SEAVFs	Spinal epidural arteriovenous fistulas

Introduction

Spinal dural arteriovenous fistulas (SDAVFs) are the most common spinal vascular malformation. The clinical symptoms, however, are usually nonspecific. Therefore, the neurosurgeon or neuroradiologist is often the first clinician to make the initial diagnosis based on MR imaging, with differential diagnoses causing confusion [1–4]. Recent imaging technology can visualize the detailed angioarchitecture of SDAVFs at the level of the shunt point. We retrospectively analyzed 22 consecutive cases of SDAVFs and identified the shunt point and the related vasculatures of SDAVFs based on the MRI, CE-MRA, high-resolution cone beam CT (CBCT), spinal angiography, and 3D-CT. The efficacy and sensitivity of these imaging modalities were assessed, and a new concept of classification of SDAVFs was introduced in terms of the anatomical point of view.

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Materials and Methods

From 2005 to 2017, 22 consecutive cases of SDAVFs were diagnosed with MRI and angiography. Spinal epidural arteriovenous fistulas (SEAVFs) located at the lumbar spine were excluded from this study. Our population was composed of 21 men and one woman. The mean patient age was 67 ± 12.4 years (range 42–79 years). High-resolution cone beam CT (CBCT) was introduced in 2013 in our institute, and a total of 11 cases received CBCT. The visualization of anterior spinal artery (ASA), posterior spinal artery (PSA), dorsal somatic branch (DSB), and the primary foot of the draining vein (DV) were confirmed. If transarterial embolization was indicated, superselective angiography from the dominant feeder was referred to in order to confirm the precise topographical location of the shunt point. A total of 18 cases were treated with superselective transarterial embolization with Histoacryl glue. The other four cases were treated by surgical clipping of the arterialized bridging vein after laminectomy.

MR Imaging and Contrast-Enhanced MR-DSA

All 22 patients underwent extensive spinal MR-DSA with gadolinium contrast and MR imaging (1.5 T and/or 3 T). The extension of the T2 signal hyperintensity and the medullary contrast enhancement was qualified by the number of vertebral levels shown to be affected on T1 and T2 MR images. The appearance of the perimedullary veins was rated subjectively as absent or prominent due to their tortuous and dilated appearance in the T1 and T2 images. Contrast-enhanced MR angiography (CE-MRA) is similar to contrast-enhanced CT angiography, except a gadolinium-based agent (instead of an iodine compound) is injected. Just as iodine produces X-ray attenuation allowing visualization of vessels on CTA, gadolinium shortens the T1 of blood, rendering vessels bright on CE-MRA (Fig. 1).

Fig. 1 (a) T1-weighted image on sagittal view showed the swelling of spinal cord with the appearance of central myelopathy. (b) CE-MRA depicted the shunt point at the level of mid-thoracic spine. This modality enabled effective identification of the level of the shunt point



3D-CT

The introduction of multi-detector row computed tomography (MDCT) has allowed further refinements in detecting microstructures in the spinal cord region. MDCT was performed with a commercially available MDCT scanner (Aquilion ONE™/GENESIS Toshiba Medical Systems, Tokyo, Japan) with a gantry rotation speed of 0.35 s and a detector configuration of 32.0 × 1.0 mm; the moving speed of the table was 27 mm/s. All scans were acquired in a cephalocaudal direction. Patients underwent MDCT followed by arterial and venous phases. Patients received 100 mL of iomeprol (Iomeron, 350 mg/mL, Bracco-Eisai, Otsuka, Japan) with a monophasic injection technique by means of a power injector. Analysis of the three-dimensional (3D) data set for the region of interest in all subjects was also done by experienced radiological technicians using a commercially available workstation (ZIOSOFT, ZIOSOFT Inc., Tokyo, Japan). With ZIOSOFT, 3D reconstruction images of the shunt point and the artery of Adamkiewicz were created using CT images of the arterial phase with a slice thickness

of 0.5 mm, manually removing adjacent structures such as vertebral bony structures and the outside of the spinal canal.

DSA and High-Resolution CBCT

Digital subtraction angiography (DSA) was performed with a femoral approach in a dedicated biplanar neuroangiographic suite. The equipped DSA machine was a flat-panel detector biplane angiography unit (Allura Clarity FD20/20; Philips Medical Systems). Spinal angiography was performed using the standard angiographic technique and investigated total spinal level, including bilateral intercostal artery and adjacent level of the shunt point. Standardized angiography included selective manual injections of 4–5 mL of 300 mg/mL of iodinated nonionic contrast medium into the lumbar and intercostal arteries using a 4 or 5 French in the outer diameter of the catheter designed for the spinal angiography. Furthermore, injections into both vertebral arteries, the costocervical arteries, the thyrocervical trunks, and the arterial feeders of the sacral region were added. Once the

shunt point and the Adamkiewicz artery were identified, the high-resolution CBCT was performed in each corresponding artery after the complete set of the entire spinal angiography. High-resolution CBCT was based on motorized rotational angiography acquisition. The shunt lesion and the region of interest were positioned in the system isocenter around which the C-arm takes a circular trajectory of 220°. The motorized frontal C-arm was used to acquire 30 projection images/s at 80 kV, the scanning time was 20 s, and the detector format used was 22 cm × 22 cm. All procedures and acquisitions were performed under general anesthesia. During this acquisition, the anesthesiologist paused the ventilator for around 20 s of apnea to avoid motion artifact. The acquisition dataset was transferred to the workstation (Xtra Vision; Philips Medical Systems) for the reconstruction process. All high-resolution CBCT images were reconstructed with 512³ matrixes centered about the regional shunt point and optimized for the visualization of the ASA, PSA, DSB, and DV. After reconstruction of the three-dimensional volume of interest, anatomical details were evaluated by multiplanar reconstructions with volume rendering and manipulation of the parameters on the maximum intensity projection mode.

Results

The shunt points were well identified on the DSA and CBCT with 100% of sensitivity, while MRI and MR-DSA showed the shunt points in only 9% of the cases. 3D-CT showed 18% of sensitivity (Table 1).

ASA was well-visualized on DSA and CBCT with 100% of sensitivity; however, MRI and 3D-CT could depict ASA with less than 60% of the cases (Figs. 1 and 2).

The sensitivity of CBCT was so remarkable that it successfully showed the exact location of the shunt point, ASA, and DV in 100% of the cases (Fig. 3), but was less able to visualize DSB. According to the analysis of the serial axial and coronal images based on the slab maximum intensity projection (Slab MIP), the exact shunt point in most of the cases was located on the surface of the nerve sleeves. DSB could also be depicted on this slab MIP mode in 68% of the cases (Fig. 4). The basket formation of the anastomosis between ASA and bilateral PSA was well visualized on

CBCT (Fig. 5). It is usually difficult to identify the PSA on the conventional DSA; in this series, however, the sensitivity to PSA with CBCT was more than 70% (Fig. 6).

Meningeal branches of the radiculomeningeal artery were the main feeding arteries in 21 of 22 cases (95.5%). These feeding arteries ran medially on the surface of the dural sleeve and turned longitudinally along the dura mater of the thecal sac. Then they gathered and joined the single vein on the inner dural surface. In 16 cases (72%), we observed these longitudinal meningeal feeders and a drainage vein that resembled the horizontal T sign in an anteroposterior view of angiography as well as in CBCT (Fig. 3a).



Fig. 2 3D-CT delineated the course of the intercostal artery (short arrow) and the terminal feeder toward the shunt point (long arrow) corresponding to the meningeal branches of the radiculomeningeal artery

Table 1 Visibility of the anatomical structure on each imaging modality associated with SDAVFs

	MRI	CE-MRA	3D-CT	DSA	CBCT
Shunt point	2 (9%)	2 (9%)	4 (18%)	22 (100%)	11 (100%)
ASA	12 (55%)	13 (59%)	13 (59%)	22 (100%)	11 (100%)
PSA	0 (0%)	0 (0%)	1 (4.5%)	16 (73%)	8 (73%)
DSB	0 (0%)	0 (0%)	0 (0%)	13 (59%)	7 (64%)
DV	21 (90%)	21 (90%)	18 (81%)	22 (100%)	22 (100%)

This table shows the number of the prominent and well visible structures on five different radiological images

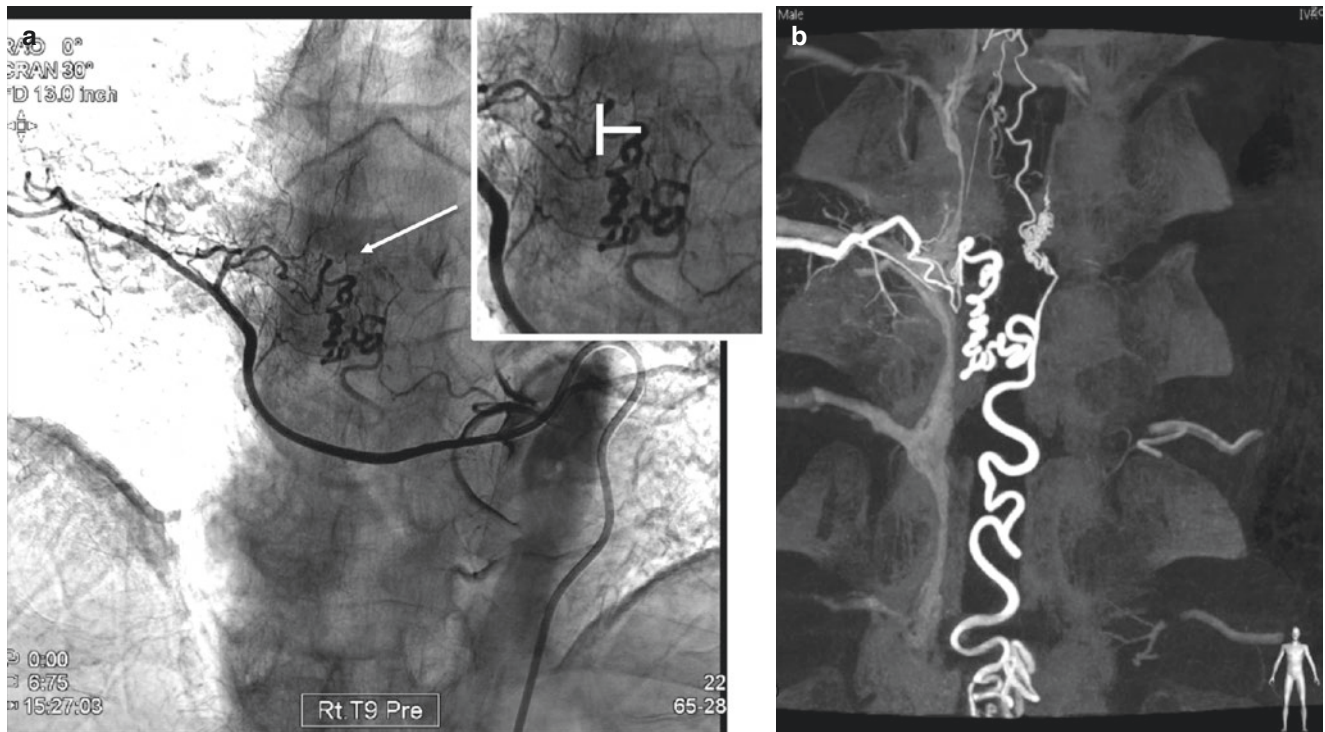


Fig. 3 (a) Conventional DSA injected from the right intercostal artery at the level of T9. It showed the SDAVF with the longitudinal meningeal feeders and a drainage vein. The configuration of this longitudinal meningeal feeder and a drainage vein resembled the horizontal T sign in an anteroposterior view. (b) CBCT depicted the shunt point, precisely locating it on the lateral surface of the dura mater

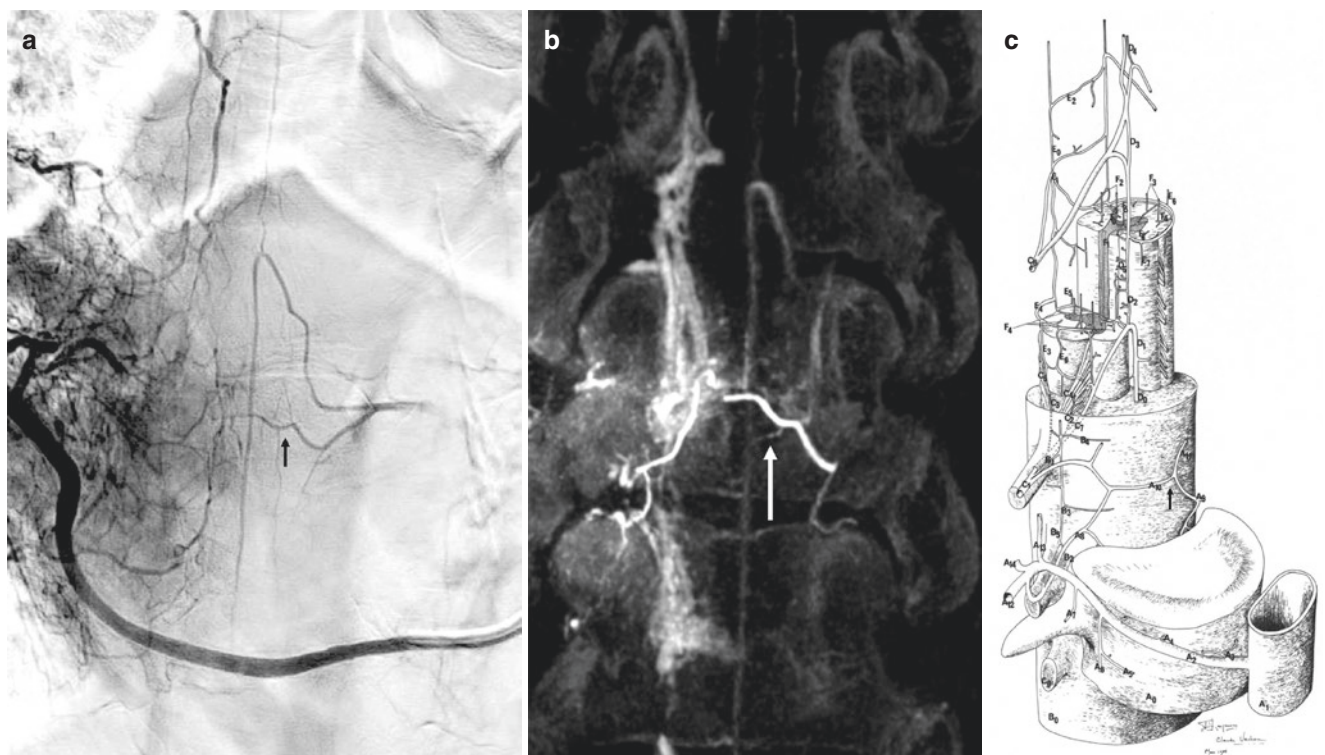


Fig. 4 (a) Right intercostal artery injection of DSA (AP view). (b) CBCT after complete elimination of the shunt. (c) Schematic representation of spine and spinal cord supply at the upper thoracic level. Note the contralateral DSB (arrow) is opacified through the anastomosis. The artery of Adamkiewicz is also visualized through this collateral supply



Fig. 5 CBCT showed the great anterior radiculomedullary artery (Adamkiewicz artery) and the basket formation (arrow) at the level of conus medullaris

Discussion

In terms of digital images, spatial resolution refers to the number of pixels utilized in the construction of the image. The higher spatial resolution of medical images is essential in the management and giving the indication of therapeutic options for SDAVF [2, 3].

Recent advancements in imaging technology improved the performance and efficacies of MRI, CE-MRA, and MDCT in terms of the definition of the shunt point as well as the adjacent vasculatures. These imaging modalities are less invasive and are available in the outpatient clinic. However, the degree of definition and the sensitivities to the region of interest on these modalities are still inferior to the conventional DSA and CBCT with the use of invasive catheter angiography.

The discrimination between SDAVFs and spinal epidural fistulas (SEAVFs) is very important to the process of making a strategy of treatment and indicating the intervention. Kiyosue et al. reported on 168 patients with spinal dural and epidural arteriovenous fistulas from 31 centers in Japan [5]. Six readers analyzed the angioarchitecture. Approximately half of the epidural fistulas were incorrectly diagnosed as dural fistulas at the individual centers, highlighting the need

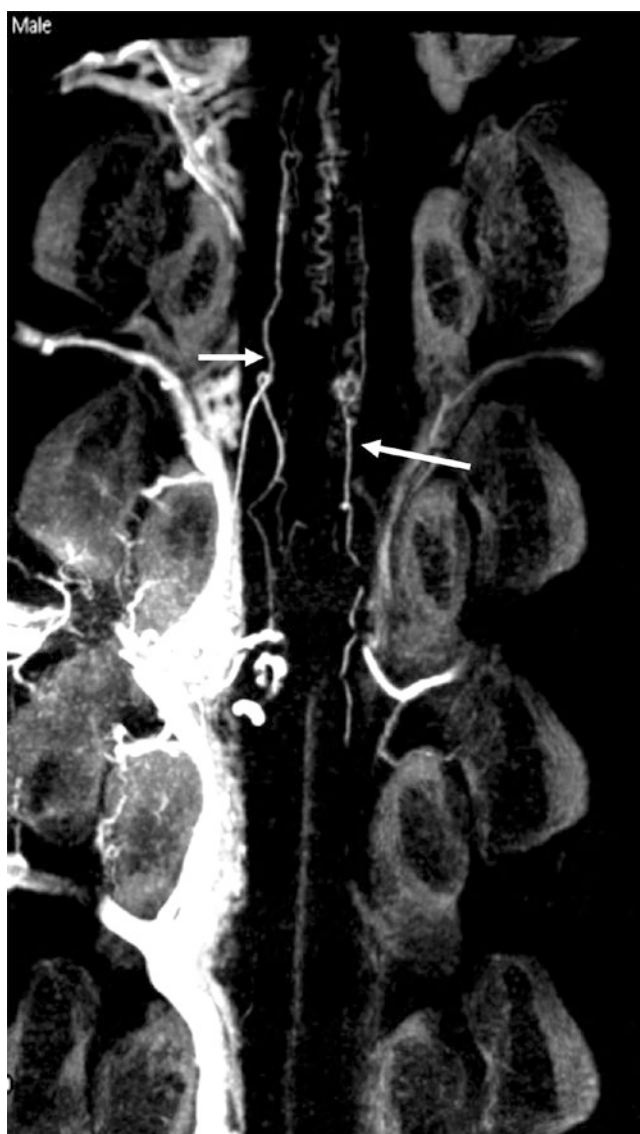


Fig. 6 CBCT after complete elimination of the shunt. Note bilateral PSA were well-visualized on this plane (arrow)

to establish and publish distinguishing features. The shunt points of SDAVFs are more commonly located in the thoracic spine, whereas SEAVFs have a propensity to be in the lumbar spine and are associated with a history of spinal injury or surgery [5]. Both are more common in males and present with myelopathy. SDAVFs have their shunt point medial to the medial interpedicle line that indicates the estimated lateral margin of the thecal sac. They are supplied by meningeal branches of the radiculomeningeal artery. SEAVFs form epidural venous pouches located in the epidural space and shunt into the perimedullary vein, paravertebral veins, or both. They are supplied by epidural arteries, usually the DSB (dorsal somatic branch) [2, 3, 5].

The distinction is also relevant for treatment. Whereas dural fistulas are favorable for open surgery and intradural

division of the draining vein, epidural fistulas are better served by endovascular embolization [6, 7]. Feeders to epidural fistulas also tend to be straight and more easily accessible using the endovascular route.

Classification of SDAVFs Based on the Advanced Images in Terms of the Embryological Origin of the Dura Mater

The higher definition images showed that typical SDAVFs had the shunt point on the lateral surface of the dura mater of the spinal canal, and it was more or less associated with the dura mater covering the nerve sleeve. The majority of SDAVFs are mainly supplied by meningeal branches from the radiculomeningeal artery. These meningeal branches anastomose vertically and drain into the single intradural vein, which typically forms horizontal T sign on a frontal view of spinal angiography and CBCT. It is generally thought that SDAVFs are located at the dura mater of the spinal nerve root sleeve and drain into the radiculomedullary vein. In normal anatomy, the drainage veins from the spinal cord, called radiculomedullary veins, run along the nerve root and penetrate the dura at the spinal nerve root sleeve. These radiculomedullary veins are found in 60% of the healthy population [8]. The remaining 40% show venous drainage of the spinal cord via the bridging vein, which runs apart from the nerve root and pierces the dura mater of the spinal cord to join the epidural venous plexus. SDAVFs can involve either the radiculomedullary vein or the bridging vein [2, 3, 5]. The dura mater at the level of the spinal cord are derived from the neural crest cell and consist of the single layer of dura propria, while the intracranial dura mater consists of dura propria and periosteal dura [9–12]. Thus, the characteristics of the dura mater of spinal cord are similar to the dura mater of crista galli (olfactory groove), falx cerebri, tentorium cerebelli, and falx cerebelli, because these dura maters consist only of the dura propria [13–16]. Additionally, those dura maters (dura propria) have the same origin of neural crest cell, while the convexity area of intracranial dura mater might derive from paraxial mesoderm, according to recent studies based on the immunostaining analysis of experimental model [10, 14, 17–19].

Conclusions

Three-dimensional angiography, particularly multiplanar reconstruction images with CBCT, is quite useful for evaluating the microangioarchitecture of SDAVFs. This modality showed the exact localization of the shunt point. There are

certain susceptibilities to the formation of the shunt on the lateral surface of the spinal canal, which is frequently independent from the nerve sleeves. The vulnerability of the dura mater might be associated with the fact that dura mater in the spinal canal consists only of the dura propria and derives from neural crest. SDAVFs and intracranial DAVFs located on the dura mater of the falco-tentorial, olfactory groove, falx cerebri, and tentorium cerebelli might belong to the same anatomical entity and they are composed only of the dura propria derived from neural crest.

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Part IV

Miscellaneous



Intraoperative BOLD-fMRI Cerebrovascular Reactivity Assessment

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and Jorn Fierstra

Introduction

Cerebrovascular reactivity (CVR) is the physiological capacity of the brain vessels to modulate cerebral blood flow (CBF) by changing their caliber in response to a vasoactive stimulus: this allows an adequate supply of oxygenated blood to the brain despite wide variations of perfusion pressure [1, 2].

Diverse neurological diseases can strain this physiological capacity beyond a limit that the brain vessels cannot further compensate, leading to exhaustion of the cerebrovascular reserve and, therefore, to CVR impairment [3]. Impaired CVR can be used as a measure of the hemodynamic stress the brain is undergoing in a particular anatomical area. Many studies have confirmed the validity of CVR as a marker of the hemodynamic state in vascular diseases [4–9]. The clinical relevance of CVR in predicting stroke risk has been confirmed, and CVR is widely investigated with different techniques, allowing risk stratification and providing valuable information for therapeutic decision-making [9, 10]. We have recently proposed and tested an intraoperative CVR assessment to obtain early information that could potentially help during the surgical procedure [11, 12].

CVR can be studied by applying a vasoactive stimulus to a patient and measuring the resulting changes at the brain level, either by CBF modifications or by surrogate of blood flow. As vasoactive stimulus, drugs or endogenous substances like CO₂ can be used [1]. Variations in the arterial CO₂ concentrations are obtainable by induced or voluntary apnea [1, 13]. To measure hemodynamic changes after administration of a vasoactive stimulus, many methods are granted, like Doppler sonography [9], arterial spin labeling (ASL) [14], or blood oxygenation-level dependent functional magnetic resonance imaging (BOLD-CVR) [3]. Detecting changes in the BOLD signal has proved a valid method with high imaging resolution, allowing a good depiction of the hemodynamic state at brain tissue level. This exploits deoxyhemoglobin paramagnetic properties, which make the BOLD signal get lower with higher blood deoxyhemoglobin concentrations [1, 15]. Areas with a higher blood flow achieve a higher deoxyhemoglobin clearance, thereby displaying a higher oxyhemoglobin/deoxyhemoglobin ratio, which ultimately results in higher BOLD signal [1].

Materials and Methods

This study has been approved by the cantonal ethics board of the Canton of Zurich, Switzerland (KEK-ZH-Nr. 2012–0427) and all participants signed informed consent prior to the study. An attempt to measure BOLD-CVR intraoperatively was first accomplished in oncological patients [11, 12]. Considering the technical issues associated with obtaining controlled iso-oxic hypercapnic stimuli and the need of a cooperative patient for this purpose [1], only breath-holding tasks were feasible so far to obtain CO₂ raises in unconscious patients. In the operating setting, a sedated and intubated patient is transferred from the operating theater to the adjacent MR suite, following a previously described protocol used at our institution [11, 16] and scanned on a 3-tesla device, obtaining BOLD, T1-weighted without contrast enhancement, plus other sequences according

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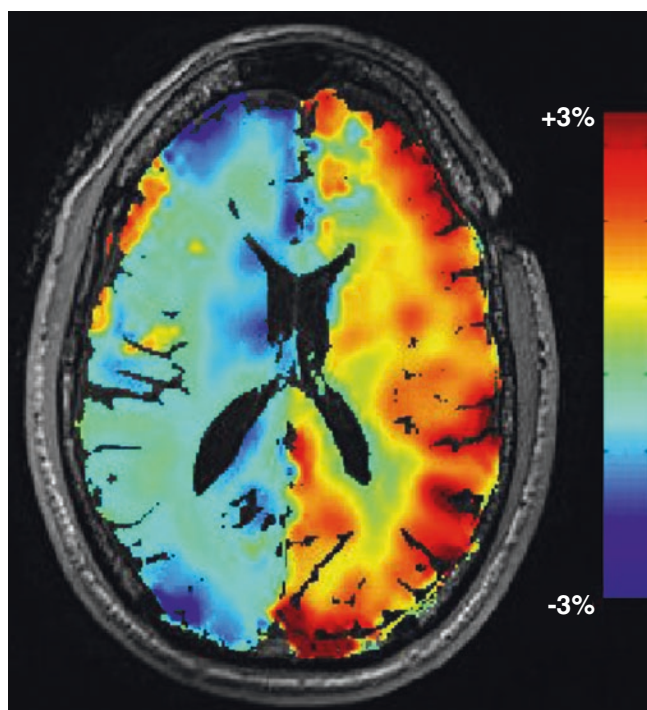


Fig. 1 Example of intraoperative BOLD-CVR color-coded map. Intraoperative BOLD-CVR assessment in a patient with occlusion of the right internal carotid artery after STA-MCA bypass for flow-augmentation. Areas with impaired hemodynamic status are depicted in blue. The color scale refers to the mean percentage change in BOLD signal per voxel between baseline and hypercapnic state

to the specific patient's case (i.e., T1-weighted with contrast, T2-weighted, fluid attenuation inversion recovery [FLAIR] and susceptibility weighted [SWI] sequences for tumor patients, TOF-MRA or diffusion weighted imaging [DWI] in vascular diseases). The technical details about acquisition parameters can be found in our previous publications [11, 12, 17]. During acquisition of the BOLD sequences, hypercapnia is induced by three 44-s apnea cycles obtained by halting the ventilator, followed by hyperventilation to return to the subject's baseline CO_2 . Between each hypercapnic challenge, an 88-s baseline CO_2 period is maintained. This allows obtaining satisfactory CO_2 oscillations and therefore adequate vasoactive stimuli resulting in coherent BOLD-signal fluctuations [11].

Pre-processing and data analysis are performed following a method described previously [11, 18, 19]. CVR can be thus calculated on a voxel-by-voxel basis and measured as the mean percentage BOLD signal change between baseline and hypercapnia. For optimal depiction, the percentage changes values are color-coded and overlaid on the T1-weighted anatomical scan acquired during the same session (see Fig. 1).

Results

The intraoperative BOLD-CVR assessment was performed at our institution on both oncological and vascular diseases [11, 12, 17, 20] (Table 1). In a first attempt to assess its fea-

Table 1 Patient sex, age, diagnosis and intraoperative CVR values of all the patients undergoing intraoperative BOLD-CVR assessment included in previous studies

Sex/age	Diagnosis	CVR values whole brain	Affected hemisphere	Unaffected hemisphere	Difference affected vs. unaffected
1. M 43	Anaplastic astrocytoma (grade III WHO)	0.9	1.18	0.94	125.5%
2. M 31	Oligoastrocytoma (grade III WHO)	0.13	0.83	0.18	461.1%
3. M 18	Inconclusive	1.12	1.24	1.05	118.1%
4. M 51	Glioblastoma (grade IV WHO)	1.01	1.02	0.8	127.5%
5. F 41	Anaplastic astrocytoma (grade III WHO)	0.95	1.01	0.89	113.5%
6. M 38	Anaplastic oligoastrocytoma (grade III WHO)	0.85	0.1	0.69	14.5%
7. M 18	Medulloblastoma	0.14	1.37	0.19	721.1%
8. M 46	Morbus Biswanger	1.35	0.48	1.33	36.1%
9. M 76	3-vessel atherosclerosis	0.43	0.42	0.38	110.5%
10. F 42	Intravasal and mural myxomas	0.4	0.72	0.37	194.6%
11. F 68	ICA occlusion	1.4	1	1.95	51.3%
12. F 66	ICA occlusion	2.08	1.54	2.61	59.0%
13. F 49	Moyamoya disease	1.44	1.64	1.22	134.4%
14. F 62	ICA, MCA and ACA occlusion	0.16	0.03	0.28	10.7%
15. M 50	ICA occlusion	0.76	0.71	0.81	87.7%
16. F 46	Anaplastic astrocytoma (grade III WHO)	1.77	1.62	1.83	88.5%

CVR values are calculated as mean % BOLD signal change between baseline and the hypercapnic (breath-hold) challenge

sibility, ten patients (two with vascular diseases and eight with oncological diseases) who were scheduled to undergo an intraoperative MR assessment to assess extent of resection in tumor cases or bypass anastomosis in STA-MCA revascularization surgery for flow augmentation were also scanned as described above with a BOLD scan.

As a preliminary finding, none of the patients displayed intra- or postoperative complications due to the prolonged time for anesthesia or for the breath-hold task. Analyzing CVR data showed impaired values for oncologic patients within the lesion and on both hemispheres [17]. We then scanned more patients and obtained a small cohort of five patients with high-grade gliomas. Interestingly, they showed a lower CVR in brain areas that showed tumor recurrence on follow-up [12].

In patients undergoing STA-MCA flow augmentation bypass surgery, intraoperative CVR values were on average higher after revascularization [20] and again, none of them had peri- or postoperative complications.

Discussion

The aim of introducing and developing BOLD-CVR assessment is to offer a new tool, which could help surgery and influence decision-making by offering an early feedback on the hemodynamic state of the brain. To this aim, further studies with larger cohorts and long follow-up are still needed. BOLD-CVR could be useful in discriminating normal brain from tumor tissue beyond the limits of current standards, like T1-weighted imaging with contrast enhancement [21] and, if future studies confirmed our preliminary results, offer a better depiction of areas of tumor infiltration. This information, if gained intraoperatively, could be helpful to achieve a better extent of resection. It is important to stress, however, that BOLD signal is not a measure of CBF alone, being that it is dependent on other physiological parameters such as cerebral blood volume (CBV), hematocrit, and cerebral metabolic rate of oxygen (CMRO₂) consumption [15, 22]. More precisely, CVR is a measure of the vessels' ability to modulate blood flow [2]. As mentioned previously, cerebrovascular reserve can be exhausted in some areas undergoing relevant hemodynamic stress. In these areas, a vasoactive stimulus produces a "steal" blood flow to areas with consumed reserve capacity to others with preserved CVR [23]. This is depicted by a lower BOLD-signal in areas with exhausted capacity [3].

In patients undergoing STA-MCA bypass revascularization for flow augmentation (for example in Moyamoya disease), an immediate intraoperative feedback on the brain hemodynamic state after the microanastomosis could prove its efficacy in actually revascularizing the hypoperfused areas of the brain by depicting early CVR improvements, if

present [20]. This information could also help in the operative decision-making process and to estimate the success of the bypass.

Despite these promising possibilities, this type of information is currently not available. First, the technique associated with the vasoactive stimulus (i.e., breath-holding) has inherent limitations that impede a precise comparison between data. Specifically, breath-holding allows for a raise in CO₂ arterial concentration, but since it also causes concomitant hypoxia, it can alter the cellular metabolism and therefore also the CO₂ production [1]. Moreover, breath-holding allows for a raise in the CO₂ arterial concentration, which varies between subjects according to each subject's features and physiologic parameters (age, sex, weight, metabolic status, and physical fitness) and in the same subject over time [1]. The entity of this change is therefore unpredictable, and the vasoactive stimulus cannot be controlled or modulated [1], thereby providing different entities of vasoactive stimulus in different investigations. This hinders inter- and intrasubject comparisons. These limitations are avoided by using a custom gas blender (Respiract™, Thornhill Medical, Toronto, Canada), which allows acquisition of targeted hyoxic pseudo-square waved changes of arterial CO₂ concentration: a controlled and consistent stimulus can be provided by letting the subject inhale and rebreath a gas mixture to obtain 10 mmHg raises of the CO₂ arterial concentration from the previously registered subject's baseline [1, 3] (Fig. 2). Nevertheless, this has technical nuisances that hinder its intraoperative employment. With the future improvements of currently used technologies [10, 24] to obtain controlled changes of the inhaled CO₂ concentration, we expect to be able to perform BOLD-CVR investigations with controlled vasoactive stimuli also intraoperatively in the near future. In our experience, this also impeded a direct quantitative comparison between intra- and pre- or postoperative scans, since these were acquired with different techniques (see also van Niftrik and Piccirelli [18, 19] for further technical details on the techniques and data analysis).

Secondly, we dealt with cohorts with limited numbers, which therefore does not allow us to extend our conclusions to other patients.

Nevertheless, intraoperative BOLD-CVR assessment offered interesting results, which we think deserve further investigation: first, we observed an early intraoperative change after revascularization in patients undergoing bypass revascularization surgery for flow augmentation with BOLD-CVR. Second, we identified an association with intraoperative findings and the evolution of the disease. Third, we confirmed that this assessment is not associated with higher complication rates. All these findings offer, in our opinion, a reasonable basis for further investigations.

Further developments of this application will include patients with aneurysmal subarachnoid hemorrhage.

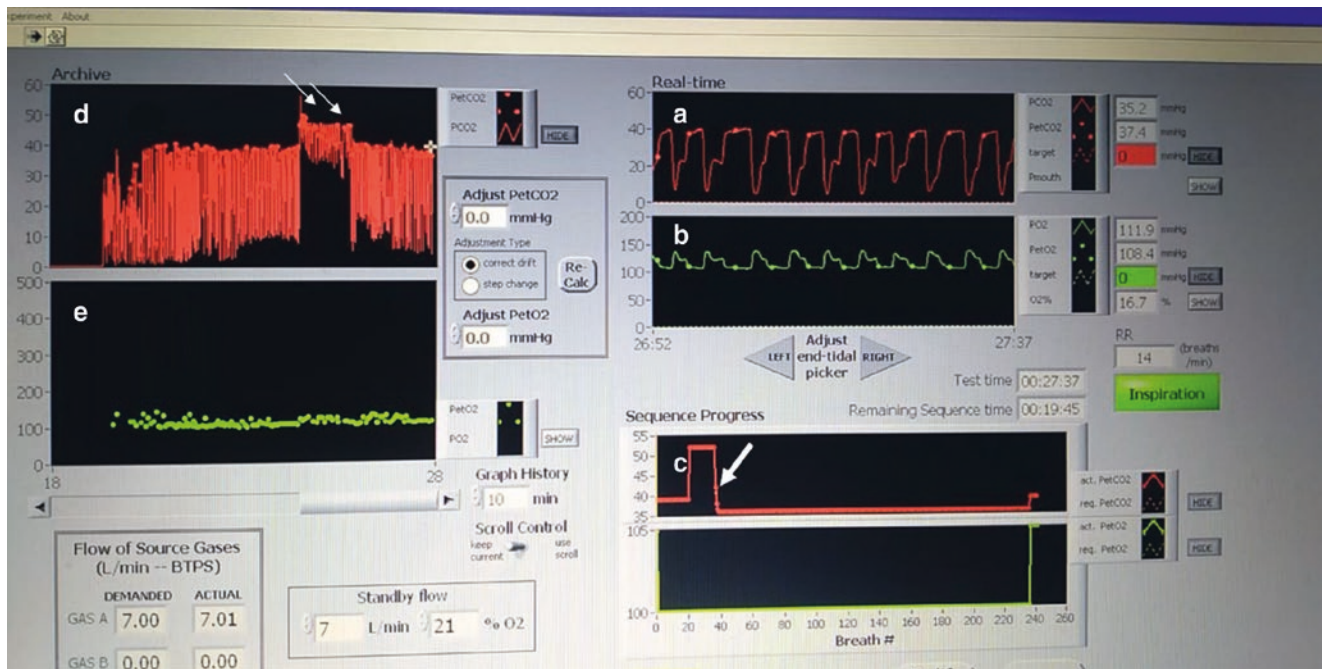


Fig. 2 Interface of the custom gas blender (Respiract™, Thornhill Medical, Toronto, Canada). This allows providing controlled hypercapnic stimuli of 10 mmHg CO₂ concentration raises and cannot be currently used intraoperatively due to hardware nuisances. Future developments of this techniques will allow to employ it also in an intraoperative setting. (a: breath-by-breath registered subject's CO₂ concentration and b: O₂ concentration; c: targeted CO₂ concentration during

the exam: a 10 mmHg increase in CO₂ concentration of the inhaled gas is provided to the patient [arrow]; d: subject's CO₂ concentration registered during the exam—10 mmHg CO₂ pseudo-square raises are obtained [double arrow], providing a valid vasoactive stimulus; e: subject's O₂ concentration during the exam—note that the concentration remains stable during the whole exam)

Specifically, impaired CVR has been found after aneurysmal subarachnoid hemorrhage (SAH) in patients with lower clinical grade, and progressive impairment of CVR was associated with a higher risk of delayed cerebral ischemia (DCI) [25]. The purpose of obtaining an intraoperative or ultra-early BOLD-CVR assessment would be to identify areas with impaired CVR at risk for DCI or to assess a CVR value for future comparison for follow-up, in order to predict DCI.

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The Hybrid Neurosurgeon: The Japanese Experience

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Introduction

In Japan, hybrid neurosurgeons who perform both open surgical clipping as well as endovascular embolization for the treatment of intracranial aneurysms are common. Over 90% of Japanese board-certified neuroendovascular therapists are board-certified neurosurgeons. Reasons for this situation include the fact that cerebral angiography and management of stroke patients are primarily performed by neurosurgeons. Although many Japanese neurosurgeons can perform surgical clipping of middle cerebral artery (MCA) or internal carotid-posterior communicating artery aneurysms and coil embolization of cerebral aneurysms using simple techniques, only a limited number of neurosurgeons are able to perform surgical clipping and endovascular procedures for anterior communicating artery (A-com), paraclinoid internal carotid artery (ICA), or posterior circulation aneurysms using both treatment modalities equally and safely.

Materials and Methods

The senior author's personal experience of more than 500 cases each of surgical clipping and endovascular embolization over the past 25 years included 110 cases of basilar tip aneurysms and 104 cases of paraclinoid ICA aneurysms.

Results

The safety and efficacy of both treatments appears to be the same, while the durability of surgical clipping is superior to

that of endovascular embolization. Among the 110 basilar tip aneurysms, 18 patients were treated by surgical clipping and 94 were treated by endovascular embolization. The initial results of endovascular therapy seemed to be better than those of surgical clipping, although the rate of retreatment was higher (Table 1). Among the 104 cases of paraclinoid ICA aneurysm, 23 patients were treated by surgical clipping and 81 were treated by endovascular embolization. The results of both treatments seemed to be same, while surgical clipping had apparently good long-term durability (Table 2).

Illustrative Cases

Case 1 A 67-year-old woman had a non-ruptured large basilar tip aneurysm associated with Moyamoya disease. The bilateral posterior cerebral arteries (PCA) were incorporated in the aneurysm (Fig. 1a). As surgical clipping for such an aneurysm was thought to be extremely difficult, horizontal stent-assisted coil embolization via the right posterior communicating artery was performed. A micro-catheter was

Table 1 Treatment of basilar tip aneurysms

	Clipping (16 cases; 1 large)	Coil embolization (94 cases; 9 large)
Morbidity	1/16 (6.3%)	2/94 (2.1%)
Mortality	1/16 (6.3%)	3/94 (3.1%)
Late re-rupture	0	2/94 (2.1%)
Retreatment	0	10/94 (10.6%)

Table 2 Treatment of paraclinoid IC aneurysms

	Clipping (23 cases; 8 large)	Coil embolization (81 cases; 11 large)
Morbidity	2/23 (8.7%); minor	4/81 (4.9%)
Mortality	0	0
Regrowth	0	3/81 (3.7%)
Retreatment	0	10/81 (12.3%)

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advanced to the right P-com and turned medial to the right P1 of PCA, across the aneurysmal orifice, ultimately reaching the left P2 of the PCA. A Neuroform Atlas stent (Target Therapeutics, CA, USA) was deployed across the entire orifice (Fig. 1b). Coil embolization was then completed without significant difficulty. Complete obliteration of the aneurysm with preservation of the bilateral PCA was achieved (Fig. 1c). The patient had a good clinical course without any neurological deficits.

Case 2 An 80-year-old woman had a left IC-ophthalmic large aneurysm (Fig. 2a) that demonstrated remarkable recanalization and regrowth following incomplete coil embolization (Fig. 2b). Three years later, she became blind due to severe compression of the bilateral optic nerves.

Case 3 A 41-year-old woman had a large left IC-ophthalmic aneurysm with mass effect (Fig. 3a). She had bilateral visual

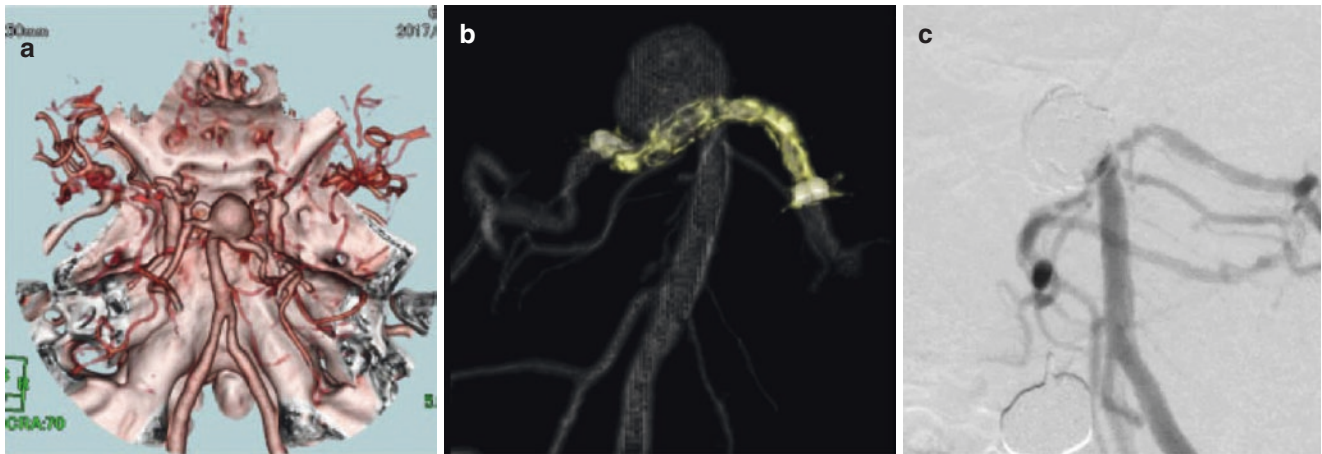


Fig. 1 (a) 3D CTA demonstrating a non-ruptured large basilar tip aneurysm associated with Moyamoya disease. The bilateral posterior cerebral arteries (PCAs) are incorporated in the aneurysm. (b) A

Neuroform Atlas stent was deployed across the entire orifice. (c) A post-embolization angiogram demonstrating complete obliteration of the aneurysm with preservation of the bilateral PCAs

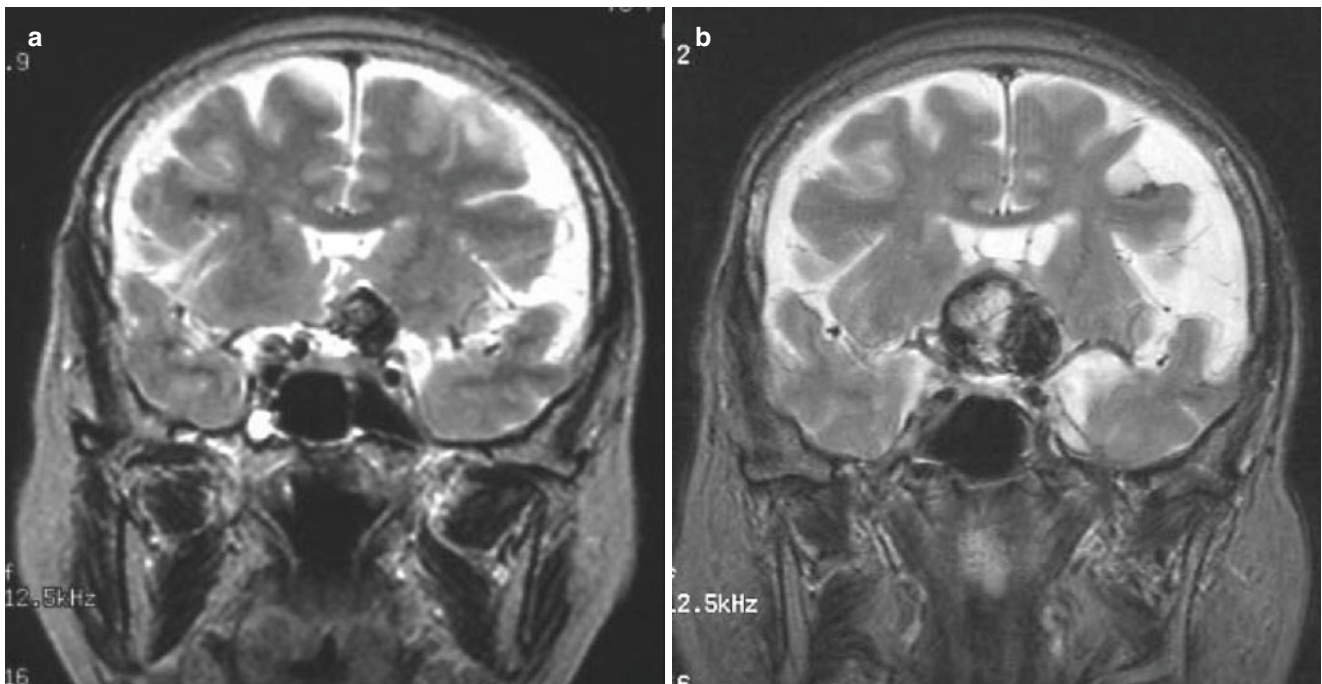


Fig. 2 (a) MRI demonstrating a left IC-ophthalmic large aneurysm. (b) MRI obtained 3 years later showing remarkable recanalization and regrowth of the aneurysm following incomplete coil embolization

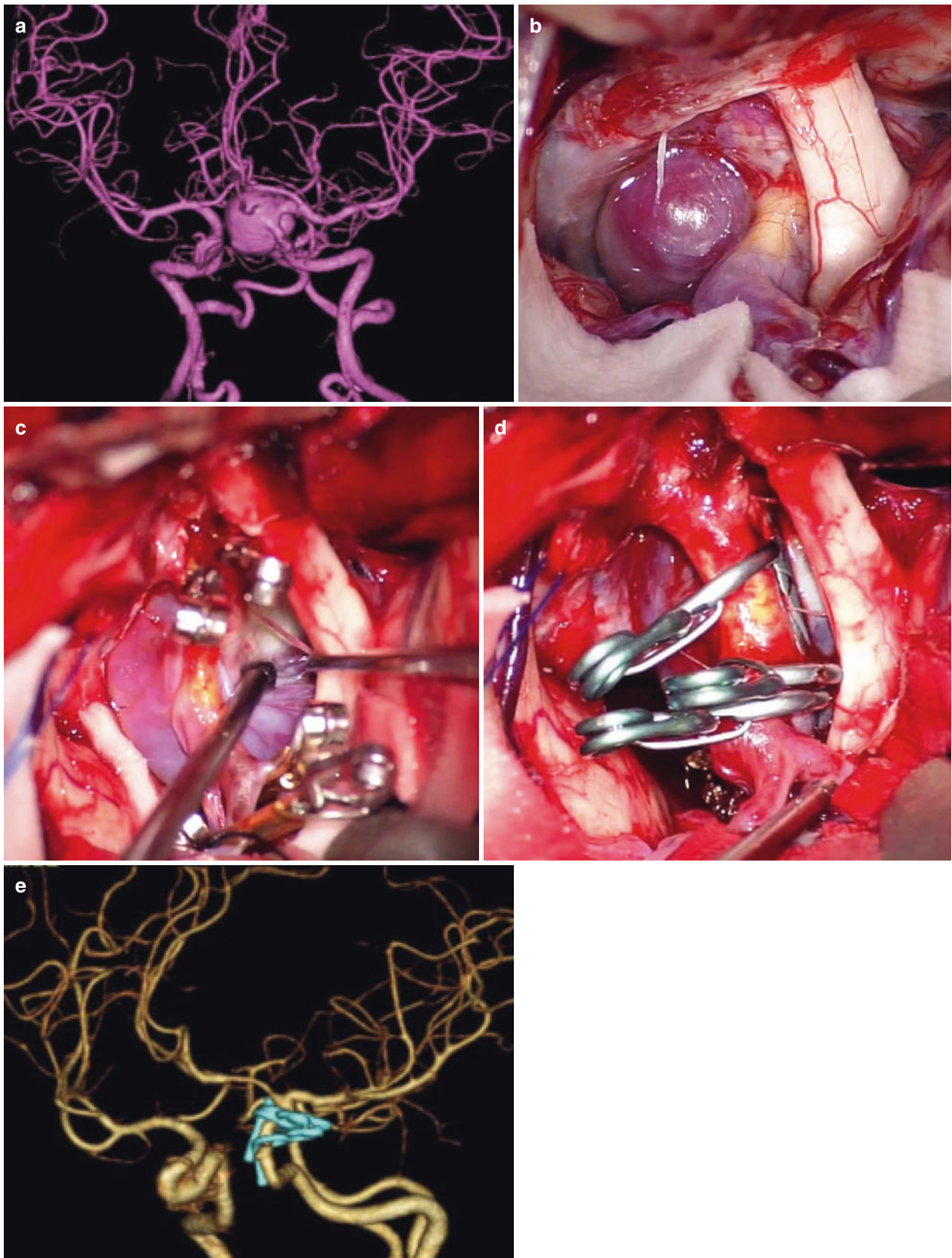


Fig. 3 (a) 3D CTA demonstrating a large left IC-ophthalmic aneurysm. (b) An intraoperative photograph demonstrating an aneurysm and the left optic nerve through standard left pterional craniotomy. (c) The aneurysm was punctured, and suction decompression was performed.

(d) Reconstructive clipping was performed using three fenestrated clips, sparing all branches. (e) Postoperative 3D CTA demonstrating complete obliteration of the aneurysm with preservation of the ICA flow

field defects. Through standard left pterional craniotomy, the aneurysm and left optic nerve were exposed (Fig. 3b). After extradural one-block anterior clinoidectomy, the proximal IC and ophthalmic arteries were secured. Temporary clips were applied to the proximal IC, distal IC, and ophthalmic artery. The aneurysm was punctured, and suction decompression was performed. After decompression, the superior hypophyseal artery was dissected (Fig. 3c). Reconstructive clipping was performed using three fenestrated clips while sparing all of the branches (Fig. 3d). The patency of the branches was confirmed by indocyanine green video-angiography. Postoperative three-dimensional computed tomography angiography (3D CTA) revealed complete obliteration of the aneurysm with preservation of the ICA flow (Fig. 3e). Her right-side visual field defect improved after the clipping.

Discussion

In training programs in Japan for hybrid neurosurgeons, trainees start their training program as a resident in the department of neurosurgery, where they learn about general neurosurgical practices and perform cerebral angiography as well. The trainees finish the programs for both neurosurgery and neuro-endovascular treatment simultaneously, after which they take examinations and are finally certified for both programs at the fifth year of the senior resident program. Thereafter, they gain further experience in both treatments. While Japanese hybrid neurosurgeons who perform both open surgical clipping and endovascular embolization for the treatment of intracranial aneurysms are common, relatively few neurosurgeons are able to perform surgical clipping and endovascular procedures for difficult cerebral aneurysms, such as those of the A-com, paraclinoid ICA, or posterior circulation. Ideally, hybrid neurosurgeons need to have skills to treat such difficult aneurysms using both treatment modalities equally and safely.

The senior author has performed more than 500 cases each of surgical clipping and endovascular embolization over the past 25 years. The safety and efficacy of both treatments appears to be the same, while the durability of surgical clipping is superior to that of endovascular embolization [1–7]. Technical advances in coils and intracranial stents has meant that the treatment choice for cerebral aneurysms has changed over the years, especially that for basilar tip aneurysms. Over the past 15 years, the frequency of surgical clipping for basilar tip aneurysms has decreased, and the procedure may eventually be abandoned for this type of

aneurysm. However, surgical clipping still offers several advantages in the treatment of paraclinoid ICA aneurysms. In the senior author's personal experience of treating paraclinoid IC aneurysms both surgically and endovascularly, the results of surgical clipping seemed to be the same as endovascular treatment with good long-term durability. Even when using a flow-diverting stent, endovascular treatment is still associated with some morbidity or the recanalization/regrowth of aneurysms.

According to the senior author's personal impression, neurosurgeons tend to overestimate the efficacy and safety of endovascular treatment instead of long-term durability, while endovascular interventionists tend to exaggerate the invasiveness of modern surgical clippings. Endovascular interventionists are overconfident regarding the feasibility of the treatment, as this approach can be easily performed with the aid of satisfactory initial morphological results, although the long-term durability of the endovascular treatment seems less satisfactory than that of clipping. Hybrid neurosurgeons can make reasonable decisions concerning the choice of treatment for cerebral aneurysms, as they perform both treatments and understand the benefits and drawbacks of each modality [8].

Conclusions

Although many Japanese neurosurgeons can perform surgical clipping of MCA or IC-P-com aneurysms and coil embolization of cerebral aneurysms using simple techniques, only a limited number of neurosurgeons are able to perform surgical clipping and endovascular procedures for A-com, paraclinoid ICA, or posterior circulation aneurysms. Ideally, hybrid neurosurgeons should be able to treat such difficult aneurysms using both treatment modalities equally and safely, allowing them to make reasonable decisions on the choice of treatment for cerebral aneurysms.

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