UNIVERSITY OF TURIN
DEPARTMENT OF NEUROSCIENCE RITA LEVI MONTALCINI
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ANALYSIS OF INTRAOPERATIVE BLOOD FLOW IN ARTERIOVENOUS MALFORMATIONS LOCATED NEAR TO ELOQUENT AREA: INDICATIONS, FEASIBILITY AND UTILITY

Candidate:
Dr. Emanuela Crobeddu

Thesis Supervisor:
Prof. M. M. Lanotte

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“Imparare prima di agire o agire e così imparare?
…Proviamo ad invertire il processo
invece di “capisco e poi faccio”
“capisco in quanto faccio
cioè faccio e quindi capisco”
e, per fare ciò, ci vuole un dispositivo speciale
che è…il Cervello”
(*cit. “Competenza senza comprensione”*)

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INDICE

CHAPTER I

INTRODUCTION

Epidemiology and natural history of Arteriovenous Malformations (AVMs) remain incomplete. Many factors play a role of primary importance as regards their evolution.

The incidence and prevalence of AVMs are difficult to estimate as they are rare and refer to prospective studies based on restricted, genetically isolated populations.

A study conducted by Al-Shahi et al.[5] estimated a prevalence of 14.8 per 100,000 people, of which affected men are significantly younger than women (average age 39 years vs. 51 years). 10% have a coexistence with aneurysms; 62% of AVMs are located in the eloquent areas (hypothalamus, thalamus, cerebellar peduncles, sensorimotor area, area of language and visual cortex). According to the "New York Islands Arteriovenous Malformation Study" the estimated incidence is 1.21 per 100,000 years - a person who is correlated with an incidence of AVM-induced hemorrhage of 0.42 over 1000000 person-years. Approximately 8% of all subarachnoid hemorrhages and 1-2% of all hemorrhagic strokes are attributable to an AVM.

Furthermore, there was an overall annual bleeding risk of 2-4%, with a combined mortality and morbidity of 3% per year.

A study was conducted in 1996 by E. Pollock and J.C. Flickinger[176] to define through clinical and radiological conditions what could be the predictors of bleeding risk in patients with AVM. The following variables were examined:

- History of a previous bleeding: RR 9.09; 95% CI (5.44 - 15.59) P <0.01[176];
- Age: evolution over time of the bleeding risk around 20% up to the twentieth year[100,101];
- Size: <3 cm are a higher risk of bleeding related to these[115,208];

- Venous drainage: single and deep has a RR 1.66; CI95% (1.13 - 2.38) P <0.01 [140,153];
- Aneurysms within the nest: the coexistence of AVM and aneurysms has been documented in 6-19% of patients [RR 1.64; CI 95% (1.12 - 2.46) P <0.01]; the pathogenesis seems to be due to the high pressure inside the arteries that feed the MAV[10];
- High pressure in the arteries that feed the AVM: Spetzler, Zabramski et al. consider that this is a relationship between the pressure in the arteries that feed the AVM and the size of this[206], on the contrary Kader, Young W.L Mast H. consider this type of relationship very weak[115];
- Lesion site: thalamic localization and base nuclei have a greater risk of bleeding (9.8% according to Fleetwood[73]), greater morbidity with an incidence of paresis / plegia of 85% and lower presentation age (22.7 vs. 33.7 years according to Fleetwood[73]), but not all authors agree [27,77].

Cerebral hemorrhage appears to be the first manifestation of the presence of an AVM in one third of young adult subjects[5] and up to 50% of subjects at 55 years.[110]

The incidence of neurological deficits is about 50% for each hemorrhagic episode; [50,80, 167,173] the risk of having a physical deterioration involving work capacity ranges from 40% to 50% during the 20-40 years following the presentation.[230] In addition to this disability must be added the neurological deterioration as a result of the growth of MAV and "the steal syndrome". Michelsen estimated that after 20 years, 33% of all patients reported no significant deficits, 22% developed moderate deficits, 29% became disabled, and 10% died as a result of an arteriovenous malformation[152].

These data highlight how this results in a considerable socio-economic impact related to this type of pathology, as there is a high incidence of fatal or highly debilitating hemorrhages, with onset of symptoms at a young adult age.

1.1 Natural history

Knowledge of the natural history of AVMs has been learned thanks to the observation of various generations of patients, who have helped to learn about the possible evolution of these lesions. 90% of patients with AVM remain asymptomatic for a long time, while the remaining percentage shows a series of symptoms related to the

presence of the lesion or to the appearance of complications. Over time, AVMs can grow and increase in size, thus occupying an ever greater volume, even if most of the time they remain static. The increase in size may be due to the growth of the vascular component and the recruitment of new vessels from the adjacent tissue. With the growth of the malformation there will be the appearance or increase of symptoms due to the mass effect and the ischemia derived from the "vascular theft".[83,84,155,220]

The event weighed down by an important neurological compromise is undoubtedly the cerebral hemorrhage caused by AVM rupture, an event that occurs less frequently than microscopic bleeding. Several causes have been identified that may be responsible for rupture, many authors have observed post-traumatic rupture [65,66,73,77] even though it is difficult or almost impossible to prove the close correlation.

The natural evolution of the malformation can lead to the onset of an ischemic stroke due to a lack of blood flow in areas of brain tissue not involved in the pathological process. [16,22,27,36] This secondary effect is easily found in large AVMs, while it is rarely observed in other types of vascular malformations. It is also more frequent in case of association with aneurysmal dilatation of the Galen vein. [16,22,27,36]

This is accompanied by histological alterations such as gliosis, calcifications, necrosis, neurological dysfunctions and epileptic seizures. Once considered rare, today spontaneous thrombosis appears to be present in varying degrees in a number of vascular malformations. This evolution can lead to the complete obliteration of the AVM with subsequent reduction in size, until its complete disappearance.

1.2 Etiopathology

Several years ago it was thought vascular malformations were congenital lesions, due to an error in the development of the cerebral vascular system during embryogenesis around the third week of gestation, but the responsible anomaly is not known to date. Arteries and veins of the cerebral vasculature originate from a primordial capillary network during a process called metamorphosis, controlled by angiogenetic and hereditary factors.

Some theories [47,48,87,128,212] attempt to explain the genesis of AVMs, hypothesizing a failure or incomplete development of the primordial capillary network

or its secondary destruction, resulting in direct communication between the arterial and venous systems. These, however, cannot explain the variety of AVMs in which a convoluted skein of vessels is interposed between arteries and veins.

According to Yasargil [235,236] it is possible the primum movens is not an absence or destruction of the capillaries, but one of their anomalies, so they proliferate and become dysplastic vessels. These metamorphic vessels are not histologically characterized in arteries, veins or capillaries and have been called "structural hybrids" by Hamada.[95] As confirmation of these hypotheses, Yasargil[235] observed the presence of apparently abnormal vessels with fenestrated endothelium within the AVM, since this type of endothelium is not present in normal cerebral vessels except for some areas (postrema area, plexus), choroid, pineal gland, pituitary gland, intercolonnar tubercle and some hypothalamic nuclei).[48] Because of this "primitive capillaropathy" we will have a malformation of both arteries / arterioles and veins / venules. This theory is able to explain all vascular malformations and not only arteriovenous fistulas.

A long-held dogma in neurosurgery is that parenchymal arteriovenous malformations (AVMs) are congenital. However, there is no strong evidence supporting this theory. An increasing number of documented cases of de novo formation of parenchymal AVMs cast doubt on their congenital nature and suggest that indeed the majority of these lesions may form after birth. Further evidence suggesting the postnatal development of parenchymal AVMs comes from the exceedingly rare diagnosis of these lesions in utero despite the widespread availability of high-resolution imaging modalities such as ultrasound and fetal MRI. The exact mechanism of AVM formation has yet to be elucidated, but most likely involves genetic susceptibility and environmental triggering factors. [155]

Based on observations of the normal development of the cerebral vasculature, it has been hypothesized that AVMs originate early during embryonic development in the interval when the embryo is between 40 and 80 mm in length. During this period, numerous processes such as vasculogenesis, angiogenesis, vascular remodeling, and differentiation take place, leading to a mature intracranial vasculature when the fetus reaches 80 mm in length.[155,220] Based on this theory and on the observation that AVMs can be found in infants, it is commonly accepted that parenchymal AVMs are present at birth and follow a silent course before becoming clinically evident. This long- held the-

ory is widely accepted even though there is little evidence that parenchymal AVMs are indeed congenital lesions.

A growing number of cases of de novo AVM formation are being documented, which challenges the concept of this lesion's congenital nature. Including the patients described in the present report, we were able to find 16 cases of de novo AVMs. All of these patients had undergone high-resolution baseline imaging that showed no evidence of vascular malformations, although only 6 of these patients were initially evaluated with catheter angiography.[155] The indications for the initial evaluation were variable. These included vascular abnormalities (such as moyamoya disease, dural arteriovenous fistula, cavernous malformation with developmental venous anomaly,4 AVMs 2 in other location, and intraparenchymal hemorrhage) and nonvascular conditions such as a brain tumor, neuronal migration abnormality, Bell's palsy, head trauma, and demyelinating lesions. Repeat imaging leading to the diagnosis of the de novo AVM was performed after a prolonged interval, ranging from 2 to 17 years, for the purpose of following up the original lesion or due to the acute development of symptoms (which were related to AVM rupture in 3 cases). The age distribution of these patients is wide, ranging from 6 to 68 years at the time of de novo AVM diagnosis (mean 26.4 years)[73,78,155].

The refinement of prenatal imaging techniques such as 3D ultrasonography and fetal MRI has improved the rate of detection of anomalies such as neural tube defects and neuronal migration and proliferation disorders.[103,129] Similarly, modern color Doppler ultrasound allows a thorough evaluation of the fetal cerebrovascular circulation. However, prenatal diagnosis of a parenchymal AVM is exceedingly rare,[83, 84, 155] which is in contrast to other vascular lesions (for example, vein of Galen aneurysmal malformations) that are frequently detected in utero or shortly after birth. Furthermore, the number of AVMs diagnosed in the neonatal period is also limited, and it is estimated that only 1% of AVMs are diagnosed during the first 2 years of life. These facts further bring into question the assumption that AVMs develop early during embryonic development and are present at birth.

The congenital nature of brain AVMs has been previously questioned by others,[1,8,10] and as others authors[115] have discussed, there is compelling evidence suggesting

the post- natal development of many of these lesions. However, the exact mechanism of AVM formation has yet to be elucidated, and it may involve an interaction between genetic susceptibility and environmental (acquired) factors. Several studies of patients with hereditary hemorrhagic teleangiectasia (HHT), an autosomal dominant disease that includes AVMs in multiple sites (brain included) as part of its clinical spectrum, have improved our understanding of these vascular lesions. Loss-of-function mutations have been identified in the 2 main subtypes of the disease. Specifically, the gene coding for endoglin (ENG) is altered in patients with HHT Type 1 and the gene coding for activin-like kinase 1 (ALK1) is mutated in patients with HHT Type 2. Both ENG and ALK1 are proteins involved in signaling pathways of the transforming growth factor–b, critical for angiogenesis and inflammation[119,121].

A possible genetic influence in the formation of AVMs outside the setting of HHT is suggested by various reports of familial clustering of sporadic AVMs.[103] In addition, a variety of candidate gene studies in patients with sporadic AVMs have identified single-nucleotide polymorphisms (SNPs) associated with a susceptibility to develop AVMs and with their progression to intracerebral hemorrhage.[175] Most of the studied genes code for essential proteins in the angiogenic and inflammatory cascades. A recent systematic review included all the studies reporting SNPs associated with sporadic brain AVMs, and after a joint analysis of the risk estimates described in the different reports, a statistically significant association was found between an SNP in the ALK1 gene (intervening sequence 3–35A>G) and a susceptibility to develop a brain AVM (OR 2.19, 95% CI 1.25–3.83).[2,31,175] A significant association was also found between SNPs in genes coding for interleukin 6 and tumor necrosis factor–a and risk of intracranial hemorrhage. In addition to their genetic basis, the biology and microenvironment of AVMs is now better understood.[155] Studies of AVM tissue have shown increased endothelial cell proliferation and increased expression of angiopoietin-2 and vascular endothelial growth factor, which pro- mote vascular destabilization and proliferation, respectively. However, the exact triggering event that leads to increased and disorganized angiogenesis ultimately leading to AVM formation has not been identified. Mice with ALK1 deficiency develop de novo AVMs after angiogenic stimulation.[2,220] This finding suggests that the presence of a genetic abnormality alone is not enough to trigger AVM formation and a “second hit” is required. Genome-wide association studies can potentially

disclose novel genetic loci influencing AVM formation. The first of such studies in patients with sporadic brain AVMs examined the association of common and rare copy number variations (CNVs) and disease susceptibility in 371 patients with sporadic brain AVMs and 563 controls. A CNV was identified on initial screening but did not replicate in an independent cohort of patients. Similarly, no association was found between rare CNVs and disease susceptibility. However, larger, well-powered studies might be able to detect significant associations.

In the pertinent literature, there is an increasing number of reported de novo cerebral AVMs.[95,112,115,220] It is known that, the number of AVMs diagnosed in the neonatal period is limited. It has been reported that only 1% of these lesions are identified during the first two years of life[155]. In 1996 Mullan et al., considered that AVMs originate early during embryonic development when the embryo is between 40-80 mm in length[155]. They also stated that adult AVMs frequently incorporate evidence of an early failure in venous maturation. Currently, after a meticulous MEDLINE search found 29 AVM cases of de novo formation. All of the patients had undergone negative high-resolution imaging at some point prior to the AVM diagnosis[72]. Actually, a digital subtraction angiography (DSA) was performed in 9 out of 29 cases.[72] According to the literature, de novo AVM formation seems to be the result of a previous cerebral insult such as brain tumor stroke, trauma, inflammation, or other non-specific disorders[220]. Thus, de novo AVM formation may represent a "second hit" with abnormal angiogenesis and vessel formation[220].

A possible mechanism to explain AVM formation may not be dissimilar to that responsible for dural arteriovenous fistulas that is, venous thrombosis leading to impaired venous outflow, ischemia, and increased angiogenesis.[155] In the case of brain AVMs, asymptomatic parenchymal venous thrombosis could trigger local venous hypertension and ischemia. The ischemic stimulus triggers vascular proliferation (through increased expression of hypoxia-inducible factor–1), which in normal circumstances is self-limited. However, in the presence of genetic susceptibility and abnormalities of the angiogenesis and inflammatory cascades, there may be uncontrolled vascular proliferation and arteriovenous shunt formation. Once high flow is established through the vas-

cular lesion, endothelial shear stress contributes to a continued angiogenic stimulus and a hyperangiogenic environment[8,155].

1.3 Physiology

The nidus of the AVM is a very complex structure that can present infinite variations of its arterial and venous components. Type of afferent arteries and draining veins, variously involving cortical and perforating arteries and veins that can flow together or drain into different systems. If the nests are multiple they can be confluent or separated by parenchyma. The drainage veins can converge or flow into different systems, but they are much more than one that must have at least one discharge vein. From this description it clearly emerges that these are very variegated lesions and that complicates their treatment, since it is not easy to investigate in the homogeneous category.[52]

The nidus can be composed by one or more compartments that are not an anatomical entity, but it is hemodynamics that is defined as a second of the print discrepancy between afferent and efferent vessels. Therefore, it is clear that there is no AVM equal to another and so there are a different therapeutic approach for each one. The surgeon and the interventional radiologist must know the peculiarity of the AVM before intervening; for this reason AVM can be studied carefully using, if necessary, superselective angiography[58].

Generally AVMs are a low pressure system. This would explain why the occlusion, especially of the venous side, leads to an increase in intraluminal pressure with an increased risk of rupture in some patients subjected to embolization, or in those subjected to surgery in which the venous side is occluded before the arterial one.

AVM may increase in volume over time, due to repeated small silent hemorrhages that destroy the supporting tissue and lead to vessel dilatation and the formation of pseudoaneurysms (due to the weakness of vessels subjected to continuous wall stress) or for training of new collateral channels, especially in the case of partial embolization.[10,16,24] Generally the brain area that the AVM occupies in an adult is not functional, so if the surgeon is able to remain tightly on the periphery of the AVM and to expose it, this can be removed without permanent neurological deficits. Growth can

also be only apparent (pseudo-growth) if the initial angiographic evaluation was incomplete (nidus-compressing hematoma), or if surgical removal was not radical due to the scarce accessibility or inattention of the surgeon, especially in the case of AVM temporal, parietal, of the callous and pericallosal zone, localized in the territories of border of the internal carotid and of the vertebro-basilar system. For this reason it is a good rule to perform a post-operative control angiography (which can however be negative due to vasospasm) and a CT scan two months later.

Rarely AVM may be reduced in volume by spontaneous obliteration, probably triggered by an extrinsic compression due to a parenchymal hemorrhage or, in the case of AVM residue due to vein collapse which occurs following the reduction of the flow. This occurs more frequently in small lesions with a single venous drain.[1,145]

1.4 Hemodynamic

In normal conditions the brain receives 20% of the cardiac output with an average flow of 52 ml / 100g / min. This last value can be tripled in patients carrying an MAV, reaching up to 170 ml / 100 g / min.[57] The cerebral flow is calculable with the formula $Q = \Delta P / R$ where Q is the flow, ΔP is the difference between pressures at the two extremes of the vessel and R is the resistance. The flow is inversely proportional to the resistance and directly proportional not to the absolute pressure in the vessel, but to the difference in the pressures between its two extremes. In the case of a patient with an AVM, his total brain flow is given by the normal cerebral flow directed to the parenchyma plus the direct flow to the malformation.

Furthermore, the MAV is a system in which resistances in parallel coexist, such as the vessels that belong to both the MAV and the cerebral parenchyma, for which the $Rtot = 1 / (1 / R1 + 1 / R2)$ rule applies, and resistances in series with a greater total resistance given by the formula: $Rtot = R1 + R2$.

The other factors influencing brain flow are exemplified by the formula $R = 8 \eta L / \pi r^4$ where the viscosity η, the length of the vessel in cm L and the radius of the vessel r are raised to the fourth. By applying this last formula to the one used to calculate the flow, we obtain the Hagen-Poiseuille formula (Fig.1)

$$Q = \frac{\pi r^4 \Delta p}{8 \eta l}$$

Fig.1 The cerebral blood flow through the cerebral vessels is defined by the Hagen-Poiseuille law. Q: blood flow; ΔP: pressure gradient; r: radius of the vessel; L: length; η: viscosity.

This law explains the characteristics of an AVM including the reason for massive bleeding in the event of rupture in the venous side. In this case, in fact, ΔP becomes maximum by increasing the flow through the vessel. Additional variables to the formula are blood viscosities, flow characteristics (which can be both laminar and turbulent), vessel tortuosity from vessel distensibility (which are not rigid tubes but are able to adapt to flow variations).

1.5 Clinical presentation

AVM is often symptomatic and manifests itself with the characteristic triad: cerebral hemorrhage, epilepsy and recurrent headache; occasional feedback is rare. The onset of symptoms typically begins in young adulthood even if the lesion is congenital.

Cerebral hemorrhage is the most frequent presenting symptom; prospective population-based studies show that about 50% of patients have cerebral haemorrhage at onset. In 63% of cases it is localized at the intraparenchymal level, in 32% it is ESA, and finally in 6% of cases it is found at an intraventricular level[3,9,32,43,45]. AVMs located in the posterior fossa begin with either subarachnoid, intraparenchymal or intraventricular hemorrhage (present in 92% of patients). For the supratentorial locations this percentage is reduced to 66.7% in the cooperative study.[171] Other forms of presentation for malformations here include headache, trigeminal neuralgia, and hydrocephalus.

From these data it can be observed that the most frequently involved site is at the level of the parenchyma and normally it is also less hemorrhaging than those derived from the rupture of an aneurysmal sac. The explanation is given by the fact that it is often a matter of bleeding originating from the venous compartment, limited at the parenchymal level, onset often at a young age and less risk of vasospasm and subsequent bleeding. The onset is generally subtle, manifested by a worsening headache and initial focal neurological deficit. The risk of bleeding is higher for small AVMs (86% of cases) compared to giant ones, for which there is a frequency of 46%.[158]

This diversity can be explained by the greater resistance and pressure existing inside these and by the onset of hemorrhage in the venous side because the veins are subjected to increased wall stress due to their arterialization.[86,110,113,] Bleeding due to AVM bleeding occurs at the level of the white substance and in the subcortical area of the brain, but often extends to affect the ventricle or brain surface. There seems to be a good prognosis in cases of hemorrhage due to AVM, the reversibility and marked recovery of a series of deficits are particularly striking even in cases with a large hematoma. The extent of the lesion at the level of the basal ganglia and thalamus appears to be linked to minimal or almost no deficits.[145,151,163] It is possible to conclude that patients with AVM parenchymal hemorrhage have a better outcome than other cause bleedings.

The risk of recurrent bleeding after an initial bleeding episode is 3.5 - 4% (52).

In children the hemorrhagic stroke occurs in half of the cases in comparison to 20% of the adults and most of the time it is to be attributed to the presence of a cerebral AVM. In these cases the risk of recurrence of bleeding is greater,[161,170,173] however there is no common agreement on this statement.

Heather J. Fullerton, Achal S. Achrol et al.[2,32,83] have concluded that children have an annual risk similar to that of adults. The reason why the AVM occurs more frequently giving hemorrhage in the child may be due to a more "malignant" type in these small patients, reflecting a biological difference in accordance with the age of presentation.

Hemorrhage as an initial event is seven times more frequent than convulsive access. Arterial hypertension, exercise, pregnancy, childbirth and even traumatic events were once considered as factors responsible for an increased bleeding risk. These

statements were mostly discredited by functional studies and a more thorough evaluation of the natural history of AVM.

A work by Troupp and Ondra conducted in Finland, 160 patients were followed for an average period of 24 years.[167] The rate of re-bleeding in this series is 4% per year, with a mortality rate of 1% and morbidity of 2.7%; these data do not appear to be modified by the type of disease onset (hemorrhage, seizures, headache in the absence of hemorrhage). Furthermore, the average interval between presentation and subsequent hemorrhage turned out to be on average 8 years, which underlines the importance of a long-term evaluation of these patients. According to the authors, the AVMs located in the parietal, central and posterior fossa area are more frequently resected than those located elsewhere. AVMs that occur during pregnancy pose a particular problem. The probability of re-bleeding is greater than in non-pregnant patients, with a frequency of recurrence of hemorrhage similar to that of saccular aneurysms. Surprisingly, the moment of bleeding does not seem to correspond with the change in the cardiovascular system during pregnancy. The highest incidence of AVM bleeding occurs between the fifth and twentieth week. In Yokoyama's case series, only 2 out of 77 AVM hemorrhages in pregnancy were in labor.[237]

In elderly subjects> 25% of cases present small or medium-sized MAV in the infratentorial area with haemorrhagic presentation. A study conducted by Crawford et al. showed that subjects over the age of 60 have an increased risk of cerebral hemorrhage during follow-up. The risk was 89% after 9 years compared to 15% in subjects aged 20-29 kept in observation for the same period of time. A considerable number of elderly subjects who present with onset hemorrhage are treated with conservative methods.

*Seizur*e occurs in 25-50% of patients without signs of obvious bleeding, thus representing the second most frequent presentation symptom; average age of appearance of epilepsy as an initial symptom is about 25 years. They are often due to AVM located at the frontal, temporal, parietal level, while in general they do not occur if it is located at the level of the posterior fossa. Crises can be controlled by simple anti-seizures therapy, so their onset is not an absolute indication to surgery. Also, this clinical manifestation seems to be correlated to the size of the AVM, in the presence of a large

nest the probability of having as initial symptoms convulsive attacks instead of hemorrhage is more than double; the opposite for smaller lesions.[234]

The types of epileptic seizures can be different: 49% generalized, 22% focal, 22% focal with secondary generalization, 4% partial complex, and 4% unclassified (32). In elderly subjects this type of clinical manifestation is clearly less frequent at diagnosis, but may develop during follow-up.

Headache is another symptom, found in 16% of cases, but may also not be correlated with the lesion. The incidence of headache as an early symptom of AVM before the onset of a seizure or haemorrhage varies from 5 to 35% [87](Pool et al. 1965, Troost et al. 1975). Predominates in the female sex, often non-pulsating, and always ipsilateral to the lesion (86). In some patients (<10%) it may cause focal neurological deficits not due to haemorrhage (87-89)[91]. The literature reports cases of migraine due to the presence of MAV located at the level of the occipital lobe, partly disappeared following removal surgery.[3,11,25]

The development of *papilloedema* due to the increase in blood pressure is possible in a small proportion of patients, unrelated to the size of AVM but to localization (superficial effects) and to the pattern of venous drainage (abundant).

The progressive *neurological deficit* in the absence of hemorrhage may be due to the hypoxic effect to which the surrounding healthy parenchyma is subjected due to the theft of cerebral flow carried out by the AVM.[33,40,41]

1.6 Classifications

Spetzler-Martin classification

The surgical treatment of cerebral MAV is aimed at preventing the risk of a possible disastrous intracranial hemorrhage. The decision to undertake the surgical procedure, and the risks associated with it, must be compared to the long-term risks in choosing not to treat the malformation. In this regard a graduated system was proposed that could estimate the percentage of mortality and operative morbidity and, at the same time, could be applicable in the clinical reality.

The first attempt at classification was developed by Luessenhop and Gennarelli (1977)[137] which was based on the size and distribution of the "feeding" arteries but these

turned out to be inappropriate. Other systems were applied by Pellettieri and Grevsten (1980)[171] but these turned out to be very difficult to be applied easily and quickly. Only in 1986 Spetzler-Martin [208] introduced what is considered one of the most complete and appropriate classifications on which therapeutic choices can be based. This divides the classification system into five grades by taking into consideration the following as the most important factors in determining the difficulty of surgical resection:

1. Size
2. Number of "feeding" arteries
3. Degree of blood theft from the normal cerebral parenchyma
4. Seat
5. Surgical accessibility
6. An eloquent area
7. Pattern of venous drainage

A system based on all these variables proved to be too complicated for clinical practice. The treatment of AVMs later established that some of these factors were correlated so that it was possible to simplify the scheme without ignoring the critical factors. Three variables are taken:

1. *Size* - The size of the AVM is obtained by measuring on the angiography the diameter in width of the nidus of the malformation. It may be small (<3 cm); medium (3-6 cm); large (> 6 cm). The size of the AVM is responsible for the technical difficulty that can be encountered during surgical removal, ie long operating times and increased anesthetic risks. The dimensions are also connected with the number of "feeding" arteries, blood flow and theft.

2. *Pattern of venous drainage* - This is also determined during angiography. It is considered superficial if all the drains from the AVM occur through the cortical venous system; it is instead considered deep if it occurs through veins located in depth (such as the internal cerebral vein; the basal vein or the pre-central cerebellar vein). In the posterior fossa only the cerebellar hemispheric vein is considered superficial venous drainage because it drains directly into the transverse sinus or in the straight sinus. This factor is also closely related to surgical accessibility in fact deep venous drainage

presents a greater risk of complications. The small subependymal arterialized veins that make up the deep drainage are friable, resistant to bipolar coagulation and are prone to bleed in the parenchyma or in the ventricular system when they are broken.

3. *Eloquent brain area* - These are defined as those areas that perform specific neurological functions. For this reason the following are considered eloquent areas: sense of movement; language; visual cortex; thalamus and hypothalamus; internal capsule; brain stem; cerebellar peduncles and deep cerebellar nuclei. Areas with more indefinable neurological functions or areas where damage does not cause permanent disability (anterior portion of the frontal lobe or temporal lobe or cerebellar cortex) are considered not eloquent. For simplicity it is assumed that the eloquent cortical regions occupy their normal anatomical localization. In this regard, electrophysiological techniques or the Wada test are not required to designate them. The removal of an AVM located in a location adjacent to an eloquent area involves major risks of neurological morbidity greater than in non-critical regions; this for possible damage during surgery by dissection or retention of the AVM or in the post-operative period due to edema or hemorrhage.

Determination of the degree

In order to assign the grade of the MAV, it is necessary to determine the size, venous drainage and eloquence of the adjacent brain area through angiography, CT and / or MRI. In particular, for supratentorial or posterior fossa localizations, CT and MRI are useful in delineating the relationship between the MAV and the eloquent area. In this way a numerical value is assigned for each of the categories. The degree of injury is obtained from the sum of the points awarded for each category.

GRADE = DIMENSION + ELOQUENT AREA + VENOUS DRAINAGE

- DIMENSION:

  small (<3 cm) score = 1, medium (3-6 cm) score = 2; large (> 6 cm) score = 3;

- ADJACENT ELOQUENCE AREA:

  not eloquent, score = 0; eloquent, score = 1

- VENOUS DRAINAGE:

  superficial, score = 0; deep, score = 1

Surgical difficulty and prognosis are examined on the basis of the level in the manner described above. They are considered multiple and arranged in different eloquent areas or because the nidus of the malformation compresses critical structures such as the beam and the hypothalamus. In these cases a surgical resection could be a permanent disability or high mortality: to tell the reason AVM included in a single separate category defined "grade VI" or more simply "inoperable". Grades I and II have a good prognosis with low incidence of iatrogenic neurological deficits, contrary to what happens with those of grade IV or V.

This is a retrospective assessment of 100 completely resected AVMs, evaluating the angiographic aspect and surgical complications. Complications were divided into 4 categories: no deficiency, minor deficiency, slight worsening of aphasia and hemiparesis, increase in trigeminal nerve deficit, slight residual ataxia), major deficit (homonymous hemianopia, severe aphasia and hemiparesis, neurological deficits severe with aphasia and very serious hemiparesis) and death, excluding temporary deficits regressed in less than three days. I found a good correlation between the grade assigned to the AVM and the incidence of neurological complications.

Using the Spetzler-Martin classification in clinical practice it has been shown that patients are divided into two distinct groups: low grade (grade I and II), have a morbidity between 0-5% associated with resection, so they are often treated surgically;[96,105,208,212] high grade (grade IV and V), have a 12-38% morbidity associated with resection, so they are often monitored. [96,105,208,212]

Among the surgically treated AVMs and those considered non-surgical, there are those that fall, according to the classification, in grade III. This is the most heterogeneous group in that it is formed by 4 different combinations of size, venous drainage, and eloquent area: S1V1E1 (small nidus, deep venous drainage, eloquent area); S2V1E0 (medium-sized nidus, deep venous drainage, non-eloquent area); S2V0E1 (medium-sized nidus, superficial venous drainage, eloquent area); S3V0E0 (large nidus, superficial venous drainage, non-eloquent area).

Lawton in 2002,[130] analyzing the surgical results of Grade III AVM, demonstrates how there is a high variability in the outcomes of the patients examined

for the study, and introduces a modification to the Spetzler-Martin classification. For the study in question, from 1997 to 2002, 174 patients were recruited and of these only 75 (45.2%) were affected by AVM. 46.1% (34 patients) were small S1 V1 E1, 18.4% (14 patients) were medium-deep S2 V1 E0, 35% (27 patients) were medium-eloquent S2 V0 E1 and none was large S3 V0 E0, since the latter is probably a theoretical type of injury only, since it is highly unlikely that such a large malformation will not reach eloquent areas and does not have deep drainages. Subsequently, the outcomes of Grade III AVMs were analyzed for each of the three possible categories. The small S1 V1 E1 malformations are those that had the best results, with a surgical risk of 2.9%, the medium-deep S2 V1 E0 had an intermediate result with surgical risk of 7.1% of the cases, while the worst prognosis was due to Medium-eloquent AVM S2 V0 E1 with a surgical risk of 14.8% and worsening of neurological conditions or death. On the basis of these data, it is possible to highlight the heterogeneity of grade III, so a further subdivision was proposed by the same author:

On the basis of these data, it is possible to highlight the heterogeneity of grade III, so a further subdivision was proposed by the same author:

III -: small AVM

III: medium-deep AVM

III +: medium-eloquent AVM

III *: large AVM

Grade III-AVMs present a surgical risk similar to that of Grade II AVM, similarly Grade III + have an operative risk equal to that of grade IV and V malformations. Grade III lesions exhibit an intermediate risk similar to that of the overall grade III malformations according to Spetzler-Martin.

de Oliveira et al. (1998)[52] reported their results on 141 patients with grade III AVM. These malformations have been subdivided into two subgroups: grade IIIA which included those "large" and grade IIIB to which the "small" belonged and located in eloquent areas, without defining quantitatively. Also in this case an important difference of the outcomes between the two degrees was underlined. In fact the MIIs of IIIA degree treated surgically had a good result in 95.5% of the patients, while the AVMs of grade IIIB had a minimum improvement in 27.8% and died in 2.1% of cases, in fact for these it was recommended radiosurgery.

Spetzler-Martin classification cannot be used to predict the true outcome of patients treated with radiosurgery,[6,150,176-178] since it does not take into consideration important parameters for radiotherapy such as lesion volume and its location. In fact, lesions <3cm deep and placed at greater risk of radio-induced complications.

Pollock et al.,[179] studying 220 patients, found that the characteristics of a AVM significantly related to radiosurgical outcome are: lesion volume (P = 0.001), patient age (P <0.001) and localization (frontal or temporal = 0, parietal, occipital, intraventricular, corpus callosum or cerebellum = 1, basal ganglia, thalamus or brainstem = 3) (P <0.001). The authors therefore proposed assigning a score to the lesion by calculating (0.1 x volume in cm3) + (0.02 x patient age) + (0.3 x location). The system was able to predict the outcome of radiosurgical treatment in a statistically significant manner (P <0.0001). In fact, all patients with scores less than or equal to 1 had an excellent outcome, while only 39% of those with scores above 2 had the same results. Pollock et al. subsequently examined another series of 136 patients and, through the data obtained, confirmed the non-predictability of the radiosurgical outcome of the Spetzler classification (P = 0.13) and of other classifications.[118,194]

Lawton supplement Spetzler-Martin grading system

Lawton and colleagues[130] envisioned a grading system that would supplement rather than replace the already entrenched Spetzler-Martin grading system (Fig.2). This supplementary grading system has its own unique variables separate from the Spetzler-Martin scale. Points were assigned for patient age, hemorrhagic presentation, and AVM diffuseness, analogous to the Spetzler- Martin scoring system. Pediatric patients (age <20 years) were assigned 1 point; adults (age 20–40 years) were assigned 2 points; and older patients (>40 years) were assigned 3 points. Patients presenting with unruptured AVMs were assigned 1 point and ruptured AVMs 0 points. Diffuse AVMs were assigned 1 point and compact AVMs 0 point. These points were added together for a supplementary AVM grade that ranged from 1 to 5. Simplicity is a critical aspect of a popular grading scale, and a supplementary grading scale was designed with this in mind. In addition, the 2 grading systems are analogous in their structure to make the supplementary grading scale memorable. These investigators analyzed a consecutive surgical series of 300 patients to compare the predictive accuracy using the Spetzler-

Martin scale and the supplementary scale. The supplementary grading scale had high predictive accuracy (area under the ROC curve, 0.73 vs 0.65 for the Spetzler-Martin grading system) and stratified surgical risk more evenly.

Lawton and colleagues proposed that this supplementary grading system be used to improve and refine patient selection for AVM surgery. Clinical decisions begin with an analysis of nidus size, venous drainage, location, diffuseness, age, and presentation, generating Spetzler-Martin and supplementary grades. The Spetzler-Martin grade provides an initial risk estimate. The supplementary grade can be considered separately, with supplementary grades 3 having an acceptably low risk of AVM resection. It can also be added to the Spetzler-Martin grade, with combined grades 6 having an acceptably low surgical morbidity. An analysis of supplementary factors can affect a management decision by confirming the risk predicted by the Spetzler-Martin grade. For example, an AVM with a low Spetzler-Martin grade (grade I–III) may be favorable for microsurgical resection, and a low supplementary grade (I–III) may strengthen the recommendation for surgery. Lawton and colleagues found that 62% of patients had low-grade AVMs according to both grading systems, and 85% of these patients were improved or unchanged after surgery. Conversely, an AVM with a high Spetzler-Martin grade (IV–V) may be unfavorable for microsurgical resection, and a high supplementary grade (IV–V) may strengthen the recommendation for non-operative management. In these cases of matched Spetzler-Martin and supplementary grades, the supplementary grading system has a confirmatory role and may not alter management decisions. However, in cases of mismatched Spetzler-Martin and supplementary grades, the supplementary grading system may alter management decisions and therefore has a more important role. Lawton and colleagues found that 28% of patients had low Spetzler-Martin grades and high supplementary grades, and 41% of these patients were neurologically worse after surgery, which is a higher morbidity than that of Spetzler-Martin grade IV AVMs (31%). Insight pro- vided by the supplementary grade might have discouraged the recommendation for surgery in some of these patients. Similarly, 7% of patients had high Spetzler-Martin grades and low supplementary grades, and 29% of these patients were neurologically worse after surgery. This proportion of worsening was lower than the 35% morbidity for the overall group of Spetzler- Martin grade IV and V AVMs, and equivalent to the 30% morbidity seen for grade III AVMs. Again,

insight provided by the supplementary grade might have encouraged the recommendation for surgery in some of these patients. Spetzler-Martin grade III AVMs have surgical risks that depend on the subtype, with small grade III- lesions associated with lower risk and medium/eloquent grade III1 lesions associated with higher risk. In addition to considering the grade III subtype, considering the supplementary grade may influence surgical decisions for patients with AVM at the borderline between high and low risk. The University of California at San Francisco experience shows that factors outside the Spetzler-Martin grading system improve the prediction of neurologic outcome after AVM resection, and that a simple supplementary grading system can be easily applied at the bedside to refine patient selection for AVM surgery.

Table 3
Comparison of the Spetzler-Martin grading system and the supplementary grading system

Spetzler-Martin		Points	Supplementary	
Size	<3 cm	1	Age	<20 y
	3–6 cm	2		20–40 y
	>6 cm	3		>40 y
Venous Drainage	Superficial	0	Unruptured	No
	Deep	1		Yes
Eloquence	No	0	Diffuse	No
	Yes	1		Yes
Total		5		

Adapted from Lawton MT, Kim H, McCulloch CE, et al. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery 2010;66:702–13 [discussion: 713].

Fig. 2: Supplementary grading system

1.7 Imaging

Most cerebral AVMs can be assessed by observation of Computed Tomography (CT), considering what are the main and suggestive features of lesion in patients with subarachnoid hemorrhage, seizures, headache, stroke, or progressive neurological deficits. Abnormalities associated with the presence of AVM, such as focal atrophy, infarction, encephalomalacia related to blood theft or previous hemorrhage, ipsilateral dilatation of the ventricle, and the presence of calcium, must be distinguished in the use of high-quality CT. All angiography is used to characterize the type of lesion more accurately and to delineate its anatomical structure in detail. This instrumental

investigation lays the foundation for therapeutic decisions, and establishes the presence or otherwise of other associated vascular anomalies (eg Aneurysms) that are found in 5% of patients with AVM. The spatial relationship between the malformation and the adjacent cerebral parenchyma, the presence of hematoma and the site can be obtained together with hagiographic images and CT images.

Computerized tomography

The information obtained through CT with or without the use of contrast medium can be adapted to define the diagnosis of AVM. The enhancement mechanism for AVM occurs in two steps: (a) the contrast medium accumulates in the intravascular compartment, and (b) the contrast binds to the malformation matrix which, like all other lesions of the vascular system, presents a defect at the level of the blood-brain barrier. Based on the clinical presentation of the AVM, it is possible to decide how the CT scan should be performed, in fact the evidence of bleeding AVM will be investigated differently from a malformation with another clinical presentation. Patients presenting with symptoms suggestive of hemorrhage are investigated with CT without the contrast medium to assess whether there is presence or absence of bleeding. Hayward reported the results of a study conducted by him in which it is shown that the use of CT without contrast medium in case of suspected hemorrhage confirms the picture in 86% of cases. The location of the hemorrhage is determined by the site of the AVM and secondarily by the volume of extravasated blood. From an estimate conducted by Stein et al. it has been seen that more than 90% of the AVMs are located above the dyer. When a malformation is projected inside the ventricle, the dilated vessels are covered only by a thin layer of ependyma, which probably explains why an AVM here is at greater risk of breakage. 73% of patients have intraparenchymal hemorrhage, some a picture of ESA or intraventricular hemorrhage, and more than 50% of patients have both associated situations.[132]

In typical cases of bleeding AVM, the CT without contrast medium shows: the presence of a parenchymal blood mass associated or not with hemorrhage inside the cisterns, or of the ventricles; the mass effect with contralateral displacement of the brain; and often a thin, low-density rhyme that indicates the presence of edema around

the blood collection. Calcifications within the vascular wall suggests more specifically the possible site of a AVM.

In the event of haemorrhage, other potential causes of bleeding beyond AVM, such as hypertensive crisis, rupture of an aneurysm, the presence of a richly vascularized tumor must be taken into consideration in the differential diagnosis. A cerebral hemorrhage in the unusual place due to a hypertensive crisis (not involving the basal ganglia or the cerebellum) suggests the possibility of a vascular malformation. In these cases the study after the use of the contrast medium shows an area of enhancement contiguous to the hematoma and frequently there is a vermiform extension or tubular structures representing the afferent arteries or venous drainage. The CT image changes depending on the time elapsed since bleeding. If the bleeding is recent you will see the ipsilateral compression of the ventricle and the contralateral shift of the parenchyma, if instead it dates back to 1 to 3 weeks before, you will have an isodense image, with the only evident mass effect at the study carried out without contrast medium .

In the CT scan with AVM contrast medium images are obtained having areas of enhancement interposed to low density areas that are home to infarction or encephalomalacia or to small cystic and fluid degeneration areas.[221] Rarely an AVM does not show enhancement, it can occur when a recent hemorrhage has obliterated the lesion, or when the AVM is so small that it cannot be visualized in the hematoma structure. In many cases, a comparison between images without contrast and those obtained after its use, allow to distinguish those that are the components of the AVM from the adjacent hematoma, the calcifications inside the vascular wall and the thrombosis of the lesion.

AVMs do not always manifest themselves with cerebral hemorrhage, but with headache, seizures, or neurological disorders. Due to the diversity of signs and symptoms, a CT evaluation may be indicated for these patients based on clinical data only. Images obtained without contrast may not show anomalies in 33% of the cases,[150] If instead the lesion is highlighted, this may appear as a high density area in 45% of cases or at low density in 14% of cases.[132] More frequently high irregular density areas are obtained mixed with low density areas, both within the lesional matrix. Low density areas are due to infarction due to previous minor bleeding or parenchymal damage due to shunt or theft phenomena. In contrast, high-density areas are often dystrophic

calcifications in the AVM matrix or vessels afferent to the lesion. Further anomalies may affect the ventricles, in fact it is possible to highlight an enlargement of the ipsilateral ventricle or even a generalized hydrocephalus.[132] Arteriovenous malformations are not always highlighted despite the use of diagnostic methods appropriate for their investigation. The term "cryptic malformations" was first coined by Crawford and Russel.[40]

Cryptic malformations are considered to be those small vascular malformations that are not found even after routine angiographic study, but which are subsequently identified after pathological examination as the cause of spontaneous cerebral hemorrhage. Today that CT is widely used, it has been possible to highlight a greater number of asymptomatic occult malformations. Becker et al.[16] they added 25 to 50% of the cavernomas among their cases that were considered occult malformations and a 25% overall of AVM, venous angiomas, and telangiectasias. Considering the images obtained without contrast, these lesions appear as areas of increased density and noticeably inhomogeneous. Half of them show minimal mass effect, in one third of the cases there is a modest degree of edema, and in approximately two thirds of cases the contrastographic enhancement is minimal or moderate. Both clinically and by CT study it is difficult to determine when the lesion represents a tumor or it is an AVM. A diagnosis of cryptic malformation is suggested by the presence of chronic symptoms, the rapid or slow growth of the lesion and the presence of a high density area in the CT study without contrast medium.

Digital subtraction angiography

Angiography often plays a decisive role in establishing the diagnosis of AVM and in making decisions regarding the most appropriate treatment. All arteries that contribute to AVM, as well as drainage veins, can be anatomically delineated through a detailed angiographic study. The exact extension of the AVM and the nature of the afferent arteries can be appreciated only after selective injection of the contrast medium. The technique involves the insertion of a transfemoral catheter which is advanced along the larger caliber vessels to reach the level of the internal carotid artery and from there to the cerebral circle, by means of smaller catheters. Angiography can often include the internal and external carotid artery and vertebral arteries. Rapid angiographic series are

necessary to define the origin of nutrient arteries and the course of venous drainage. Digital image subtractions follow the injection of the contrast medium and serve to demonstrate the presence of AVMs of any size even those that are decidedly small in size. Generally AVMs are characterized by coarsely dilated afferent vessels with a serpiginous course, normal efferent vessels or, also remarkably dilated, and a nidus racemose of pathological vessels, with rapid flow within the arteriovenous shunts. The tortuosity of the arteries is present both at the proximal level and at the level of the arterial terminal branches. Few cerebral spaces are contained within the intrinsic vascularization.[16,89] The remaining brain tissue is often grossly gliotic.[149] The venous drainage also tends to become tortuous and redundant over time. When AVM bleeds, bleeding commonly occurs within the subarachnoid space or often affects the parenchymal tissue generating a cerebral hematoma. Blood often also involves the ventricular system and can be detected in CT; precisely this possibility can often lead to suspect the presence of an AVM. The intracerebral hematoma is located more frequently near the AVM and appears surrounded by an avascular area. It can behave like a space-occupying mass and displace the malformation or compress the venous drainage, thus allowing to highlight in angiography only a minimal residue of the efferent arteries or venous drainage. Angiographically, AVMs can be classified according to their etiology and location.

In relation to their arterial supplement they may be purely pial, pial mixed and dural or purely dural. Those that are entirely flat are supplied only by the cerebral or cerebellar arteries. The dural mixed AVMs receive blood flow also through the meningeal vessels. Purely dural malformations are limited exclusively to the dura mater and therefore receive only meningeal arterial contributions. A review of 800 cases by Yasargil et al found that 85.7% of cerebral AVM are supratentorial while 6.2% are infratentorial.[235] Extracerebral malformations occur in 8.1% of cases and these are fed from the external carotid artery or muscular branches of the vertebral artery in the posterior fossa dural or mixed dural malformations are very common, only 50% are purely pleasing. There are no significant differences between the right side and the left side, just as the distribution is equal in both sexes.

PURE PIAL MALFORMATIONS

Pure pial AVMs are brain lesions that receive branches only from the cerebral or cerebellar arteries, without any contribution from meningeal arteries. The angiographic features consist of dilated and tortuous afferent arteries, a group of pathological vascular canaliculi that constitute the malformation, and a rapid shunt within a dilated venous drainage. Houser et al have noted that parenchymal AVMs tend to be located in areas present between major arterial areas, which explains the predominant posterior localization in the cerebral hemisphere. They also observed that the afferent blood flow to the AVM consists of a single pial artery in 30% of cases. When more major cerebral arteries represent the lesion afferent they tend to supply a large number of malformation vessels. The cortical branches of the middle cerebral artery are the most frequently involved (53%), followed by the posterior cerebral artery (40%) and anterior cerebral artery (36%). The posterior choroidal arteries (involved in 22% of the cases) are rarely the only afferent ones, even for the AVMs arranged in depth; this is also true for the anterior choroidal artery, lenticolostriata and thalamoperforating arteries (each contributes in 8% of cases). 50% of posterior fossa AVMs are fed by a single major cerebellar artery.

The venous drainage of the pial AVM tends to be superficial (more than 60% of the cases), even through the intermediate venous component of the malformation it tends to take the form of a wedge, with the apex placed in depth facing the ventricle. Superficial venous drainage runs over the superior sagittal sinus (especially in the case of frontal AVM), below the superficial middle cerebral vein or more commonly towards the transverse sinus (especially in temporal AVMs). Venous dilatation occur commonly in association with AVM having deep venous drainage. In a series of detailed angiographic analyzes, Zia showed that, while the afferent arteries and venous drainage are rapidly identifiable with reference to normal anatomy, the abnormal vascular channels are probably embryonic veins which, due to the high flow in them, they did not experience atresia.[241] In a cooperative study, 37 of 549 AVM patients also had aneurysms, with an incidence of 7%. 43% of these were located in arteries that did not feed the malformation and only 37% in the afferent arteries. Approximately in 1.5% of cases the clinical presentation was due to subarachnoid hemorrhage, but it was not clear which vascular lesion was responsible. Abnormalities of cerebral circulation

(persistence of the trigeminal artery) have been reported in association with cerebral AVM. Vasospasm of cerebral vessels after hemorrhage has been reported but appears to be considerably less common than the spasm associated with aneurysmal rupture. Postoperative angiography usually demonstrates a dramatic reduction in the size of the afferent arteries which, in the preoperative phase, were found to be strongly dilated. Sometimes coarsely ectatic vessels remain dilated in the postoperative study but, repeating the examination after weeks or months, a return to normal size is demonstrated.

MIXED DURAL PIAL MALFORMATIONS

The participation of the dural meningeal branches in feeding the cerebral AVM is unusual according to a series of reports.[66,171] Ondra et al have described 5 cases out of 125 patients.[167] Yasargil described the contribution of dural vessels in a patient of the 90 examined with cerebral AVM.[236] On the other hand, dural involvement in posterior fossa is more common. In a review of 129 cerebral AVMs, Nukui described the dural involvement given by the meningeal artery in 27% of cases (15.5% mixed dural pylons, 11.5% purely durals).[164]

AVMs placed in the posterior parietal lobe or in the occipital region more commonly receive meningeal branches than those located in the frontal or temporal lobes. Large malformations receive more dural contribution than small lesions. The latter are arranged adjacent to the dura mater of the convexity, to the sickle, or to the tentorium which can be fed partly by meningeal arteries. The meningeal branches of the internal carotid artery contribute to feeding the AVM in 28% of the cases and in some situations they represent the only blood source for meningeal. In contrast, Newton et al demonstrated involvement of the external carotid artery in 89% of patients with dural involvement. The posterior meningeal branches of the vertebral artery rarely contribute to feeding the AVM.

Magnetic resonance imaging

MRI are the typical initial imaging examinations performed on patients with AVMs, as the most common presentations are not specific for AVM and include intracranial hemorrhage, seizure, headache, and focal neurologic deficit.[24]

On conventional MRI, dilated arterial feeding arteries, the nidus, and draining veins are represented as flow voids (Fig. 3C, D). T2 and FLAIR (fluid-attenuated inversion recovery) hyperintensity involving the adjacent brain parenchyma frequently relates to gliosis (see Fig. 3C, D), which is a result of hypoperfusion of portions of the surrounding brain secondary to cerebrovascular steal. There can be T1 and T2 hypointensity and susceptibility on b0 sequences in the adjacent brain structures, relating to hemosiderin from previous hemorrhage. [147]

MRI can depict important details of mass effect on adjacent brain structures or involvement of eloquent cortex, which cannot be readily shown on DSA. On postcontrast T1-weighted sequences, there will frequently be enhancement of portions of the AVM nidus. With small AVMs, a small area of cortical and subcortical enhancement may be the only finding on conventional imaging (Fig. 4).[147]

MRI in conjunction with MRA can be a useful noninvasive imaging tool in the postradiosurgery setting to evaluate for residual AVM, even though DSA remains the gold standard. The residual nidus is represented as residual flow voids, with persistent feeding arteries and draining veins. On post- contrast sequences, evaluation for AVM-related enhancement is limited, as postradiosurgery patients can frequently have radiation-induced parenchymal enhancement. There was 80% sensitivity (64/80) and 100% specificity (84/84) on conventional MRI for residual AVM postradiosurgery when compared with DSA, according to Pollock and colleagues.[179]

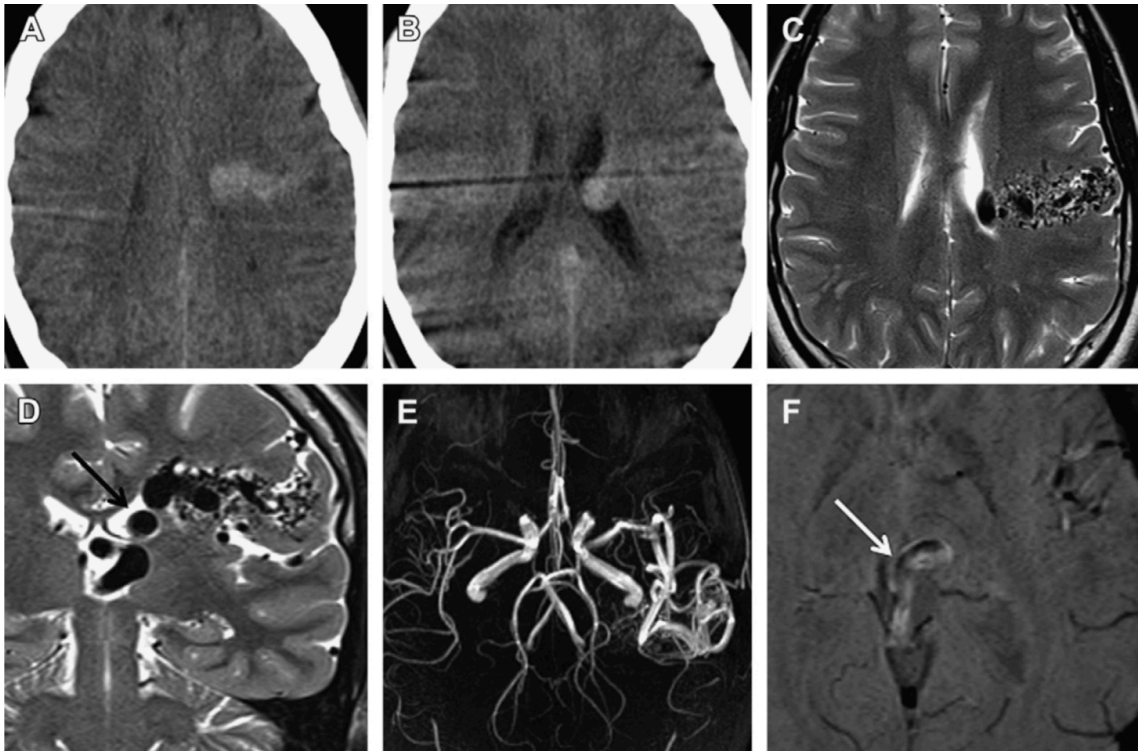

Fig. 3. A 16-year-old female patient who initially presented to the emergency department after tonic-clonic seizures. Axial noncontrast CT images (A and B) show a hyperattenuating serpentine vascular structure coursing from the left corona radiata into the left lateral ventricle. On axial (C) and coronal (D) T2-weighted sequences, there is a prominent plexiform transmantle perirolandic arteriovenous malformation with a prominent draining terminal vein (arrow), which empties deeply into the left basal vein of Rosenthal. Perinidal T2 hyperintensity relates to gliosis. Noncontrast enhanced 3-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) 3D reformat image in axial plane (E) again shows AVM nidus being supplied by multiple distal left middle cerebral artery (MCA) branches. Draining venous structures are not well depicted. Axial susceptibility- weighted image (F) shows hyperintense signal within prominent left basal vein of Rosenthal (arrow) relating to high-flow arteriovenous shunting.

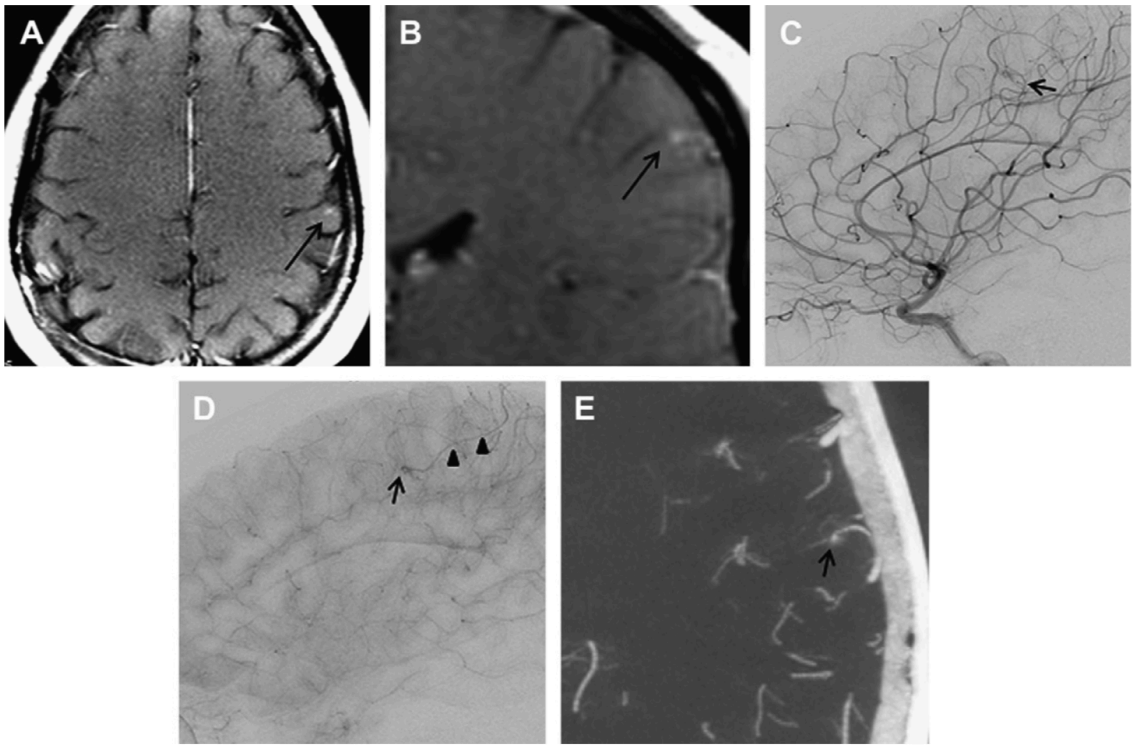

Fig. 4. A 28-year-old man with recent diagnosis of hereditary hemorrhagic telangiectasia (HHT). Axial (A) and magnified coronal (B) T1 postcontrast images of the brain show an enhancing cortical lesion (long arrow) involving the left precentral gyrus. Although nonspecific, a lesion like this should raise a suspicion for a micro- AVM in patients with HHT. Micro-AVM nidus (short arrow) was confirmed on sagittal digital subtraction angiography (DSA) image in early arterial phase (C). Sagittal DSA image in capillary phase (D) shows micro-AVM nidus (short arrow) with single early draining vein (arrowheads). The nidus (short arrow) is presented on axial, magni- fied C-arm cone-beam CT image (E).

Susceptibility-weighted imaging

Susceptibility-weighted imaging (SWI) relies on exquisite sensitivity to magnetic susceptibility effects.[147] Sensitivity to magnetic susceptibility is optimized by using long echo time high- resolution flow-compensated 3-dimensional (3D) gradient echo sequences with filtered phase information. This technique relies on the paramagnetic characteristics of deoxyhemoglobin and the resultant phase differences between venous blood and the surrounding brain parenchyma, as well as arterial blood. SWI is very sensitive for the depiction of venous structures as well as extravascular blood.[150]

SWI can provide helpful information in the evaluation of venous structures draining AVMs. Frequently on conventional imaging and time-of- flight (TOF) MRA, differentiation between arterial feeders and draining veins can be difficult. SWI more accurately shows draining venous structures than TOF MRA and conventional MRI. High-flow arteriovenous shunting in AVM can be accurately depicted on SWI as a hyperintense venous signal, which correlates well with findings of arteriovenous shunting on DSA (see Fig. 3F).[147] This finding relates to rapid wash-in of high-flow oxygenated blood into draining veins. SWI is accurate in the evaluation of residual arteriovenous shunting after AVM treatment; in the posttreatment setting, residual ectatic veins will have decreased signal due to deoxyhemoglobin, whereas persistent arteriovenous shunting will show a hyperintense venous signal.[188] SWI is advantageous to TOF MR venography because it is more sensitive to slow flow within draining venous structures, and there is no loss of signal in vessels coursing in the imaging plane.25 SWI can be helpful in depicting micro-AVMs, which may not be depicted on conventional MRI or TOF MRA, by accurately portraying small draining venous structures otherwise not seen.[192] Early identification of micro-AVMs is important, as these lesions have an increased risk of hemorrhage.

Diffusion Tensor Imaging

Diffusion tensor imaging relies on directional diffusion (anisotropy) of water molecules along nerve axons and nerve bundles. In normal white matter tracts, myelin sheaths and axonal cell membranes restrict water diffusion in the direction perpendicular to the nerve fibers. The primary direction of water motion is parallel to

the orientation of the white matter tract. Tensor maps can be used to generate 3D tractogram maps, which represent the trajectory of the white matter tract.

Diffusion tensor imaging can be use as a valuable noninvasive preoperative and pre-radiosurgery tool to evaluate for involvement and proximity of cerebral AVMs to white matter tracts.[188] Accurate assessment of white matter tracts can be performed in the setting of adjacent AVMs with or without hemorrhage. The proximity of the AVM to eloquent white matter tracts may eliminate surgery as a treatment option, due to the risk of white matter tract injury intraoperatively or secondary to hemorrhage. Diffusion tensor tractography can be useful in determining the radiation dose to the corticospinal tract prior to stereotactic radiosurgery, and thus can help in therapeutic planning, allowing for delivery of an effective dose to the nidus while minimizing the risk of post-treatment complications.[193,203]

Diffusion tensor imaging and tractography of AVMs can depict fiber tract displacement or disruption, or decreased fiber tract density relating to involvement. Some reports have indicated that there is a strong correlation between involvement of the corticospinal tract by hemorrhage or edema from AVM and contralateral hemiparesis, whereas others have not been able to find an association. In the authors' experience with diffusion tensor imaging, there may be the appearance of displacement, compression, or involvement of eloquent white matter tracts, without associated clinical deficits.[17]

There are a few limitations of diffusion tensor imaging and tractography that are important. Hemorrhage or calcifications related to cerebral AVM, surgical clips, or postoperative changes can cause susceptibility artifacts on diffusion tensor imaging, which are problematic because the echo planar imaging technique is typically used.48 In the setting of edema or involvement of a white matter tract, a drop in fractional anisotropy (FA) values may fall below the preset threshold for tractography, leading to the false-positive appearance of disruption of this fiber tract. The FA threshold can be lowered to allow for detection through low-anisotropy regions; however, this may allow for the appearance of spurious white matter tracts. The authors prefer to rely on the color FA maps to evaluate for eloquent white matter tract involvement or displacement, due to the aforementioned limitations of tractography. At their institution the authors typically perform diffusion tensor imaging in conjunction with task- based functional

MRI for preoperative planning, mostly in the setting of brain tumors, but occasionally in the setting of AVMs.[18]

Functional MRI in the Assessment of Cerebral Arteriovenous Malformation

Blood oxygen level–dependent (BOLD) functional MRI is a noninvasive technique that has developed into an important tool for preoperative planning. This technique relies on changes of susceptibility in regions of brain activated by specific tasks, related to slight changes of blood oxygenation. With neuronal activation there is a change in the microenvironment, leading to vascular dilatation, and an increase in blood oxygenation. Functional MRI allows for eloquent cortical mapping (both lateralization and localization) and evaluation of the spatial relationship of eloquent brain to the pathologic lesions that are being evaluated preoperatively. Frequently structures such as the motor or sensory strips, Broca's area, or Wernicke's area can be displaced, distorted, or involved by pathologic processes such as AVMs. In addition, normal variations of cortical surface anatomy make localization difficult or even impossible without functional imaging.[35] Functional imaging allows for prediction of resectability of a lesion, and identification of the components of a lesion that can be removed without sacrificing eloquent brain structures. Preoperative functional MRI can shorten the surgical time as well as alter the surgical approach.[19] With preoperative functional MRI smaller craniotomies are needed, as limited intraoperative cortical mapping can be used. Negative cortical mapping can be performed with electrical stimulation of the margins of the lesions to evaluate for any eloquent cortex.

Functional MRI can serve as a helpful planning tool in the treatment of AVMs. Damage to eloquent cortex can be avoided before embolization, surgical resection, or radiosurgery of these lesions. Preoperative functional MRI may also alter the clinical plan, from surgery to radiosurgery, depending on the anatomic relationship to eloquent cortex.[35] When considering that AVMs represent congenital lesions, it is no surprise that intrahemispheric and interhemispheric cortical reorganization can be seen in such patients. An important limitation of task-based functional MRI in the evaluation of AVMs, as well as tumors, is neurovascular uncoupling. Functional MRI relies on cerebrovascular dilatation related to increased neuronal activity, leading to increased blood oxygen content. In the setting of cerebrovascular abnormality, such as is seen

with AVM and dysplastic vessels supplying tumors, the abnormal vessels do not respond to these stimuli, and there can be diminished or no task-related BOLD activation of normal functioning neurons within the lesion or in the adjacent cortex. Neuro-vascular uncoupling can simulate cortical reorganization, as the normal cortex will have no task-related BOLD activation (see Fig. 5D, E).[75] At their institution, the authors use breath-hold BOLD cerebrovascular reactivity (CVR) maps to qualitatively evaluate for neurovascular uncoupling. Abnormal vessels such as those seen within and around cerebral AVM will not vasodilate in response to increased carbon dioxide levels, and will show absent or diminished activity on the CVR map relative to the rest of the brain.[123,147]

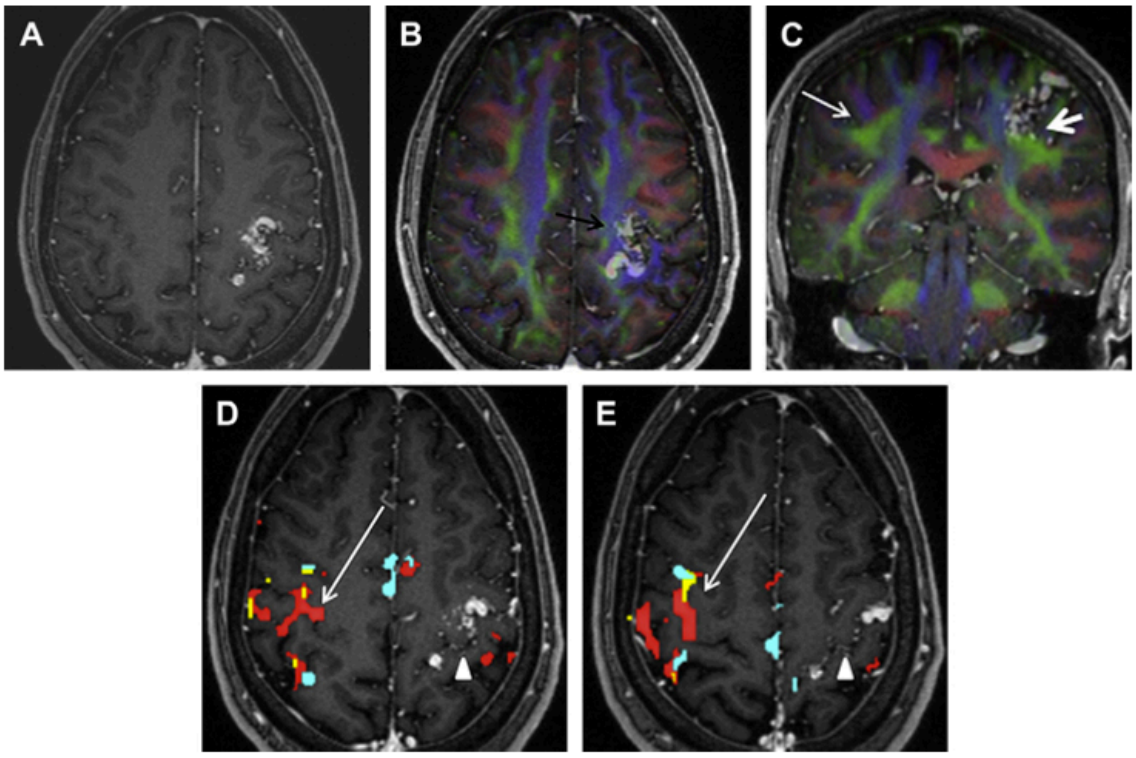

Fig. 5 Axial postcontrast T1- weighted sequence (A) shows left perirolandic arteriovenous malformation. Axial postcontrast T1-weighted sequence with overlaid color fractional anisotropy (FA) map (B) shows AVM nidus and prominent draining vein abutting and impressing on the left corticospinal tract (arrow, surrounding blue white matter tracts). On coronal postcontrast T1-weighted sequence with overlaid color FA map (C), the AVM is abutting and displacing the left superior longitudinal fasciculus (SLF) (short arrow, green white matter tract), in comparison with the normal contralateral SLF (arrow). Composite motor activation maps (D and E), with hand (red), foot (blue), and tongue (yellow) task-based BOLD functional MRI maps overlaid on axial T1 postcontrast sequences. There is no task-based activation overlaying the left motor cortex (arrowhead), whereas there is normal task-based activation on the right (long arrow). On breath-hold cerebrovascular reactivity maps (not shown), there was evidence of neurovascular uncoupling involving the left perirolandic regions

CHAPTER II

MANAGEMENT

2.1 Surgery

There are at least two main prerequisites in choosing the patient's position during the operative phase:

- The AVM must be oriented along a horizontal plane roughly at the level of the heart;
- There must not be any kind of interference with the venous drainage coming from the AVM or for the whole brain.

In order not to obstruct the venous outflow along the jugular vein, the patient's head must be as much in axis as possible, neither rotated nor bent. For AVM surgical procedures located at the convex level, an appropriate position would be given by the raised head and the malformation parallel to the floor. Surgery in posterior fossa are present on patients seated, prone or in the "parkbench" position. Once the head has been positioned, it is kept in place by a headboard, detractors are used to exchange normal brain tissue during AVM resection. for these pathologies the craniotomy must be as wide as possible, so as to reach below the margin of the malformation, and so as to identify the normal brain tissue around the AVM. This is remarkably important when the AVM is located in depth and the anatomical surface of the veins and arteries is obscured by the malformation itself. After organizing the craniotomy, the dura mater is opened around the area occupied by the AVM. During this maneuver, considerable care must be taken not to risk damaging the major underlying venous vessels. In some cases it is possible that finding small arterial vessels that start from the dura, supply the AVM; the model and the extensions of this vascular network present a remarkable variability

from patient to patient. The use of cauterization with bipolar together with profuse irrigation is essential during the dissection of the dura especially if it is in close contact with the AVM. In cases of interhemispheric AVM, the reflection of the dura on the sagittal sinus can be difficult, due to an arterialized venous drainage that prevents the exposure of the medial portion of the hemisphere. In this situation, some of the smallest venous drainages must be coagulated and divided, while the main venous drainage must not be occluded at this stage of the operation. The complete extension of the AVM can be appreciated only after exposure of the subcortical surface; the presence of conspicuous anomalous vessels at the level of the cortex often represent the tip of the iceberg.[235] Generally, the AVM have a cylindrical or conical conformation with the apex turned towards the depth or towards the periventricular region. From the surface of the cerebral convexity it is easier to observe venous vessels, since even if they originate in depth or within the malformation, they generally reach the surface. When the afferent arteries reach the depth of the AVM through the passage in a sulcus, so the portion of the afferent artery visible from the surface could be very far from the margin of the AVM. An important trick to be implemented during the operation in order to maintain a brain relaxation, is to induce a modest hypotension.[75] This is especially true when it comes to large, difficult AVMs, with deep arteries and venous drainage. When the operation is performed on a patient in a sitting position, hypotension should be induced with particular caution because the pressure could be lower in the cranial area than in the heart, from which it is usually monitored. A low-flow condition in the major venous sinuses in the case of posterior fossa AVM can generate thrombosis with postoperative complications of venous infarction. The tissue within the AVM is composed of vessels and gliotic brain tissue and is therefore not functioning.[65,85]

Surgery must preserve the adjacent healthy brain tissue, so every precaution must be put in place to preserve the tissue at the edge of the lesion. During surgery the operating microscope is used for resection of particularly deep AVMs or in areas that are difficult to access. For the removal of large AVM occupying the convexity of the brain, a magnification of 2.5x4 is used. Retraction of the AVM should be moderately vigorous so as not to pierce the surface of the lesion otherwise bleeding may obscure important areas. Although retraction on the AVM can reduce its extension, it cannot be

used to create space between the brain and the AVM. The main arteries afferent to the AVM are cauterized, sometimes a clip is placed in the seat, and subsequently they are dissected. If only the cauterization was used on an afferent artery of considerable size and the vessel was subsequently dissected, the proximal portion could be recanalized by the existing arterial pressure inside the vessel. In contrast, small arteries can only be cauterized before being sectioned. While the vessels are cauterized they must be made wet by continuous irrigation. Indeed, if the tissue placed between the tips of the bipolar is wet, the instrument will be able to stop the blood flow inside the vessel, while if the irrigation was too limited, especially in combination with profuse bleeding, the current would not be able to cauterize the fabric. Thus, using copious irrigation and avoiding damage to normal brain tissue, AVM is circumscribed by means of the cauterization obtained using bipolar. In circumscribing the lesion it is important not to dissect too deeply because this would result in too narrow exposure.[86,105,107]

Since the margin of the AVM is often delimited by a groove, it is important to follow it as much as possible by exploring and then resecting the malformation. In some cases it becomes necessary to open the arachnoid above the sulcus while circumscribing the lesion in order to identify the major afferent arteries that lie deep. Although it is preferable to cauterize rather than use clips, some arteries have a very thick wall and do not respond to cauterization, it is necessary to put a clip on the vessels in order to be more sure of the occlusion seal. Working in depth around the malformation, the surgeon often encounters a gliotic tissue or remnants of old hemorrhages, between the skein of abnormal vessels and healthy brain tissue. It is important to work within the pseudocapsule that surrounds the AVM so as not to risk damaging it. AVMs located in depth are surrounded by white matter of a uniform nature. The gypsy white substance is carefully isolated, cauterized, and finally sectioned. Some areas are filled with large arteries, while others are small and have a fragile wall, so when action is taken to try to cauterize them, they often give rise to high-pressure bleeding without sufficient tissue in the vessel wall to allow the haemorrhage through cauterization. In these cases the use of Gelfoam and other hemostatic substances is used in the bleeding region, since in these circumstances they are more effective than cauterization.[107] Arteries emerging from the choroid plexus can enter the AVM and approach the ventricle. These can be small, but

they are often those that give a profuse bleeding and represent a significant problem for the surgeon if this occurs in depth and in a very restricted space.

The difficulty linked to this possible event can be somehow reduced by the AVM and previously treated by endovascular treatment; this is especially true when branches of the posterior cerebral artery or lenticulostriate arteries are involved.

Many large AVM s are wedge-shaped, with the axis facing the ventricular surface and receiving blood from the choroid plexus. The subependymal and intraventricular portion of AVM presents particular problems, rarely in this case endovascular treatment manages to reduce arterial blood supply. Furthermore, there are often ectatic venous children with a high intraoperative risk of bleeding and postoperative hydrocephalus in the subordinate space. AVMs located near the choroid plexus present a peculiar problem because the arterial circulation in that area involves numerous "feeder" arteries directed towards the connected directions. Small cotton ribbons protect the healthy brain tissue and adjacent to the cleavage plane of AVM. It is important not to occlude the main venous drainage before all the blood flow coming from the arteries is not definitively interrupted. Otherwise, in fact, the AVM would expand and become turgid with an increased risk of rupture and bleeding in numerous sites, identifying the so-called "catastrophic situation".[107,110] In this case the surgeon's decision must be immediate and will be decisive for the outcome. An experienced surgeon can sometimes anticipate the catastrophic event if he perceives changes in the color or tension of the vascular wall. In these cases we try to immediately reduce the cerebral tension and the blood flow inducing hyperventilation, hypotension and liquor drainage. Gelfoam and other hemostatics are subjected to preventing rupture or controlling bleeding in the event of rupture. If all these tricks fail the surgeon we must quickly remove the AVM, considerably bleeding.[109]

Further consideration must be given to trying to preserve the major cerebral arteries that send branches to the AVM, but which on the distal side continue to supply blood to the healthy distal areas of the brain. Once the AVM has been completely isolated from the adjacent brain tissue and all the afferent arteries have been occluded, it still remains connected to the pedicle constituted by the venous drainage. This is cauterized, eventually "clipped" if the tissue around the vein is insufficient to maintain closure. It is important to consider that many apparently isolated AVMs actually present

residues that are fed by small arterial branches connected to a single venous drainage.[130] The evidence of a persistent arterialization of the veins indicates a possible residual shunt. The cleavage area near a previously hemorrhagic area is malacic and with cystic dilations that facilitate resection. Once the AVM is removed, the surgical procedure is closed, but if a residual fragment remains, it must be surrounded by hemostatic material in the hope that the vessels will undergo a progressive thrombosis and disappearance.[146,151,185]

2.2 Endovascular Treatment

The percutaneous interventional techniques aimed at the treatment of cerebral AVM have rapidly evolved the previous two decades thanks to the introduction of embolizing materials, small catheters and increasingly sophisticated imaging techniques. These techniques allow radiologists to guide minute catheters within arterioles, thus achieving a high degree of selectivity in cannoning distal branches of intra- and extracranial arteries. In some cases, embolization is the first step in definitive treatment of AVM that can be completed with subsequent surgery.[198] The decision of the selectivity of the vessel and the choice of which arterial branch must be incannulated are taken by radiologists and clinicians together. The optimal setting is given by a specialized multidisciplinary team that includes a neurosurgeon and a neuroradiologist specialized in vascular pathologies. The growth pattern of the AVM and the arrangement of the "feeder" arteries must be studied carefully before embolization, since these influence the choice of the technique. Three growth patterns have been identified:

- "Fan" pattern: the arteries afferent to the AVM divide repeatedly and terminate inside the MAV without returning to the surface to spray the remaining brain tissue. This type is often found near the brain surface and towards the terminal portion of the afferent arteries. Since the arteries end inside the AVM, the embolization of the afferent arteries can definitively occlude the malformation;
- "Comb" pattern: the arteries afferent to the AVM do not end inside in the AVM, but continue to spray the healthy brain tissue below. Near the AVM comes

a multitude of vessels that cross the main arteries afferent to the malformation at right angles. In this case the embolization of the lesion is decidedly more difficult because the embolus released in the artery will tend to translate from the abnormal vessel to the arteries, thus occluding its terminal branches used to spray the healthy brain tissue. The "comb" pattern is often found in AVM located at the level of the basal ganglia, which are supplied by the lenticulostriate arteries decurrent within the Silvian fissure of the brain convexity. In this case, when an embolus is released in the distal portion of the internal carotid artery, this tends to slide along the middle cerebral artery and to stop inside one of the normal branches of the cerebral convexity, rather than entering the abnormal lenticulostriate arteries. They can also be found in the proximity of the thalamus, of the medial temporal lobe, sprayed by the branches of the posterior artery communicating artery or by the direct perforating branches pertaining to the internal carotid artery and the anterior choroidal arteries, and of the posterior fossa, where they receive the flow directly from the perforating branches of the basilar artery. AVM involving the cerebellar hemisphere is supplied by the anteroinferior cerebellar artery and the posteroinferior cerebellar artery, both arising at right angles from the basilar and vertebral arteries. From a decade to now, a microcatheter with a balloon without slits is used which allows these extremely problematic malformations to be treated for them. Infact, with the addition of this system it is possible to embolize AVM with "comb" type growth patterns by temporarily occluding with a balloon the arteries that supply normal brain tissue, in order to protect the healthy tissue from small emboli that are injected;

• "Mixed" pattern: both previous patterns are present and they are often found in large AVMs involving simultaneously the basal ganglia and cerebral convexity. Often embolization requires multiple sessions and the use of a variety of techniques and liquid embolic material with butylate, onyx or Phil.

A reduction in the flow and volume of blood shunt that occurs within the AVM improves perfusion of normal brain tissue and consequently reduces clinical symptoms

especially seizures;[106] furthermore the reduction in size positively affects the risk of bleeding. Embolization facilitates subsequent surgical treatment in two ways:

- 1. causing thrombosis of all or most of the vessels constituting the nidus. This occurs in numerous cases in which embolization is carried out with silicone and butylate. Even a partial thrombosis of the nest can help when it is obtained at the level of the deepest portion, as it can often be difficult to reach surgically. The occlusion is obtained by selectively injecting the Silastic microspheres in the anterior choroidal artery or in the small perforating branches;
- 2. reducing the number of "feeders" arteries, which is convenient especially if the blood support is provided by multiple main arteries, such as middle cerebral artery or posterior cerebral artery. The result of the reduction of the flow through the AVM involves partial collapse or complete thrombosis of venous drainage. This facilitates surgical resection, especially when access to the afferent arteries is located deep or when the venous drainage is superficial and large.

For both surgical and endovascular treatment, AVMs have been divided into: (a) small and superficial; (b) medium or large, superficial, and localized at the level of the convexity; (c) unsuitable for surgical treatment. While small and superficial AVMs are treated with surgery only, superficial, medium or large AVMs, located at the level of the hemispheric convexity, are first embolized and subsequently operated.

Therapeutic embolization of a brain AVM was first described in 1960 by Luessenhop and Spence [137]utilizing flow-directed steel spheres covered with methyl methacrylate injected directly into a surgically accessed cervical internal carotid artery. This technique relied on the proportionately greater degree of blood flow to the AVM compared with normal cerebral branches to direct the embolic agents into the AVM nidus. Accidental embolization of normal cerebral vessels resulting in cerebral infarction was a potential problem. Additionally, occlusion of proximal arterial feeders could prevent entry into the nidus, leaving the nidus unoccluded and active. This often leads to AVM recruitment of deep perforators making surgery ultimately more challenging.[56,58] In 1974, Serbinenko[198] reported on the use of a detachable balloon attached to a flexible flow-directed catheter. Similar to the problem seen with Silastic spheres, the detachable balloons sometimes occluded the proximal feeder pedicles inducing the nidus to recruit

deep perforators making surgical resection more challenging. In 1976, Krayenbuhl described the use of a microcatheter with a calibrated-leak balloon to superselectively catheterize the cerebral vasculature.[124] This novel device overcame the problems seen with the use of the diagnostic catheters, i.e. the difficulty in placing the catheter precisely in the desired area and controlling the infusion of the occluding agent. In addition, Kerber used a liquid embolic agent, isobutyl-2-cyanoacrylate. Over the last several decades, the development of smaller microcatheters, microguidewires, and novel embolic materials has led to technical achievements in AVM embolization and solidified its role as an important tool in the treatment of brain AVMs.

Although surgical resection remains the standard for the definitive eradication of most brain AVMs, endovascular embolization has the potential to enhance the safety and efficacy of AVM treatment when applied as adjuvant therapy before microsurgery.[60, 76] Preoperative embolization of AVMs has been shown to reduce operation time and intraoperative blood loss, with no difference in surgical complications or long-term neurological outcome[81]. Patients treated with embolization prior to surgery experienced fewer postoperative neurological deficits and fewer deaths, and had a lower incidence of postoperative epilepsy when compared with patients who had surgery alone. Embolization is also capable of converting high Spetzler-Martin grade lesions to lower-grade lesions, thus turning potentially inoperable lesions into operable lesions[174]. Embolization improves surgical outcomes through several mechanisms including the elimination of deep feeding arteries such as the anterior/posterior perforating vessels, choroidal vessels, and posterior cerebral vessels [164], decreasing the size of the active nidus, and the elimination of the feeding pedicle or nidal aneurysms that have either bled or are at risk of rupture.[184] Presurgical embolization decreases the risk of postsurgical hemorrhage caused by changes in hemodynamics within the surrounding normal brain, and can act as a surgical roadmap as embolized vessels are easily identifiable. Preoperative embolization in conjunction with surgery has also been shown to be cost-effective when compared with surgery alone. Another potential role of embolization is adjuvant therapy before radiotherapy. This is particularly useful for medium- and large-size AVMs. Embolization in this setting has several theoretical benefits. First, it has been shown to reduce AVM size so that the residual nidus is a smaller target that can be irradiated with a better cure rate and fewer side effects. The cure rate increases with decreasing AVM vol-

ume, and smaller lesions (<3 cm in diameter) carry lower rates of morbidity. Preradiosurgical embolization may also be used to occlude arterial feeder or intranidal aneurysms to reduce the risk of bleeding while awaiting the delayed action of radiosurgery, as well as target large high-flow AV fistulas which are less sensitive to radiosurgery. The risk-benefit ratio must be carefully considered in these cases. Untoward complications of embolization could precipitate the need for surgical extirpation of an inoperable AVM. There is also some evidence that embolization prior to radiosurgery may reduce the efficacy of radiotherapy to cure AVMs. Although the causes are not entirely clear, experienced authors have argued that radiopaque embolic material may 'shield' the nidus from adequate radiation absorption or alternatively may activate certain vascular growth factors. Embolization has also been shown to be safe and effective in treating residual lesions that persist after radiosurgery. Marks et al. [145] reported on 6 patients who underwent endovascular treatment of their brain AVMs after failing radiosurgery. One patient was cured with embolization alone, 3 patients underwent surgical resection for cure after embolization, and 2 patients went on to have successful repeat radiosurgery following embolization. Palliative embolization of brain AVMs is typically employed in patients with large, symptomatic but inoperable lesions. The indication for palliative embolization is usually acute hemorrhage. Embolization under these circumstances should be used to treat specific highrisk AVM angioarchitectural features such as aneurysms, or to alleviate specific clinical signs and symptoms related to vascular steal and/or mechanical compression[219-224]. Partial embolization may also be beneficial in patients with medically refractory seizures or with progressive neurological deficits thought to be secondary to venous hypertension or arterial 'steal' phenomenon causing ischemia. Palliative embolization is not recommended as a broad treatment strategy for inoperable lesions as it does not appear to produce better clinical results than medical management and there is no evidence to suggest that partial AVM embolization alters long-term hemorrhagic risk [164]. On the contrary, partial embolization has been shown to worsen the clinical course of the patient compared with the natural history of an untreated lesion[174]. Less frequently, embolization is used as 'primary therapy', particularly for smaller, surgically difficult AVMs that contain few arterial feeders. Published cure rates in the literature vary considerably secondary to selection bias, goals of treatment, and technique. Although cure rates of up to 40% have been reported in some series, delayed

recanalization seems to be a problem even for smaller AVMs. Furthermore, the AVMs that would have a high probability of cure with embolization are typically amenable to complete surgical resection or radiosurgical cure without the associated risks of embolization[56-58]. Deep central lesions with limited feeders are exceptions where embolization can play an important role in cure[58].

Embolic Agents

Current embolic materials used to treat brain AVMs can be divided into solid and liquid agents. Solid agents consist of polyvinyl alcohol (PVA) particles, fibers, coils, and balloons. Liquid agents, which are more commonly used, consist of cyanoacrylate monomers such as N-butyl cyanoacrylate (NBCA), as well as polymeric precipitates in solutions such as ethylene co-vinyl alcohol. Absolute (100% anhydrous) ethanol is an additional liquid embolic agent that is not commonly used now.

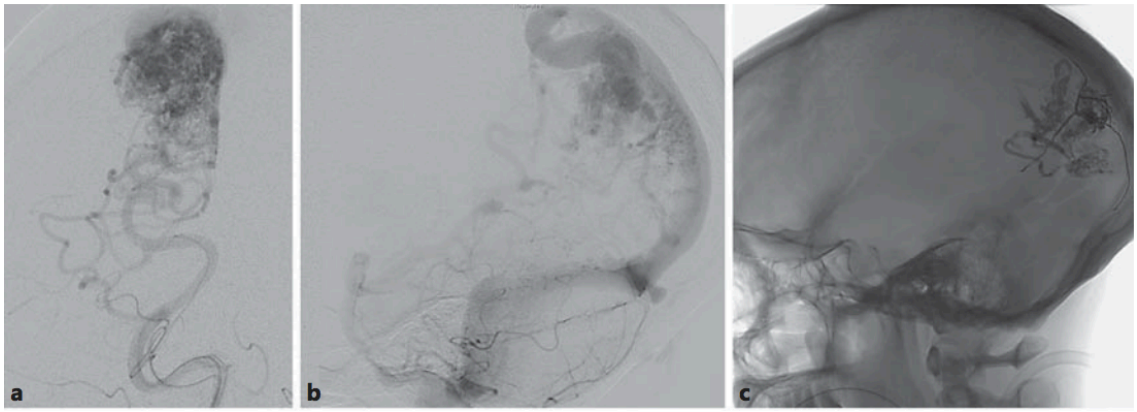

Fig. 6. A 40-year-old male with a left occipital AVM. a AP view, left vertebral artery injection – arterial phase. B Lateral view, left vertebral artery injection – venous phase. C NBCA in nidus on unsubtracted lateral image.

The principal agents currently in use for treating brain AVMs include NBCA (Trufil, Codman Inc.), Onyx (Covidien, eV3 Neurovascular, Irvine, Calif., USA), a copolymer of ethylene vinyl, and, to a lesser extent, PVA particles and coils. NBCA and Onyx are the most commonly used agents and will be discussed individually. NBCA Embolization with cyanoacrylate has evolved tremendously since its introduction nearly 30 years ago because of the development of different adhesive formulations as well as

the advancement of catheter and guidewire technologies. Isobutyl-2-cyanoacrylate has been replaced by NBCA, which was approved by the Food and Drug Administration for brain embolization in 2000 because of the more predicable polymerization qualities, ease of surgical resection, and lack of toxicity of NBCA [219]. The use of NBCA for the treatment of brain AVMs is predicted on its liquid character, which allows it to penetrate nidal vessels where it ultimately polymerizes to a solid state, and causes thrombosis and vessel occlusion. NBCA polymerizes into an adhesive, non-biodegradable solid material upon contact with blood and endothelial cells via an anionic mechanism. It induces an inflammatory response within the walls of embolized vessels that is believed to play an important role in the permanence of the occlusion created with this agent.[76] NBCA is not radiopaque and, thus, must be opacified to monitor its flow during injection. Ethiodol and, to a lesser extent, tantalum powder are mixed with NBCA to make the solution radiopaque. Ethiodol also acts as a retarding agent to slow the polymerization rate as pure NBCA polymerizes almost immediately at the catheter tip. The goal is to create a mixture of glue/ethiodol that will prevent early polymerization within the feeding artery but also late polymerization within the draining vein(s). Concentrations of 25% glue and higher are typically used to achieve nidal penetration. Concentrations below 25% will usually polymerize too slowly.[124] Due to the importance that mastery of this process represents, there is a learning curve to assure its safe and proper use. Embolization with NBCA facilitates surgical resection by helping identify the embolized vessels, differentiating them from normal vessels, as well as providing a distinct boundary between the AVM and normal brain parenchyma. Vessels embolized with NBCA are compressible and easily cut with microscissors.[125.126]

ONYX

Onyx (Covidien, Irvine, California) is one of the newest nonadhesive liquid embolic agents available for treatment of brain AVMs.[224] It consists of an ethyl-vinyl alcohol copolymer dissolved in dimethyl sulfoxide. Tantalum powder is added for radiopaque visualization. Onyx comes available in 1.5-ml ready-to-use vials in 3 different viscosities: Onyx 18, 20, and 34. The concentrations of ethyl-vinyl alcohol copolymer are 6, 6.5, and 8% for Onyx 18, 20, and 34, respectively. The Onyx vials must be shaken for at least 20 min prior to use in order to obtain a homogeneous solution consisting

of the embolic component and the tantalum powder.[219,224] Unlike NBCA which polymerizes almost immediately, Onyx has a very slow solidification rate which allows for a more prolonged and controlled injection. This, in theory, enables larger parts of the AVM to be occluded with each microcatheterization. The slow polymerization rate and lack of adherence allows for prolonged and repeated injections from the same point, resulting in deeper penetration into a larger part of the nidus.[184] However, it should be noted that these are theoretical advantages as there is currently no published evidence confirming this. One disadvantage or limitation of Onyx is its high radiopacity. It may be difficult or impossible to visualize the distribution of the material one is injecting in large AVMs previously treated with Onyx because of overprojection. This can potentially result in untoward injection of collateral arteries or the venous outflow system with catastrophic results. Another disadvantage of Onyx is its poor visualization during reflux in very small vessels.[184] Additionally, some peer-reviewed publications describe longer fluoroscopy times and higher complication rates with Onyx compared with NBCA.[224]

PHIL

PHIL (Precipitating hydrophobic injectable liquid; Micro-Vention, Tustin, California) is a newly introduced DMSO based embolic agent that is gaining wider use in AVM treatment. In this paper, we share our preliminary radiologic and surgical experience in same-day combined treatment of AVMs, acute stage histopathologic findings of PHIL, and its major differences from Onyx. PHIL comes as ready to use pre-filled syringes of 1 mL and does not require shaking prior to injection. Onyx is shaken for 20 minutes for a homogenous solution that requires anticipation of estimated time of usage.[189] Both PHIL and Onyx are DMSO-based liquid embolic agents that require DMSO-compatible microcatheters. Onyx can be delivered through the same catheter after PHIL injection, which offers the advantage of switch between agents during endovascular therapy without injecting additional DMSO. PHIL has limited visibility during passage through the microcatheter (especially PHIL 25%). After passage through the tip of microcatheter, PHIL has a lower visibility than Onyx. PHIL is bound to iodine for radiopacity and does not lose its homogeneity during prolonged injections, which offers the advantage of consistent visibility. Onyx uses tantalum for radiopacity, which can

cause inhomogeneity during prolonged injections and decrease visibility. Onyx also suffers from self-hiding effect when used in large amounts due to dense radiopaque saturation[192]. Plug formation with PHIL is faster because of less layering effect compared to Onyx, which may offer decreased duration of embolization and fluoroscopy time.[224] Backflow into arterial side is slower with PHIL, which may limit unintended proximal arterial embolization and decrease the amount of embolic agent used. PHIL has a column effect when it reaches the venous side, which decreases forward flow in the venous side. Decreased forward flow in venous side limits venous obliteration, which may decrease the rate of postembolization hemorrhage due to venous outflow obstruction.[219] Onyx causes CT beam hardening artifact and intense artifact in gradient recalled-echo (GRE) and susceptibility-weighted imaging (SWI) sequences which limit evaluation of perinidus parenchyma during post-treatment follow up.[184] PHIL has minimal CT beam hardening artifact and no artifact in GRE and SWI. Onyx and PHIL have different gross appearances inside the embolized vessels; Onyx is dark gray, which limits its use in vascular malformations in the face due to tattoo effect. PHIL has a white color, which may offer aesthetic advantage for use in vascular malformations in the face . Grossly, Onyx forms a continuous smooth surfaced gray-dark column within vessels, whereas PHIL forms a rough-surfaced whitish column interspersed by blood clots. During surgical manipulation, Onyx feels as a rubbery, pliable material, whereas PHIL is stiff and brittle.[189] When PHIL-filled vessel is cauterized with bipolar cautery, crunching and breaking of the intravascular column can be noted. This feature of PHIL is important when handling small vessels near the distal end of PHIL column, especially when working under the nidus. However, these differences do not affect the overall surgery, and material properties are easily handled during the first few minutes of dissection. Review of the literature shows limited experience with same-day embolization and surgical resection in brain AVMs.

2.3 Radiosurgery

In 1914 Magnus from Oslo first treated a cerebral AVM with radium, a radioactive substance.[142] The advantages linked to this technique are not highlighted right away, but some years are needed from the treatment. Initially neurosurgeons

believed that this technique was able to offer minimal if not zero benefits to patients treated for AVM.[78] It took more than half a century to begin to highlight the efficacy of radiosurgical treatment and to consider it a possible therapy for AVM. The vessel wall is moderately responsive to ionizing radiation, known for a long time to be able to cause damage to the small vessels of the skin and lung. Regardless of the type of radiation (penetrating electron beams, high-energy proton rays, or gamma photons emitted by a source of 60Co), the energy that is transmitted to the tissues always produces biological responses. The early changes that can be highlighted are represented by the appearance of edema in the perivascular or subendothelial area, wall fixation, hemorrhagic spots, thrombi, degeneration and necrosis of endothelial cells, increase in tissue colloids, and increase in fibroblast activity. [203] These alterations are prevalent in medium and large caliber arteries and over time tend to affect increasingly larger areas of the vascular wall. The progressive repair of the endothelium evolves towards a state of fibrosis and occlusion of the small vessels involved, which can also be the vasa vasorum of the large arteries. The wall of the vessels responds to the energy transmitted by the radiation with a reactivation of the proliferation of the cells constituting the intimate habit, culminating in a complete obliteration of the lumen. The apparent difference between the reaction of the endothelial tissue of small vessels and the reaction present in the tissue of large vessels may be due to the different size of the lumen.

In 1951, Leksell[140] first described the technique of stereotactic radiation with the use of ionizing radiation, in order to collimate the rays on a given intracranial target. Two techniques are used for radiosurgery: "Intersecting beam irradiation" and "Bragg-Peak irradiation", in which monoenergic accelerated ion beams having different masses and charges, can be made to stop in a defined volume of tissue. In this way, a high single dose of radiation can be concentrated in a precise volume, involving the surrounding brain tissue to a minimum. The use of irradiation with gamma rays for the treatment of cerebral AVM is due to Steiner L. [212] who used it first in 1970.

The main components of the 60 Co gamma units are given by:

1. the radioactive source: there are 179 sources of Co, each 2 mm long and 1 mm in diameter, arranged radially;

2. the collimator system: consists of two sections. The external section located in the central body of the equipment and an internal section (the collimator helmet)

provided with two axes and connected to the operator table the patient's head is positioned according to coordinates calculated in detail, so that the target is located in the center of the helmet collimator where the rays are made to converge. The size and shape of the point where the rays intersect are determined by the shape and size of the collimator holes;

3. the operating table: the movements of the radioactive screen are carried out by means of a hydraulic control system.

In this way the gamma rays produced by the Co sources can be collimated on the surface of the AVMs thus reaching and obliterating all the afferent arteries located at any point of the brain, without causing damage to the underlying brain tissue. The choice to submit a patient to radiosurgical rather than traditional surgical treatment must be taken by a neurosurgeon based on objective factors, such as: (a) natural history of the disease; (b) the results of both techniques taken from the literature; (c) the patient's physical condition including age and neurological status; (d) initial presentation symptoms; (e) size, location of the MAV and number and pattern of the afferent arteries and venous drainages; (f) presence of hematomas and relationships with the underlying brain tissue; (g) the volume of blood within the shunt.

A study conducted by Steiner[212] showed that patients who start with epileptic seizures have a 25% chance of having a brain hemorrhage within 15 years of being diagnosed with AVM. On the basis of this, the long latency period between the moment of irradiation and the subsequent obliteration of AVM presents a slight risk of bleeding. On the contrary, for a patient who has already had a hemorrhage, the risk of the same event occurring again is 25% within 5 years and occurring for the third time is 25% within the following year. From these data it can be deduced that radiosurgical treatment may be an option for the patient with epileptic seizures, while in all other cases surgical treatment is the first choice option. Once radiosurgery has been chosen, a careful angiographic evaluation is performed, viewing the lateral and antero-posterior cuts, so as to obtain all the information necessary to decide the dose to be administered. At the beginning of the procedure a thermoplastic shell is applied to the patient's head, which is anchored to four small metal plates screwed into the external table of the patient's skull; the stereotaxic framework is fixed to the thermoplastic shell. At this point a stereotactic angiography is performed, if the AVM is composed of one or more

vascular modules that receive blood flow from different territories, a drawing is drawn on a transparent support that corresponds to the vascular units, in order to determine the coordinates of the target. The relationship between the AVM and the adjacent brain tissue is evaluated with stereotactic CT scan.

After obtaining the X, Y and Z coordinates corresponding to the center of the target, two metal supports for the collimator helmet axes are stuck inside the plastic shell or are attached to the metal frame in the position corresponding to the X-Y coordinates. The patient is moved to the operating table and the head is positioned according to the Z coordinate. The time programmed for irradiation corresponds to the choice of dosage, when the internal and external collimators are aligned, the emission of gamma rays begins directed towards the target. At the end of the procedure the metal frame is removed and the small lesions caused by the screws are medicated. The following day the patient can go home. At the beginning angiographies will be repeated at very short intervals during the follow-up period, ie at 3,6,9,12,24 and 60 months after radiosurgery. The post-irradiation course follows a constant course that foresees a long period before the AVM goes into obliteration. During follow-up patients have a progressive improvement in neurological deficits and epileptic seizures disappear completely or are reduced in frequency; only two cases have been reported, on a series of 110 patients examined by Steiner, in which a re-bleeding occurred after radiosurgery.

The changes that can be evaluated from the angiographies performed during the follow up are classified as follows:

- Not displayable changes: in most patients the effects of the treatment can be evaluated at least 1 to 3 months after the treatment;
- Hemodynamic changes: in many cases, before appreciating morphological changes, a progressive reduction of the flow within the AVM is highlighted;
- Partial obliteration: in some cases an unimportant reduction in the size of the AVM is assessed;
- Complete obliteration: usually a couple of years after the treatment.

Steiner's study shows that in 39.5% of cases complete AVM obliteration was achieved within a year of treatment, and in 84% within 2 years

NUMBER OF CASES	LATENCY (YEARS)	COMPLETE OBLITERATION	PARTIAL OBLITERATION	NO CHANGES
81	**1**	**32(39.5%)**	**33(40.7%)**	**16(19.7%)**
63	**2**	**53(84.1%)**	**7(11.1%)**	**3(4.7%)**

Fig.7 Results at 1 and 2 years after radiosurgery.

Radiosurgery can be used as a complementary procedure to surgery in cases of: (a) multiple AVMs, to obliterate deep lesions after they are easily accessible have been surgically removed, (b) partially occluded AVMs, to complete the obliteration, (c) Inoperable AVM; it is good to keep in mind, however, that AVM with a diameter greater than 3 cm cannot be treated with radiosurgery.

The administration of gamma rays can be given by a single dose of considerable intensity or it can be divided into several sessions, however requiring a higher overall dose than the single session. To predict specifically the result of the treatment, several parameters must be taken into consideration: the macroscopic distribution of the absorbed dose, the linear transfer of energy, the dose-rate in fractional administration, the intrinsic radiation vulnerability for the tissue involved, the concentration oxygen and other relevant radiobiological parameters.

CHAPTER III

FUNCTIONAL MAPPING

If the goal of treatment for AVMs localized near eloquent area is to achieve the best possible compromise between the need to not have residual part of the malformation and the need not to cause permanent neurological deficits, to achieve this goal it is necessary to accurately identify not only the AVM but also the eloquent nervous tissue (or, from a surgical point of view, the tissue whose resection would lead to a permanent neurological deficit).

Unfortunately, in identifying the eloquent areas, the anatomical data alone are not sufficient. Anatomical data are fairly reliable in identifying the precentral gyrus and the corresponding primary motor area,[64] but extremely unreliable as regards other areas: for example, areas responsible for the expressive function of language are often found beyond the anatomical limits of the frontal operculum, and the temporal linguistic areas are statistically at a distance from the temporal pole varying between 3 and 9 cm. To overcome the anatomical interindividual variability, individualized anatomical information can be obtained through neuroimaging methods, but this does not solve the problem of functional interindividual variability, even more marked than the previous one. To complicate the picture, in patients with slow-growing brain tumors the variability is further increased by phenomena of brain plasticity. Ultimately, interindividual variability implies that any surgical act in correspondence with the eloquent areas can lead to unpredictable neurological deficits. It is therefore necessary to use an individualized approach, "tailored" for each patient, to anatomically and functionally identify the eloquent areas in that single patient.[64,180]

The goal is to "map", with various methods, the patient's brain to create a functional map that allows you to save the eloquent areas during the resection surgery.

Numerous functional cartography methods have been introduced, which are divided into two large categories:

- Preoperative functional mapping (non-invasive or invasive)
- Intraoperative functional mapping.

FUNCTIONAL PREOPERATIVE MAPPING

The non-invasive preoperative methods, that is functional neuroimaging, allow to estimate the distribution and localization of the eloquent areas, their relationships with the tumor, the hemispheric motor and language dominance. These data are essential for:[64]

- Establish surgical indications, allowing an estimate of exclusion
- Plan the intervention (type of approach, resection margins)
- Select the appropriate surgical and anesthesiological technique
- Have a functional reference for postoperative assessments

3.1 Functional magnetic resonance

Functional magnetic resonance imaging (fMRI) is based on the correlation between neuronal activity and brain hemodynamics. Among the various existing fMRI methods, the most widespread is based on signal alterations induced by deoxyhemoglobin (blood oxygenation level dependent signal, BOLD). In practice, the execution of a certain task causes an increase in neuronal activity in the brain area responsible for this function, which in turn determines a local vascular response that is recognized by the fMRI. The fMRI is therefore an indirect measurement of brain activity, based on the so-called neurovascular coupling.[123,188]

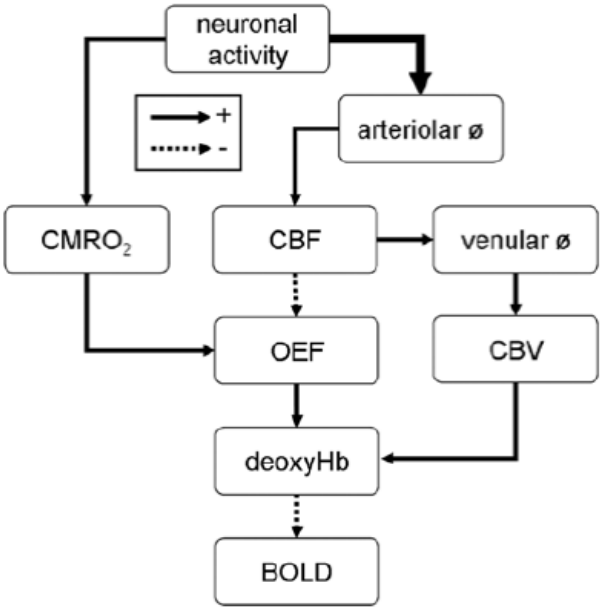

Fig.8 Generation of BOLD signal in the fMRI [188]

The collected data are visualized thanks to the fusion with an anatomical scan (usually a T1 sequence).[123] Spatial resolution is good (1-5 mm); however, temporal resolution is poor, since the hemodynamic response takes place several seconds after the neuronal response.[188]

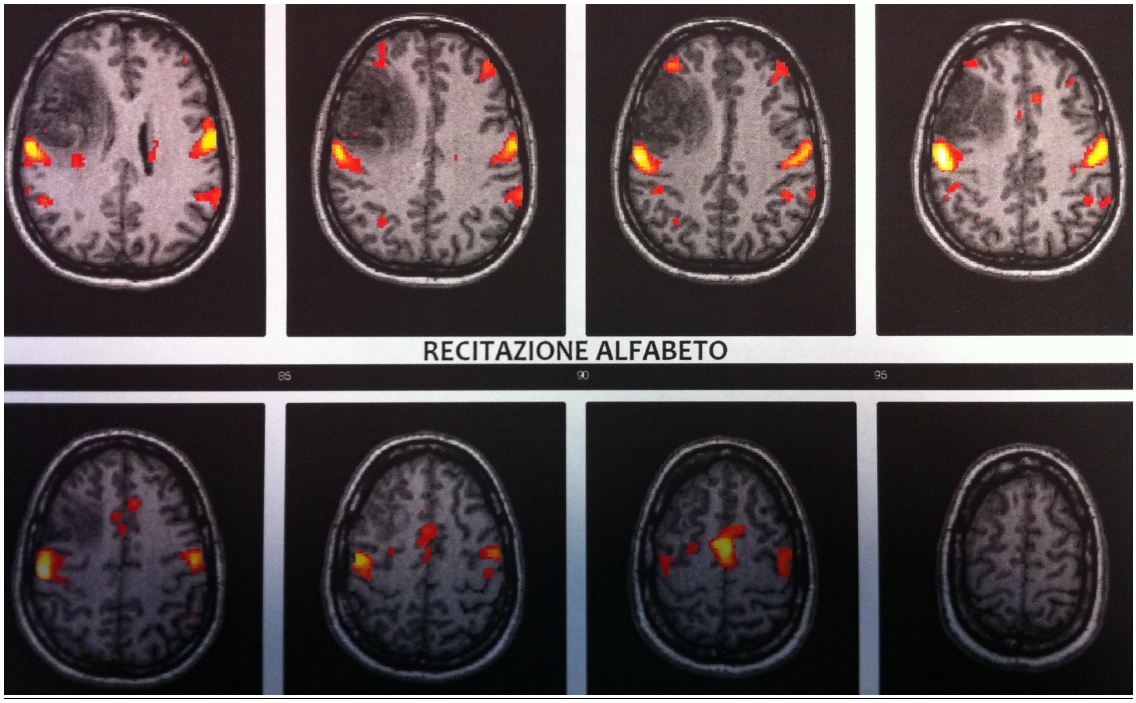

Fig.9 Example of fMRI

3.2 Diffusion tensor imaging and tractography

Diffusion tensor imaging (DTI) is a magnetic resonance technique based on the concept of anisotropic diffusion of water molecules in myelinated fibers (within the fibers the water molecules preferentially move along the direction of the axons). Fiber tracking (FT) uses DTI data to perform an anatomical three-dimensional reconstruction of the white matter beams. Such 3D reconstruction can be useful not only for preoperative planning, but also for intraoperative neuronavigation.[18,19] The tractography is an operator-dependent examination that requires the identification of a specific region of interest (ROI), in an area of white matter which represents an "obligatory passage" for the beam being reconstructed: starting from ROI a software reconstructs, following the data of the ITD, the entire course of the beam (for example the arched file, the anterior commissure, the fornix). If a bundle shares a certain ROI with other bundles, an approach based on two ROIs is used (for example in the case of the corticospinal tract, the lower longitudinal fasciculus, the lower fronto-occipital fasciculus). Finally, the

reconstructed beams are coupled to a morphological MR image (usually a FLAIR sequence) in order to view the relationships between the beams and the tumor.[19]

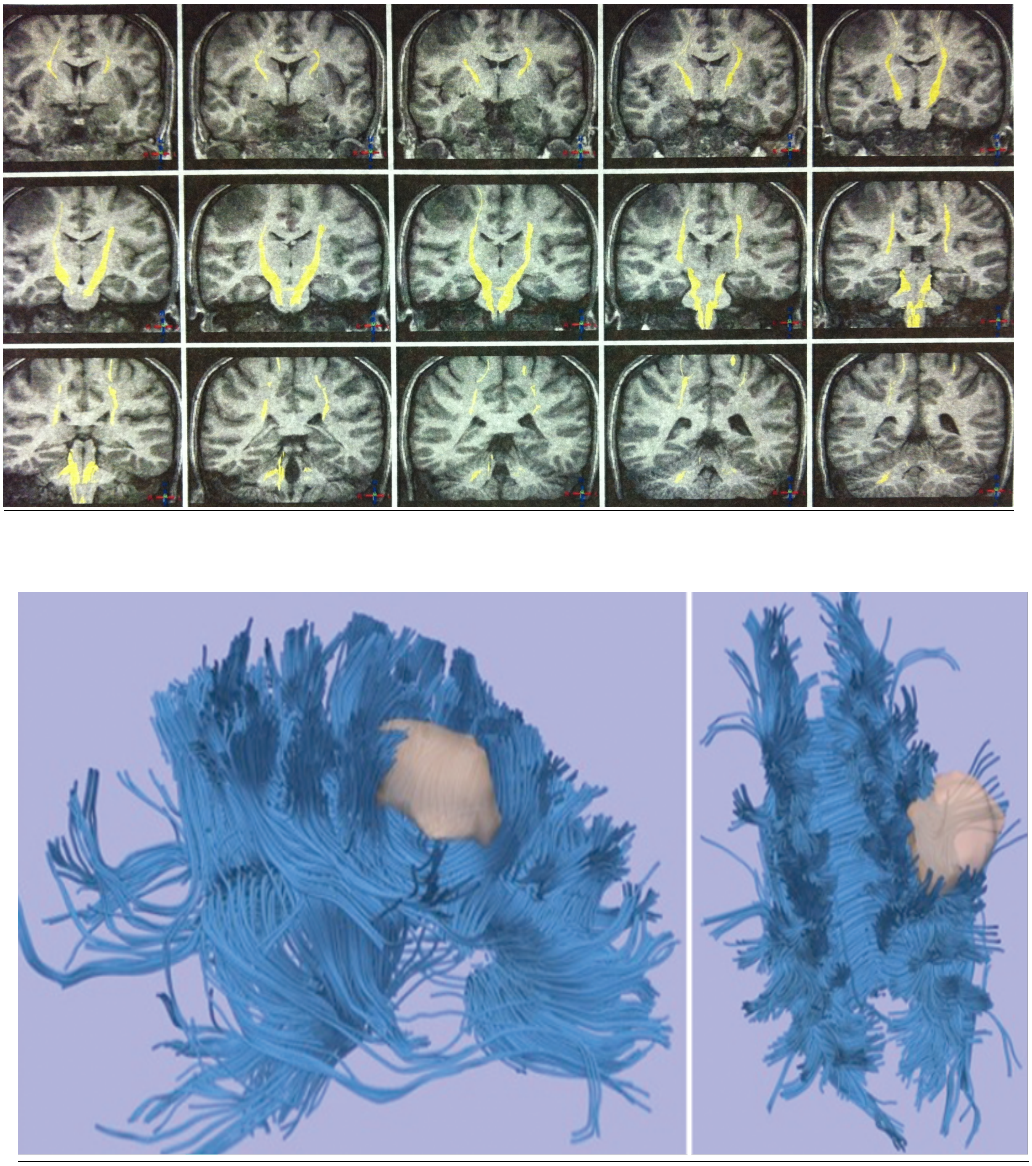

Fig. 10-11 Example of DTI

3.3 Functional neuroimaging: pitfalls

Beyond the obvious advantages, functional neuroimaging methods have some important disadvantages that make them very useful in preoperative planning but scarcely reliable if used as the only source of functional information:[18,62-64]

1. Relative reliability of fMRI: functional neuroimaging has a sensitivity of 71% for movement and 66% for language, which means that on average in almost a third of cases an eloquent area is not recognized as such (false negatives). This is mainly due to the so-called neurovascular decoupling (near the tumor there are hemodynamic alterations that cause a lower accuracy of the BOLD signal), which leads to an underestimation of the eloquent areas close to the tumor.

2. Inability by fMRI to distinguish essential eloquent areas (ie functional areas whose resection causes a permanent deficit) from accessory eloquent areas (ie redundant, and therefore compensable functional areas, whose resection can cause a transient deficit, but susceptible to compensation by other functional areas). In practice, the fMRI highlights all the areas involved in a given function rather than only those essential to this function: this is useful for scientific research purposes, but scarcely useful for the neurosurgeon, for whom it is vital to recognize strictly essential, non-compensable areas from redundant neuronal networks.

3. Relative reliability of the DTI-FT: fiber-tracking tends to underestimate the presence of white matter beams within or in the immediate vicinity of a tumor lesion (by modification of the anisotropy of water molecules). Furthermore, the DTI-FT does not allow to map the bundles of white matter from a functional point of view since it is a reconstruction based only on anatomical data. Furthermore, this reconstruction strictly depends on the biomathematic model used (different software can give different reconstructions of the same bundles).

Lately, the role of the fMRI and the DTI-FT should be to constitute a sort of preoperative planning, to be further refined with the intraoperative methods analyzed below.

3.4 Neuronavigation system

Neuronavigation allows the previously collected anatomical and functional data to be used during surgery. Morphological data (MRI) can be used, but of particular interest is the possibility of using intraoperatively the data obtained from preoperative functional neuroimaging (neuronavigation of fMRI and DTI-FT).[18] However, during the intervention, brain shift and deliquoration phenomena make neuronavigation progressively less accurate. This lower accuracy becomes particularly significant towards the end of the tumor removal process, in correspondence with the deep beams of white matter, consequently altering the reliability of the neuronavigation of DTI-FT.[18,19]

Brain shift can be reduced by performing very small craniotomies,[18] but this would interfere with correct intraoperative mapping (see below). Alternatively, there are some new methods that allow neuronavigation data to be updated in real time (integration with intraoperative ultrasound, use of intraoperative MRI).[19,63,64] At present, neuronavigation is particularly useful in planning craniotomy and in recognizing tumor margins before performing corticectomy (with the possible alternative, for the latter purpose, of intraoperative ultrasound). It is not considered fully reliable in the continuation of the intervention, in which it becomes an integration of currently gold standard methods such as direct electrical stimulation.

3.5 Invasive preoperative functional mapping

There is the possibility of performing an invasive intraoperative mapping, through the implantation of subdural electrode grids, similarly to what occurs in epilepsy surgery. The advantage is the possibility of an exhaustive mapping,

reproducible several times, and performed at the patient's bed, therefore in more physiological conditions than an intraoperative mapping, and without the time limits required by an awake surgery intervention. The disadvantages are the need for additional intervention, the lower accuracy (the electrodes are spaced 1 cm apart) and above all the execution of a mapping at the cortical but not subcortical level. [61-64,75]

3.6 Intraoperative Functional Mapping

At present the gold standard for the recognition of eloquent areas are invasive electrophysiological techniques.[63] Some brain functions, typically those related to the central region (primary motor and sensory areas), can be mapped using the potentials evoked under general anesthesia. The somatosensory evoked potentials (PESS) are induced by electrodes placed in correspondence with peripheral nerves and recorded at the level of the scalp or at the level of the exposed somatosensitive cortex. Motor evoked potentials (PEM) are induced by electrodes placed at the level of the exposed scalp or motor cortex and recorded at the peripheral level by electromyography with needle or surface electrodes. The accuracy, however, is not optimal (91-94%) and also the PEMs allow you to map simple movements but not complex movements, and limited to the monitored muscles. But above all, with the evoked potentials it is not possible to investigate cognitive functions. The mapping of these functions requires the active collaboration of the patient, who must perform tasks while the surgeon performs a direct electrical stimulation of the brain area investigated. All this inevitably requires a surgical procedure conducted under local anesthesia.[61-64] Ultimately, surgery for tumors located in eloquent areas provides mapping by direct electrical stimulation (DES) carried out under local anesthesia (awake surgery) as the gold standard. Tumors in motor areas can be approached both under general anesthesia, with the help of motor evoked potentials, and under local anesthesia with direct electrical stimulation (with the advantage of being able to examine not only simple movements but also complex movements).[63] The reasons that made DES in awake surgery the gold standard are essentially the following: The ability to map cognitive functions (especially language) The ability to distinguish essential eloquent areas from surgically irrelevant areas (i.e.

non-eloquent areas and eloquent areas but with accessory functions): this allows to identify only the structures that must be spared during the intervention The ability to functionally test subcortical connectivity (so DES is the only validated method) The execution of the mapping during surgery, in real time, without the need to refer to a mapping performed preoperatively**.**

Of all the functional mapping methods, DES in awake surgery is the one that allows you to save the eloquent areas more safely and therefore not to cause permanent deficits. The important fact is that this greater functional preservation does not limit surgical radicality.[64]

3.7 Direct electrical brain stimulation: principles and methodology

The use of direct brain electrical stimulation to perform intraoperative mapping of brain functions to save eloquent areas dates back to epilepsy surgery.[75] The technique was subsequently refined by Ojemann in the 1970s, with the introduction of a biphasic current and the optimization of intraoperative clinical tests.[63] In the 90s the technique was extended by Berger to the field of oncological neurosurgery and Duffau expanded its use to the preservation of the subcortical axonal pathways.[61-62] In the last decade the technique has spread all over the world. Stimulation depolarizes a focal brain area. The membrane potential of a resting neuron varies between -60 and -100 mV, due to a charge distribution maintained both by active mechanisms and by the diffusion of ions: negative charges on the internal side of the membrane and positive charges on the external side.

The principle of electrical stimulation is the ability to generate membrane excitability through an initial stage of passive modification of the local membrane potential at the cathode level (the negative electrode), as a result of which the internal side of the membrane becomes progressively less negative than to the external slope. If the depolarization of the membrane potential reaches a certain threshold, a second phase takes place in which the voltage-dependent Na + channels open with consequent positive ion entry and inversion of the membrane potential (+20, +30 mV). Subsequently, the inhibition of the entry of Na + ions and the exit of K + ions determine

the restoration of the steady state of the membrane potential. This rapid fluctuation of the membrane potential (which takes the name of action potential) when generated always maintains the same characteristics, regardless of the stimulation parameters, according to the "all or nothing" principle.[63,144]

The first requirement of electrical brain stimulation is that it is absolutely harmless to nerve tissue. Possible harmful effects could depend on an accumulation of negative charges at the cathode level or on an accumulation of metal ions at the anode level; however, this is avoided by using biphasic impulses (the second stimulus reverses the effects of the first). Another harmful effect could be due to a thermal effect, but is avoided by appropriately limiting the parameters of intensity of the stimulation.[61]

The second requirement of electrical brain stimulation is the reproducibility of its effects. In order for DES to be effective, and therefore its effects to be reproducible (i.e. they repeat with each stimulation), it is necessary to modulate the stimulation parameters according to the tissue examined: for example, effective stimulation on the white matter may not be on the gray matter, due to the different electrical impedance of the different fabrics (250 Ohm for sg, 500 Ohm for sb). Variations also occur according to the size of the nerve fibers and their degree of myelination, the presence of pathological tissue infiltrating the fibers, a possible post-critical state and the anesthesiological state of the patient (local or general anesthesia). Finally, rectangular impulses rather than sinusoidal impulses are used to remedy the phenomenon of accommodation in response to repeated impulses.[61,62]

Electrical stimulation always requires the presence of two electrodes, but is considered monopolar if only one of the two electrodes, usually the cathode, is located in contact with the target (the nerve tissue being investigated), while the reference electrode is located remotely. In this case, however, the entire volume of nerve tissue located along the current path is subject to stimulation: even an area distant from the exploration electrode but with a lower stimulation threshold could be stimulated before the target. To avoid these false positives, it is preferred to use a bipolar stimulation, in which both the cathode and the anode are "active" electrodes, ie localized in correspondence with the target. In this way only the small volume of tissue between the two electrodes is subject to stimulation, with a lower risk of current diffusion and, ultimately, greater precision. To avoid interference between the effects of two

electrodes so close (depolarization around the cathode and hyperpolarization around the anode), stimulation with biphasic impulses is used.[61,64]

The optimal parameters that can be used for direct electrical brain stimulation can be summarized as follows (Ojemann stimulation parameters):

- Bipolar ("fork") stimulator with a distance of 5 mm between the two electrodes Rectangular pulses Biphasic current
- Frequency: 60 Hz Intensity: usually 1.5-6 mA in awake surgery, 4-16 mA in general anesthesia
- Duration of each pulse: 1 ms Duration of each stimulation: 1-4 s

When applied to motor and sensory functions, electrical stimulation has a positive effect, i.e. it induces function (for example, it induces muscle contraction). On the contrary, when applied to higher functions such as complex movements or cognitive functions (language, calculation, spatial skills), stimulation has an inhibitory effect, i.e. it blocks the function. This is probably due to the propagation of a non-physiological electrical signal which interferes with the correct functioning of the target. In both cases, DES indicates to the surgeon that the area he is stimulating is an eloquent area: either by activating a simplified mode of operation (movement / sensation) or by mimicking the deficit that would result from surgical removal (language), creating a virtual and reversible lesion.[61,62,144]

Each positive site must be confirmed at least 3 times, preferably non-consecutive, during the cortical mapping procedure. The duration of the single stimulation is variable according to the function investigated. In the case of a motor or sensory mapping, the stimulator must remain in contact with the target for 1-2 seconds to induce positive responses. In the case of a mapping of cognitive functions, for example language, the duration of stimulation must reach 3-4 seconds in order to induce inhibitory responses (identifiable by the examiner as speech arrest or paraphasias).[61-64,144] An adverse effect of DES is the possibility of generating epileptic seizures during cortical mapping (with a 5-20% risk). This risk can be reduced by appropriately limiting the stimulation parameters (maximum intensity of 6 mA under local anesthesia and 16-18 mA under general anesthesia). In addition, there are physical methods to combat intraoperative crises, for example cortical irrigation with cold lactated Ringer, which

allows a resolution of the crisis in 10-15 seconds (thanks to the reduction of brain metabolism and electrical diffusion induced by hypothermia). Antiepileptic drugs should be used only in case of ineffectiveness of the previous technique, because they interact with the mapping.[17,61-64,185]

3.8 Data interpretation: recognition of functional areas

The simple electrical stimulation of a functional area does not lead to any useful result if the effects of this stimulation are not recognized through specific tasks performed by the patient. This recognition occurs on a clinical level. Basically, with each stimulation the surgeon has to answer the following question: "During the stimulation did I cause interference on the function of the stimulated area?". If there has been an effect, it means that an eloquent and essential area has been identified for this function. If there has been no effect, it means that either the area is not eloquent, or the stimulation has not been technically adequate, or the effects have not been recognized from a clinical point of view.

The simplest function to investigate is the motor function. In this case, the active participation of the patient is not necessary (so much so that DES can also be performed under general anesthesia with the help of motor evoked potentials). Clinical data are collected simply by observing the evoked muscle contractions, of the clonic (area 4) or tonic (area 6) type. To refine the collection of data, a continuous electromyographic recording can help. Similarly, in the somatosensitive area the patient can be awake, and therefore describe the location and characteristics of perceived dysaesthesia, or alternatively he can be sedated, and such information collected using the somatosensitive evoked potentials.[19,75]

More complex is the case of mapping in the associative motor areas, where stimulation has no direct positive effect, and instead the negative effects must be assessed: the patient must necessarily be awake and collaborative because he must perform regular and repetitive movements, and the examiner assesses the changes in motility induced by DES (slowdowns, reduction in amplitude or precision, interruption of movements).[61-64]

Other functions investigable through DES are the visual function (phosphenes or

campimetric deficits), auditory-vestibular (dizziness) and numerous cognitive functions such as language, reading, calculation, memory.[17-19]

Language mapping, compulsorily conducted when the patient is awake, usually starts with a counting test, which allows to recognize articulatory changes (slowing, dysarthria, anarthria, speech arrest), possibly associated with facial movements or dysphonia or automatic swallowing. It then continues with a test of naming objects; in this case stimulation can induce a wide spectrum of alterations, depending on the functional network involved: articulatory alterations, anomie, phonemic paraphasias, semantic paraphasias, perseveration. Everything must be done both cortically and subcortically. Finally, further tests are performed based on the precise location of the lesion and the individual characteristics that emerged from the preoperative fMRI: reading, calculation, storage and so on.[18,19,24]

When a mapping of cognitive functions is required, the presence of a speech therapist and / or a neuropsychologist is necessary in order to correctly differentiate the evoked disorders, and therefore be able to use them as an anatomical-functional guide during the intervention. For example, Broca area stimulation aphasia must be differentiated from stimulation dysarthria of the adjacent motor area of the face; or, a phonological disorder due to stimulation of the upper longitudinal fasciculus must be differentiated from a semantic disorder related to the lower occipito-frontal fasciculus, different subcortical structures and with different anatomical distribution.[62,144]

The mapping must be conducted with methodological rigor and meticulously to avoid false positive and false negative results. A false positive can results in insufficient tumor removal. A false negative can lead to the onset of a permanent neurological deficit.[18]

Mapping must be performed on both cortical areas and subcortical connectivity. In fact, a lesion of a bundle of white matter causes a more serious deficit than a lesion of a cortical area, since it damages a large network formed by parallel axonal networks that interconnect cortical areas even very distant from each other.[63,75]

An entirely negative mapping is always a risk situation. When electrical stimulation does not reveal any positive area, it can mean that there are no eloquent areas in the surgical field, but it can also be due to errors of various kinds that lead to false negative

results (very risky situation because it can lead to resection of functional areas with consequent even serious postoperative deficits):

• Technical malfunction of the stimulation system
• Incorrect stimulation parameters
• Unsuitable clinical tests
• Excessive sedation
• Craniotomic flap too small (which exposes the tumor but not the surrounding eloquent areas)
• Post-critical state following subclinical epileptic seizures

In practice, continuing a resection surgery after performing a mapping that has given only negative answers is, in fact, equivalent to the risk of performing the same surgery without mapping. The European School therefore prefers to perform very large craniotomies that expose the brain surface beyond the limits of the tumor so that it can perform a positive mapping.[17-19] The American School instead tends, lately, to consider "safe" even small craniotomies with mappings based exclusively on negative areas.[61-64]

The identification of a positive area does not exclude the presence of other positive areas. The mapping must always be completed in a systematic way and must not be interrupted at the first positive area identified, to avoid neglecting and considering negative areas that instead have a functional meaning, sometimes redundant but sometimes essential.[64]

Properly conducted surgery may also be associated with transient postoperative neurological deficits. These very frequent deficits appear in the hours following the intervention and completely regress over days / weeks. Therefore, in order to correctly evaluate the outcome of an intervention in awake surgery from a clinical point of view, it is necessary to wait for the recovery of these transitory deficits (usually a follow-up visit is scheduled 3 months after the intervention).[144]

Table I : **Check list for intraoperative electrical stimulation**.

- **Stimulation Parameters :**
  . rectangular pulses, biphasic current
  . frequencies from 50 Hz to 60 Hz
  . intensities of between 1 and 18 mA (local anesthesia) or of between 4 and 18 mA (general anesthesia)
  . progressive increase of intensities by step of 0,5 on generator display (that is to say from 1 to 1 mA)
  . stimulation duration: 1 second (sensori-motor), 4 seconds (cognitive functions)

Be careful: impedance is increased with child; impedance can vary in the immediate neighborhood and at a distance of the tumor; impedance can dicrease after excision of the lesion.

- **Practical stimulation methods:**
  . stimulate the whole of the exposed cortical area, every 5 mm^2 (because of 5 mm probe spacing)
  . Stimulate every site at least 3 times.
  . never stimulate the same cortical area twice successively.
  . always carry out a checking test without stimulation between two stimulations
  . if cognitive task, always begin the stimulation before the presentation of the item
  . for sub-cortical mapping: raise the intensities by 2 mA, and repeat very regularly the stimulations
  . always keep surfaces to be stimulated barely wet
  . in the event of crisis: irrigate with cold serum; do not re-stimulate immediately afterwards.

Be careful: do not to content with only one eloquent site, but search the possible redundancies; a negative mapping does not protect, but sets the problem of the investigation reliability.

- **Environment :**
  . adapted anesthesia (Propofol + analgesic)
  . monitoring by at least two observers of the controlateral hemibody during mapping under general anaesthesia (upper and lower limbs ± face)
  . speech-therapist and/or a neuropsychologist, if mapping of cognitive functions
  .intra-operative adapted tasks (< 4 seconds), selected according with the lesional site, to the neuropsychological assessment, and preoperative NFI.

Fig.12 Summary for intraoperative electrical stimulation

CHAPTER IV

NEUROPSYCHOLOGICAL TESTS

Neuropsychological tests are specifically designed tasks used to measure a psychological function known to be linked to a particular brain structure or pathway[25]. Tests are used for research into brain function and in a clinical setting for the diagnosis of deficits. They usually involve the systematic administration of clearly defined procedures in a formal environment. Neuropsychological tests are typically administered to a single person working with an examiner in a quiet office environment, free from distractions. As such, it can be argued that neuropsychological tests at times offer an estimate of a person's peak level of cognitive performance. Neuropsychological tests are a core component of the process of conducting neuropsychological assessment, along with personal, interpersonal and contextual factors.

Most neuropsychological tests in current use are based on traditional psychometric theory. In this model, a person's raw score on a test is compared to a large general population normative sample, that should ideally be drawn from a comparable population to the person being examined. Normative studies frequently provide data stratified by age, level of education, and/or ethnicity, where such factors have been shown by research to affect performance on a particular test. This allows for a person's performance to be compared to a suitable control group, and thus provide a fair assessment of their current cognitive function.

According to Larry J. Seidman,[196] the analysis of the wide range of neuropsychological tests can be broken down into four categories. First is an analysis of overall performance, or how well people do from test to test along with how they perform in comparison to the average score. Second is left-right comparisons: how well a person performs on specific tasks that deal with the left and right side of the body. Third is pathognomic signs, or specific test results that directly relate to a distinct

disorder. Finally, the last category is differential patterns, which are strange test scores that are typical for specific diseases or types of damage.

4.1 Categories

Most forms of cognition actually involve multiple cognitive functions working in unison, however tests can be organised into broad categories based on the cognitive function which they predominantly assess. Some tests appear under multiple headings as different versions and aspects of tests can be used to assess different functions.[13]

- Rey Auditory Verbal Learning Test used for long term memory and rievocation of event
- Forward and backward sopan verbal
- Rey's Figure (used for visual long term memory)
- Short-story recall (verbal long term memory)

4.1.1 Language

Language functions include speech, reading and writing, all of which can be selectively impaired.

- Boston Naming Test
- Word fluency phonemic
- Word fluency semantic
- Battery for the assessment of semantic memory disorders
- Picture naming battery verbs
- Cagi test

4.1.2. Executive function

Executive functions is an umbrella term for a various cognitive processes and sub-processes.[14] The executive functions include: problem solving, planning,

organizational skills, selective attention, inhibitory control and some aspects of short term memory.[13,25]

- Stroop task
- Tower of London Test
- Trail-Making Test (TMT) A & B
- Wisconsin Card Sorting Test (WCST)
- Symbol Digit Modalities Test
- Matrix test performance
- Weigl's sorting test
- Raven's progressive matrices

4.1.3 Visuospatial function

Neuropsychological tests of visuospatial function should cover the areas of visual perception, visual construction and visual integration. Though not their only functions, these tasks are to a large degree carried out by areas of the parietal lobe.[38]

- Clock Test
- Rey-Osterrieth Complex Figure
- Judgement of line orientation benton

4.1.4 Dementia specific

Dementia testing is often done by way of testing the cognitive functions that are most often impaired by the disease e.g. memory, orientation, language and problem solving. Tests such as these are by no means conclusive of deficits, but may give a good indication as to the presence or severity of dementia. [12]

- MMSE Mini Mental state Examination
- MOCA Montreal Cognitive Assessment

The most beneficial factor of neuropsychological assessment is that it provides an accurate diagnosis of the disorder for the patient when it is unclear to the psychologist what exactly he/she has. This allows for accurate treatment later on in the process because treatment is driven by the exact symptoms of the disorder and how a specific patient may react to different treatments. The assessment allows the psychologist and patient to understand the severity of the deficit and to allow better decision-making by both parties.[67] It is also helpful in understanding deteriorating diseases because the patient can be assessed multiple times to see how the disorder is progressing.

All patients are evaluated by anxiety (Zung scale) and depression (Beck scale and Zung scale), both of these scales are self-administrated. [67]

Personality tests, also called typical performance tests or non-cognitive tests, are measurement tools that aim to define the personality profile of the subject who undergoes it. These tests can measure only one aspect of the personality ("monophasic" tests) or multiple dimensions simultaneously ("multiphasic" tests). Usually the degree of reliability and validity of these tools is established through standardized assessment techniques and is indicated in the test manual itself.

Personality tests are usually divided into two large groups: "objective psychological tests" and "projective psychological tests". [209]

4.1.5 Personality Goals Test

The most well-known objective tests are mostly of US origin. They are also known as structured tests, as they are characterized by the fact that structured and unique stimuli are presented to the subject. The stimulus consists of single-answer, multiple-answer questions or, more frequently, the subject must indicate his / her degree of adhesion according to a gradation in Likert scale.[38] The objectivity of the test consists in the fact that the assignment of scores (marking or scoring) is rigidly established in the manual. The interpretation of the results, however, requires knowledge of the psychological dynamics and the theory behind the test, so the preparation of the report

requires skill and still contains a margin of arbitrariness. These - indicated in alphabetical order of acronym - are the best known and used in clinical practice:

- CBA: Cognitive Behavioural Assessment
- MCMI-III: Millon Clinical Multiaxial Inventory
- MMPI: Minnesota Multiphasic Personality Inventory

Projective tests aim to capture the subject's spontaneous processes. While objective tests measure the subject's deviation from the average, projective tests explore the individual's psychic experience. The subject is subjected to ambiguous stimulus situations (unstructured or partially structured) to which he responds according to his personal psychological meaning. Projective tests, therefore, allow us to indirectly delineate the structural characteristics of the psychic life and the cognitive and affective dynamics of the subject.[38]

4.2 Equivalent score

The method of non-parametric correction of the Equivalent Score (ES) was devised by Capitani and colleagues[30] in the context of an Italian multicentre study on the calibration of neuropsychological tests (Spinnler and Tognoni, 1987)[209], still today a cornerstone for neuropsychological evaluation (Italian standardization and calibration of neuropsychological tests: Italian group for the neuropsychological study of aging "). For the first time in Italy a collection of neuropsychological tests was published, capable of examining almost the entire horizon of cognitive functions and of making a calibration on a single national sample of large dimensions (321 subjects aged 40 and over) aimed at the diagnosis of some neurological diseases related to aging.

This methodology makes it possible to establish the position of the subject under examination with respect to normal subjects, net of the influence of variables related to sex, age and schooling. Specifically, the Italian neuropsychological tests constructed according to the described methodology use - after the correction of the raw score for sex, age and schooling - a system of scores on an ordinal scale, called Equivalent Scores, ranging from 0 to 4, corresponding to as many segments distribution:

Depending on the test and starting from the basic demographic variables (sex, age and education), the raw score (RS) obtained by the subject under examination corrects or adjusts (adds or not a corresponding value present in the calibration article in Score Correct - SC) and subsequently converts to the corresponding Equivalent Score (ES). The latter is finally classified on a 5-level scale:

- ES = 0 Deficit comprising performances that are placed in the lower "tail" of the distribution, below the 5th percentile, with a probability of 95% (ie with a known risk of error of 5%).

- ES = 1 Borderline / at the limits of the norm including the performances that are placed between the 5th percentile and the 20th percentile.

- ES = 2-3 Medium-low including the performances that are placed in the central part of the distribution, ie between the 20th and 50th percentile.

- ES = 4 Middle-upper comprising the performances that are placed in the upper half of the distribution, that is above the median, beyond the 50th percentile.

To conclude, the following points should be emphasized:

• the concept of "normality" is strictly statistical, therefore it does not describe how 'good' the subject is at a task;

• the judgment of normality is inferential, it indicates the position of the subject within its reference population and the judgment is burdened by a known risk of statistical error.

• performance in the region corresponding to the worst 5% of the population or below is considered 'non-normal'.

CHAPTER V

INTRAOPERATIVE ULTRASOUND [39]

5.1 Fundamentals of ultrasound

The chapter sets out the fundamental concepts and operating principles at the basis of the ultrasound scan, capable of detecting tissues of different densities in the region examined. The purpose of this discussion is not to provide a complete and exhaustive picture of the topic, but rather an attempt to contextualize some notions which will then prove to be fundamental for the understanding of the clinical study set out in this thesis work.

5.2 Elements of acoustic physics

Sound represents a vibration of a mechanical nature that propagates in a physical medium, more or less elastic, in the form of compression and rarefaction waves. Sound is therefore a form of mechanical energy in that it determines a movement of molecules and particles in a medium by doing work. The motion of the particles is local around their equilibrium point: the commonly understood wave is only the perceived effect of local displacements. The movement of the particles can be parallel or orthogonal to the wave propagation direction. In the first case there will be the production of longitudinal waves (P-waves) while in the second case of transverse waves (Shear waves). Finally, it should be noted that sound waves require a physical support medium (air, water, human tissues), thus distinguishing themselves from other forms of wave energy such as electromagnetic radiation, which can also propagate in a vacuum.

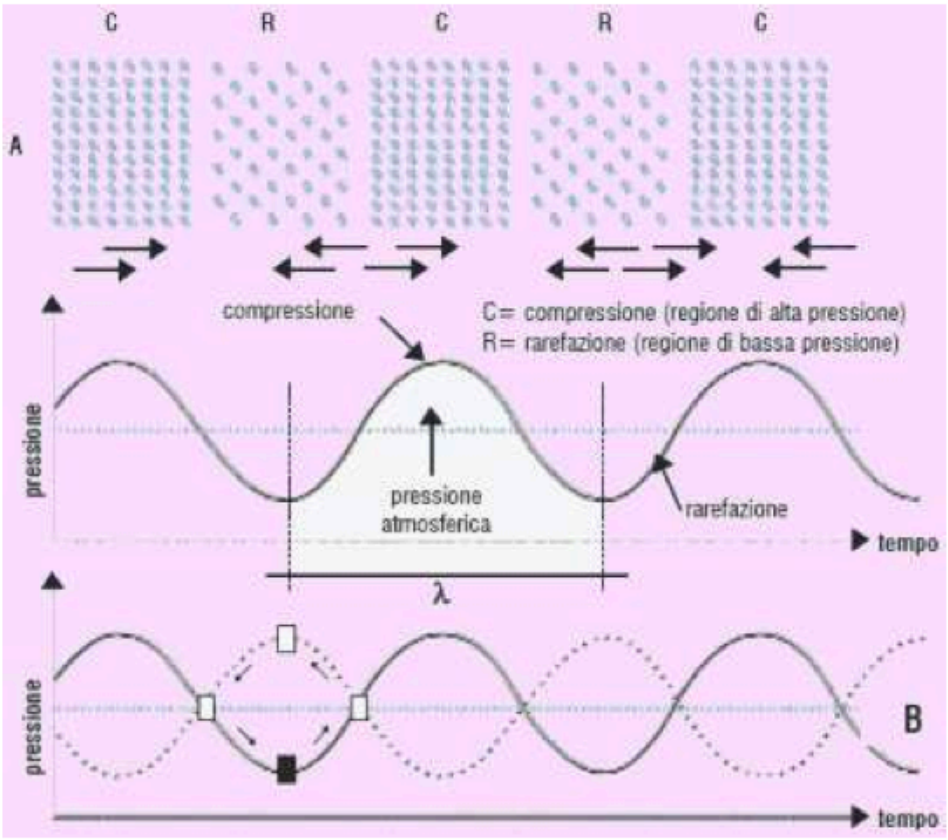

Fig. 13: Elements of acoustic physics

Listed below are some fundamental quantities that characterize sound in general.

- Frequency (v). Number of oscillations performed in the unit of time. Unit of measurement: hertz (Hz), corresponding to one cycle per second.
- Period (T). Duration of the complete oscillation. Unit of measure: seconds (s). The period is also the inverse of the frequency (T = 1 / v).
- Wavelength (l). Space covered by a complete swing in the time interval of a period. Unit of measure: meters (m).
- Propagation speed (V). Speed with which the wave propagates in the middle. Unit of measurement: meters per second (m / s). The propagation speed is a function of the density and compressibility of the medium under examination. The magnitude can be expressed as: V = l / T = l * v
- Intensity (I). Ratio between the power carried by the wave and the surface on which it affects. Unit of measure: (W / m2). The intensity is directly

proportional to the maximum displacement of the molecules with respect to the rest position. The frequencies audible to the human ear vary from a minimum of 16-20 Hz to a maximum of about 17Khz. Ultrasound corresponds to waves whose frequency is greater than 20 Khz. In ultrasound waves belonging to this category are used, usually varying in this category, usually varying between 1.5 and 15 Mhz.

The acoustic impedance (Z) represents a property of the medium that strongly conditions the speed of propagation of sound in general and consequently also of ultrasound used. It is defined as: Z = V * p where V is the propagation speed of the medium and p the density of the material, expressed in Kg / m3. Z is therefore expressed in kg / m2 * s.

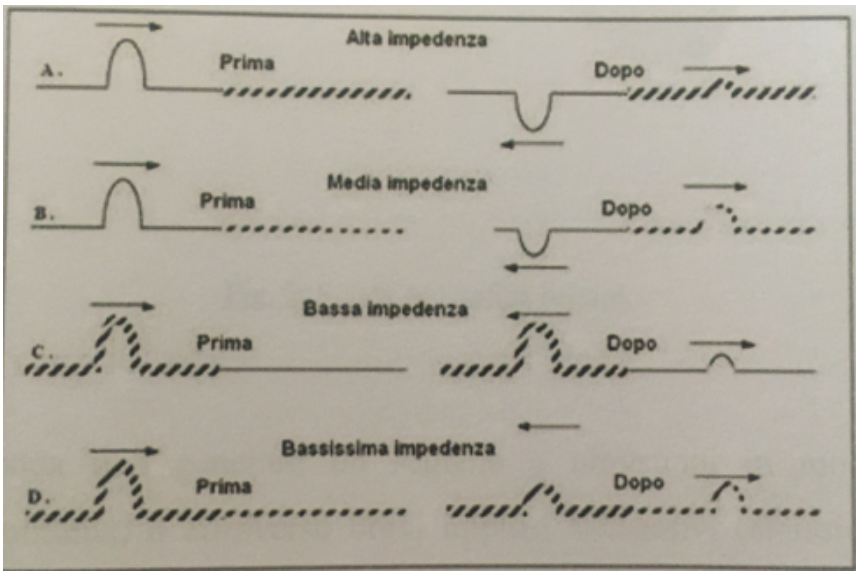

Fig.14: Variations of the sound wave to the limit of the acoustic impedance

5.3 Foundamental structure of an ultrasound system

Ultrasound equipment consists of three basic elements: the probe or transducer, the processing system and the monitor. The probe is the element in direct contact with

the patient and is used to generate or receive the ultrasonic signal. Specifically, the alternating mains current (50 Hz) is converted into ultrasound by piezoelectric effect.

Fig. 15 Ultra sound linear probe

The probe can generate an ultrasound signal continuously (continuous emission) or through short successive pulses (pulsed emission). The pulsed emission represents the modern standard of almost all applications. In the rest of this thesis, implicit reference will be made to the latter operating mode. The essential components of the probe are: Piezoelectric crystals: elements that act as transducers between the electrical signal and the ultrasonic probe and vice versa. This property is known as piezoelectricity. A pressure exerted perpendicularly to the crystal generates a potential difference between the two faces. This phenomenon is known as a direct piezoelectric effect. In the same way, a difference in potential applied on the two opposite sides of the crystal generates a mechanical deformation. The phenomenon is called inverse piezoelectric effect. Damping layer: the normal operation of the pulsed emission ultrasound probe requires the piezoelectric crystals to emit pulses of very short duration. For this purpose, an electric pulse generator is used at the desired frequency for ultrasonic waves. Too short a duration of electrical impulses leads to an equivalent lack of response in the mechanical vibration of the crystal, leading to a loss in the axial resolution of the ultrasound, as the ultrasonic impulses do not have a well-defined profile. The damping

layer is then inserted behind the crystals to quickly dampen the vibration of the excited crystal. Coupling layer: a significant problem is the reflection of ultrasound in the interface between the skin and transducer due to the high difference in acoustic impedance (2.3), thus preventing the desired depth from being reached. The coupling layer acts as an impedance adapter and is therefore characterized by an intermediate impedance between that relating to the skin and the transducer. The central processing system comprises two distinct elements: the section dedicated to transmission and that relating to the reception and treatment of the signal. In the first case, the function performed is to create the desired wavefront by applying different delays to the signals that will energize the different crystals (beamforming). In reception, reverse synchronization must be applied before the processing phase. An internal clock regulates the entire dynamics of the delays. Processing includes the following activities: pre-amplification, gain compensation, demodulation, A / D conversion, storage and conversion to video signal. Finally, the monitor allows you to view the result of the processing in grayscale (ultrasound) or in color (ecoDoppler). In particular, for the ultrasound examination the image is in grayscale and the color codes the intensity of the echo received.

5.4 Genesis of the echo

In a typical ultrasound examination, the ultarsounds emitted by the probe pass through different types of tissue characterized by different densities and consequently different impedance. At the interface points between zones with different impedances, three fundamental phenomena occur:

- *Reflection*: a small part of the wave is reflected with the same incident angle and propagates in the direction of the wave is given by $R=E_r/E_i=[(Z_1-Z_2)/(Z_1+Z_2)]^2$ where Z^1 and Z^2 are the impedances relating to the two zones of different impedance. Z^1 is the impedance of the tissue closest to the probe. R = 1 indicates that the reflected energy is equal to the incident energy, i.e. that the wave is completely reflected. On the contrary, R = 0 indicates that the wave does not undergo reflection.

- *Transmission:* part of the wave is transmitted and continues its path through the fabric, but generally at a different angle than the incident angle. The transmission coefficient, defined as the ratio between transmitted energy and incident energy $t= E_t/E_i =4Z_1*Z_2 / (Z_1+Z_2)^2 = 0$ indicates that the wave does not undergo transmission. Infact, t=1 indicates that the transmission energy is egual to to the incident energy, i.e. that the wave is completely transmitted. On the contrary, t=0 indicates that the wave does not undergo transmission.
- *Refraction*: variation of the angle of the wave transmitted with respect to the incident wave, according to Snell's law.

The echo is represented by the reflected wave that reaches the probe as a consequence of the reflection phenomenon: In reality, due to the irregularity of the interfaces, the diffusion phenomenon also occurs, characterized by multiple reflected waves with angles different from those of incidence and low intensity. For the purpose of the diagnostic examination, only the reflected wave represents useful information as it can be detected by the probe. The echo signals received will be characterized by different intensity based on the phenomena described above. If the incident wave encounters an interface characterized by an important density variation, an intense echo signal will result which will give rise to a strong contrast in the final image. Each pixel of the final image is assigned a brightness value proportional to the intensity of the detected echo: intense echoes will be associated with the white color (hyperechoic area), intermediate echoes with the gray color (iso-hypoechoic area) while the absence of eco is coded in black (anechoic).

5.5 Spatial resolution of transducers

The ultrasound image is constructed using two pieces of information:

- The time of arrival of the echoes determines the depth of the source.
- The position of the echoes with respect to the axis determines the lateral position in space.

The spatial resolution of the probe is the minimum distance of two sources placed at close range for which it is possible to discriminate the echoes produced, and

therefore expressed in mm. This resolution is determined by the axial and lateral component. The axial resolution allows you to distinguish scatterers arranged along the ultrasound propagation axis. If insufficient, the echoes will overlap and it will be impossible to distinguish the arrival times, thus losing quality in the longitudinal dimension of the final image. Similarly, a poor lateral resolution does not allow to discriminate laterally aligned sources and consequently there will be a degradation in the transverse dimension of the image.

The maximum theoretical axial resolution is determined by the wavelength (l) and the number of pulse cycles or increase the frequency. The latter solution, however, implies a greater attenuation in the medium thus decreasing the depth of field (trade-off). The direct proportionality between signal frequency and attenuation is implicit in the Lambert-Beer law: $I_1/I_0=e^{-kl*1}$

The law considers the attenuation suffered by a wave when crossing a volume of thickness 1. This attenuation is given by the ratio between I_1, the intensity of the wave leaving the volume and I_0, the intensity of the incident wave. The constant k represents the absorption coefficient and is proportional to the wave frequency. The lateral resolution is inversely proportional to the width of the ultrasonic beam, which in turn is a function of the diameter of the crystals and the frequency of the pulses emitted. With the same diameter, by increasing the frequency, the beam width is reduced, while with the same frequency the beam width is inversely proportional to the diameter. The lateral resolution is also influenced by the natural divergence of the ultrasonic beam with increasing depth with respect to the position of the probe. The sound field generated by a transducer is, in fact, divided into two regions: the near field, or Fresnel area, and the far field, or Fraunhofer area.

The ultrasonic beam in the near field has a cylindrical shape and is characterized by the maximum lateral resolution. In the far field the beam tends to diverge assuming a funnel shape and the lateral resolution declines strongly. The length of the near field is equal to: $Z_0=d^2/4l$. Where *d* is the crystal diameter and l the wavelength. The angle between the focal axis and the divergent beam in the Fraunhofer area is given by: $\sin(q)=1.2*l/d$.

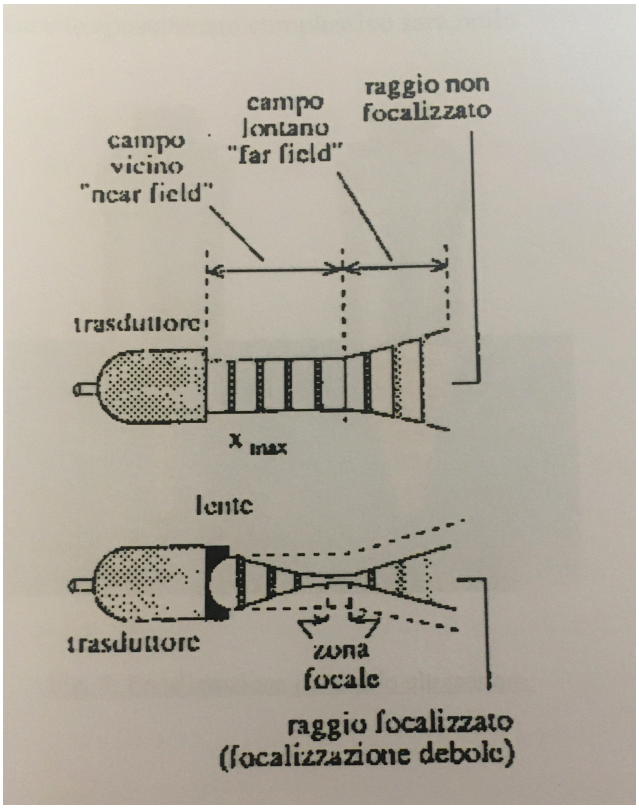

Fig.16: Concepts of near field and far field in ultrasound

5.6 Beam focusing

Sound waves generated by two different sources that meet in a region of space during propagation give rise to a phenomenon known as interference. If both waves at the meeting points are in the compression or rarefaction phase they create the so-called constructive interference. The resulting displacement will be given by the algebraic sum of the displacements relating to the two generating waves (double). On the contrary, if at the meeting point the first wave is in the compression phase and the second wave is in the rarefaction phase or vice versa a destructive interference is created, since the two waves are in phase opposition and the overall displacement will be zero.

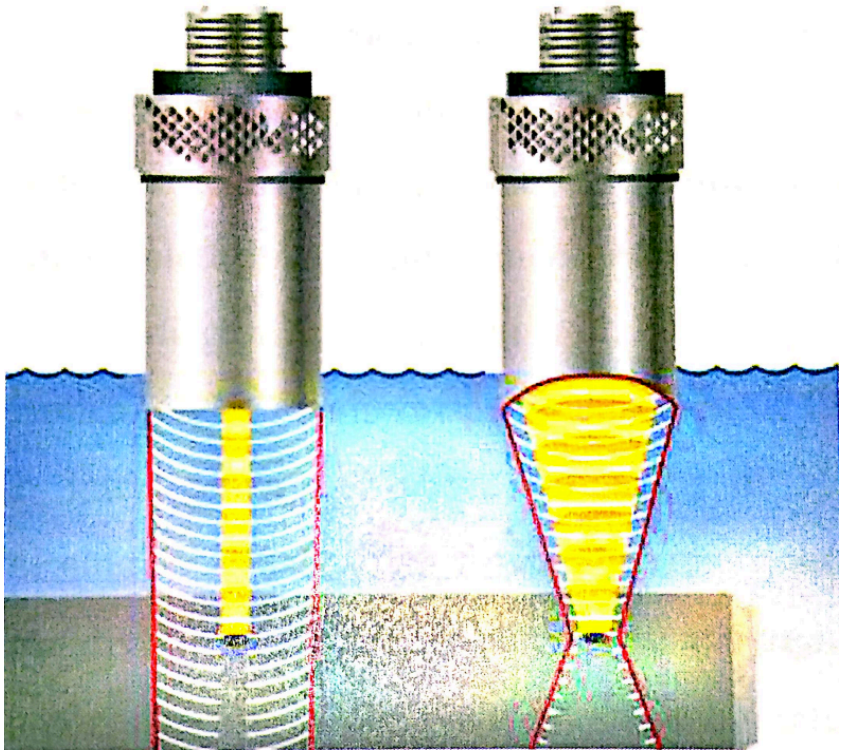

Fig.17: Focusing of the ultrasonic beam

In multi-element transducers, that is, consisting of a series of aligned piezoelectric elements, each crystal represents a single wavefront source obtained by constructive interference and according to the Huygens principle. In essence, each point of a wavefront can in turn be thought of as a source of an additional spherical wavefront.

The principle is of fundamental importance for understanding beam focusing techniques. The plane parallel to the surface of the transducer where the beam is characterized by the minimum diameter d and is called the focal plane. The point of maximum collimation is called fire and is characterized by the maximum acoustic intensity. The focal distance is the distance between the focal point and the transducer point, while the focal area is delimited by the points where the diameter of the beam is twice the diameter at the focus. The focus is on controlling the narrowing of the ultrasonic beam at the focal area in order to selectively increase the lateral resolution. This aspect is particularly relevant if one considers that in the far field the beam naturally tends to diverge, therefore focusing is necessary for depth investigations.

The focus can be achieved mechanically through an acoustic lens or electronically by controlling the delays of the transmitted impulses. The second solution is by far the most used as it allows for dynamic focusing. In electronic focusing, the focused beam is obtained through constructive interference (Huygens principle) of wave fronts generated by individual crystals. These sources do not emerge simultaneously but are generated with different delays, so as to produce by interference an overall concave rather than flat front. The electronic system that regulates the delays with which the crystals are excited is called beamformer. In addition to adjusting the focus in transmission, it has the task of decoding the echo in reception by carrying out phase compensation, as the signals received from the individual crystals will be characterized by small delays due to the different geometric distance traveled The principle is of fundamental importance for understanding beam focusing techniques. The plane parallel to the surface of the transducer where the beam is characterized by the minimum diameter d and is called the focal plane. The point of maximum collimation is called focus and is characterized by the maximum acoustic intensity. The focal distance is the distance between the focal point and the transducer point, while the focal area is delimited by the points where the diameter of the beam is twice the diameter at the focus. The focus is on controlling the narrowing of the ultrasonic beam at the focal area in order to selectively increase the lateral resolution. This aspect is particularly relevant if one considers that in the far field the beam naturally tends to diverge, therefore focusing is necessary for depth investigations.

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characterized by the maximum acoustic intensity. The focal distance is the distance between the focal point and the transducer point, while the focal area is delimited by the points where the diameter of the beam is twice the diameter at the focus. The focus is on controlling the narrowing of the Sulfur Sulfur hexafluoride is an inert, harmless gas, poorly soluble in aqueous solution. There are literature data relating to the use of this gas in the study of respiratory physiology and pneumatic retinopexy. The total quantity of sulfur hexafloride administered for diagnostic purposes is minimal (2 ml dose contains 16 microbubbles).

5.7 Display types

The most common ways of viewing in ultrasound are the following:

- *A-mode (Amplitude Modulation)*: represents the simplest mode, but at the same time poorer in information. The echo signal is displayed in a time / amplitude diagram, in which the time axis can be thought of as the line of an oscilloscope. The amplitude of the peaks generated is proportional to the intensity of the received echoes, while the temporal distance between the different peaks represents the spatial distance between the corresponding sources of the echoes. The association between the two sizes is possible thanks to the information on the speed of propagation of ultrasound in the tissues equal to 1540 m / s.

- *B-mode (Brighteness Modulation):* the information is represented through a two-dimensional image consisting of pixels, in which the brightness of each pixel is proportional to the intensity of the received echo. The coordinates of the images are directly mapped to the section of tissue analyzed by the ultrasound, in fact this area is often referred to as the image plane. The echo delay information is used to calculate the depth of the source and then determine the value of the coordinate image parallel to the axis of the probe in which to place the reflector. The B-mode technique can be thought of as a serial A-mode images performed in parallel, one for each lateral position (crystal), which scan a row of the final image.

- *TM-mode o M-mode (Time-Motion mode):* similarly to the B-mode technique, information is represented through a two-dimensional image. The

lateral spatial dimension is, however, replaced by the time diemnsion. It follows that the M-Mode provides for the acquisition of the echo signal only along a line of the scanning field parallel to the axis of the probe (depth), but allows you to monitor this information over time. The temporal resolution is generally high, therefore allowing a real-time acquisition. M-mode is also applied in the context of elastographic investigation.

5.8 Ultrasound contrast medium

Over the years, different types of ultrasound contrast have been developed, all of which however have a common denominator, the characteristic of being microbubbles of inert gas that reflected the incident sound wave. The contrast medium used today in ultrasound is SonoVue (Bracco).[34] It is marketed as a freeze-dried powder to be reconstituted immediately before use with physiological solution. The SonoVue must be reconstituted by injecting 5 ml of sodium chloride 9 mg / ml (0.9%) into the vial through the cap. The vial must then be shaken vigorously for 20 seconds and the desired dispersion volume can then be drawn into a syringe to be administered intravenously to the patient. The addition of sodium chloride 9 mg / ml (0.9%) in solution for injection to the lyophilized powder associated with strong stirring involves the production of micro-bubbles of sulfur hexafloride. The microbubbles have an average diameter of about 2.5 mm, 90% have a diameter of less than 6 mm and 99% have a diameter less than 11 mm. Every millimeter of SonoVue contains 8 ml of microbubbles. The interface between the sulfur hexafloride bubble and the aqueous medium acts as a reflector of the ultrasound wave. At the recommended clinical dose, SonoVue has been shown to significantly improve signal intensity for more than 2 minutes in B-mode echocardiography and from 3 to 8 minutes in Doppler diagnostics of large vessels and microcirculation.

Sulfur hexafluoride is an inert, harmless gas, poorly soluble in aqueous solution. There are literature data relating to the use of this gas in the study of respiratory physiology and pneumatic retinopexy. The total quantity of sulfur hexafloride administered for diagnostic purposes is minimal (in a 2 ml dose the microbubbles ctain 16 ml of gas).

Sulfur hexafluoride dissolves in the blood and is subsequently eliminated with the exhaled air. After intravenous administration of single doses of SonoVue of 0.03 and 0.3 ml / kg (about 1 and 10 times the maximum expected dose) to the healthy volunteer, sulfur hexafluoride was rapidly eliminated. The mean terminal half-life was 12 minutes (2 to 33 minutes). Over 80% of the administered dose of sulfur hexafluoride was detected with the exhaled air within 2 minutes after administration and almost 100% after 15 minutes. In patients with diffuse interstitial lung fibrosis, the percentage of the gas dose measured in the exhaled air reached 100% and the terminal half-life was similar to that recorded in healthy volunteers.

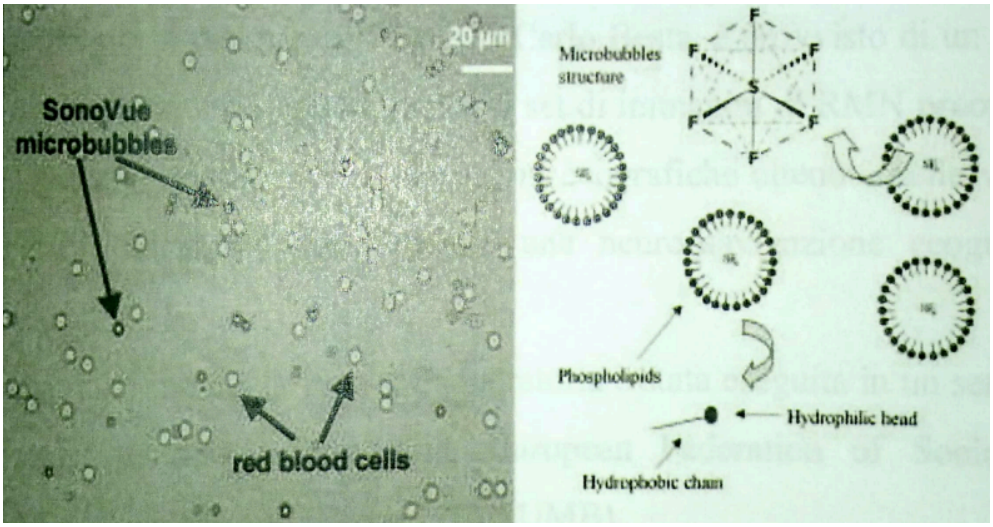


Fig. 18: Ultrasound contrast medium

CHAPTER VI

PROSPECTIVE STUDY

6.1 Methods and Materials

6.1.1 Population

This thesis is based on a prospective clinical study conducted in collaboration with Neurosurgery Division of Ospedale Maggiore della Carità di Novara and Neurosurgery Division of Città della Salute e della Scienza-University of Torino, involving patients with AVMs located near to eloquent area. All patients were treated with surgical approach, only one underwent to endovascular treatment previously.

6.1.2 Objects

This study is focused on the use of the intraoperative B-mode, color-doppler and contrast-enhanced ultrasound to evaluate if the analysis of blood flow can improve the surgical strategy of resection for AVMs located near to eloquent areas, making safer removal in terms of clinical outcome.

Also, to evaluate if and how the information obtained can help the neurosurgeon to extend the resection of AVMs located near eloquent areas in a safer manner in terms of outcome.

6.1.3 Clinical evaluation

The clinical evaluation was performed by the modified Rankin Score (mRs), both in the pre-treatment and during the follow-up.

This score has values ranging from grade 0 to grade 6, which include the absence of symptoms (grade 0) until death (grade 6):

- 0 – No symptoms at all.
- 1 – No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 – Sligth disability. Unable to carry out all prevoius activities, but able to look after own affairs without assistance
- 3 – Moderate disability. Required some help (e.g. with shopping/managing affairs) but able to walk without assistance
- 4 – Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 – Severe disability. Requires costant nursing care and attention, bedridden, incontinent.
- 6 - Dead

6.1.4 Diagnosis and follow-up

All patients underwent anatomical and functional preoperative studies as CT scan, MRI/MRA, functional MRI methods (fMRI, DTI) and neurophsicological tests. AVMs located near to motor, sensitive, visual or language areas were selected for cortical and subcortical mapping and for intraoperative echographic evaluation through the use of B-mode, color-doppler and contrast enhancement-US (CEUS). Finally, radiological (DSA, MRI) and clinical follow-up (using mRS) were performed at 6-months and at last follow up (37.3 months).

All patients underwent to surgical exclusion with preoperative acquisition of MRI images in order to use neuronavigation system. During surgical procedure, several ultrasound acquisitions were made, to document the initial status of the lesion, the surgical cavity and the presence of residue within the surgical site. The preoperative magnetic resonance images were merged with the images obtained in real time from the ultrasound probe.

The ultrasound used at Neurosurgery Division in A.O. Città della Salute e della Scienza was SonoWand (Neuraxon), while the one used at the Neurosurgery

Department of AOU Maggiore della Carità in Novara was BK Medical. Both are equipped with an integrated navigation software which uses the preoperative MRI image set as a basis to then superimpose the ultrasound images obtained in the various phases of the surgery, allowing real-time ultrasound neuronavigation.

The intraoperative ultrasound acquisition was performed in an off-label setting according to the provisions of the European Federation of Societies for ultrasound in Medicine and Biology (EFSUMB).

Patients who underwent neurosurgical removal of AVM were assessed using the latest generation ultrasound equipment equipped with Fusion Imaging software for neuronavigation (BK Medical US, Italy and BrainLab neuronavigation system, Germany).

All patients were carefully informed about the surgical procedure and the informed consent and permission of the Ethics Committee was obtained. An intraoperative qualitative analysis was performed by comparing with the ultrasound images in B-mode, echo-color Doppler and CEUS with the preoperative magnetic resonance imaging. Also, the enhancement of the malformation and residue were assessed.

For the ultrasound-guided neuronavigation, a latest generation system equipped with a multifrequency linear probe (3-11 MHz) was used. The ultrasound was equipped with software for virtual neuronavigation with Fusion Imaging, allowing real-time neuronavigation between pre-operative magnetic resonance imaging and ultrasound images obtained in real-time. A second generation SonoVue ultrasound contrast agent (Bracco, Italy) was used, consisting of microbubbles formed by an external lipid layer containing sulfur hexafluoride. This contrast medium was administered as an intravenous bolus (2,4 mL [5 mg / mL]). The intraoperative CEUS ultrasound scan was performed with the specific algorithm for identifying the microbubble resonance harmonic which allows a real-time angiosonography of the region in question.

6.2 Ultrasound acquisitions

The acquisitions of ultrasound images were repeated during the salient phases of the surgery, in order to document both the initial appearance of the lesion and the changes it undergoes during the procedure, up to the visualization of the surgical cavity and the residue of the malformation.

- Acquisition at the time of dural exposure (I and II phase): it is the first ultrasound acquisition that is performed. During the surgical procedure, after removal of the bone operculum, a linear ultrasound probe navigated from 3-11 MHz is placed, (Esaote / Sonowand). The probe is positioned over the intact brain dura mater in order to acquire a series of B-mode image scans. The lesion was then identified, together with the surrounding healthy parenchyma, on 2 axes and then measured; the acquisition was repeated with a low soundproofing power. The lesion was also localized with standard neuronavigation combined with the corresponding MRI scans. Upon further completion of phase I, the malformation was visualized after infusion of the contrast medium. The acquisition of ultrasound images with the contrast medium was performed with a linear probe, using a low soundproofing power (low mechanical index); the harmonic signals consequential passage of the microbubbles have been transduced with the Imaging Contast Tuned algorithm. The contrast agent was injected intravenously by the anesthesiologist as a bolus (2,4 mL [5 mg / mL]) followed by a bolus of saline solution (10 ml). Through this acquisition of images it is possible to identify early the AVM feeders arteries, the size of the nidus, the discharge veins and the relationships between the AVM and the surrounding parenchymal structures.

- Acquisition for the evaluation of the residue: this acquisition is carried out after the closure of the main feeders to AVM, in order to view any residues. In this way, the extent of any residue is assessed and its relationships with the surrounding structures are assessed: relationships that have changed significantly due to the detension of the parenchyma and the possible collapse of the walls of the surgical cavity. Furthermore, due to numerous artifacts, the B-mode ultrasound image often shows hyperechoic areas referable to blood clots or hyperreflection of the ultrasound beam. The acquisition in B-mode is followed by

that one in color-Doppler mode and finally with the contrast medium, so as to have a better definition of the residue.

- Final acquisition: it is carried out at the end of the surgical act of exeresis of the lesion, in order to check the surgical cavity obtained, verifying its relationship with the surrounding structures.

The various acquisitions of ultrasound images allow the neurosurgeon to have a global visual information of the AVM, of its relationships with the surrounding structures and of the modifications it undergoes during the intervention, with particular regard to the degree of residual vascularization. This last aspect is essential for a correct evaluation of the residue through the use of Doppler and ultrasound contrast medium.
The visualization of the AVM residue is first obtained with the basal B-mode only. During this acquisition we often witnessed the formation of image artifacts that did not allow a safe and unambiguous confirmation of the residual malformation.

In order to optimize the formation of the ultrasound image and to reduce the presence of artifacts, it is appropriate to soundproof the area to be investigated not directly from the surgical cavity, but by directing the ultrasound beam so that it passes through the surrounding healthy brain parenchyma. In this way, the formation of tissue echoes and reverberations is limited, obtaining a more easily interpretable image. In order to overcome the problems of visualization of the vascular residue in the B-mode only (Fig.19), ultrasound scans were performed using the Doppler mode (Fig.20) and after intravenous administration of the contrast medium. In this way it was possible to safely identify the malformation residue, also thanks to the comparison of the perfusion images with those of the malformation before the beginning of the surgical exclusion.

Subsequently, the residue was identified by localization with the navigation system coupled to the ultrasound device. Once correctly visualized, identified and localized, the surgical exclusion of the AVM residue was completed.

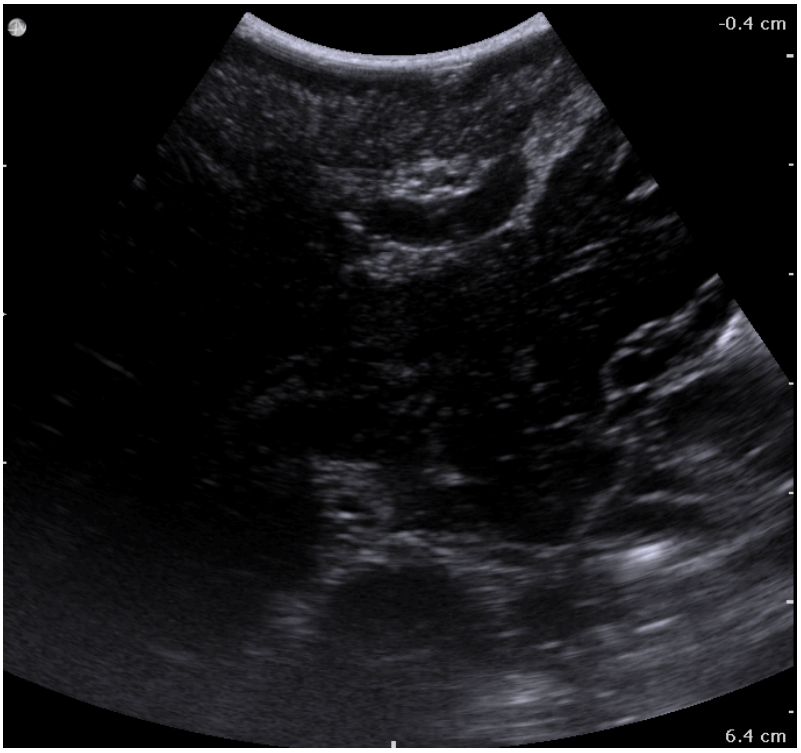


Fig. 19: B-mode ultrasound acquisition

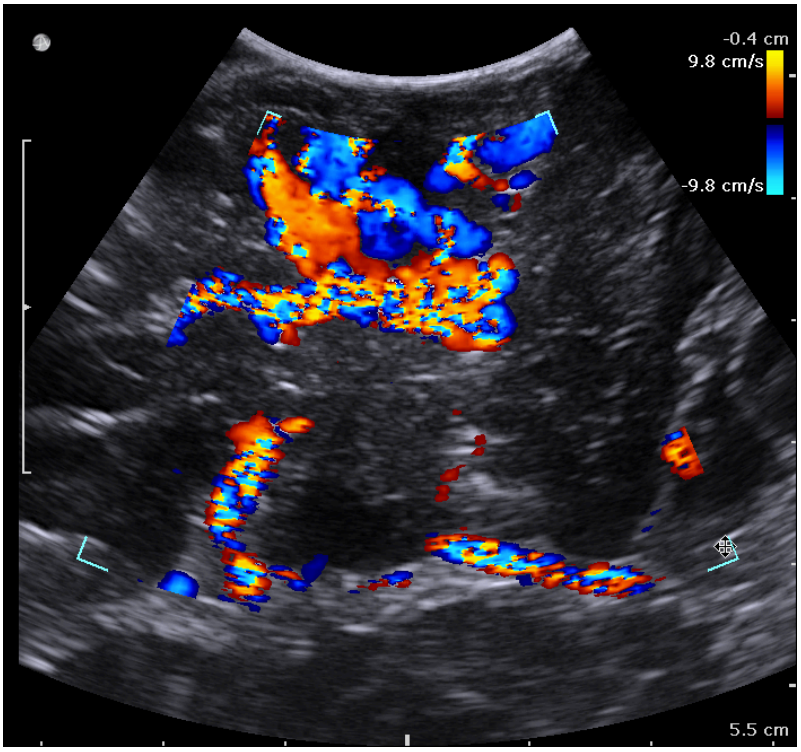


Fig. 20: Colordoppler ultrasound acquisition

CHAPTER VII

RESULTS AND DATA ANALYSIS

The prospective study has been conducted since November 2015 and August 2020. We recruited nineteen patients, eleven males and eight females with age range from 15 to 63 years (average: 45 years). The clinical signs and symptoms included seizures (n=6), neurological deficits (n=4), headache (n=1), and intracranial hemorrhage (n=9). Only one of them had undergone preoperative endovascular embolization. The Spetzler-Martin arteriovenous malformation (AVM) grading system indicated grade I for 3 patients, grade II for 10 patients and grade III for six patients (Tab.1 , see pp. 98). The informed consent was obtained from each patient. Preoperative planning used functional instrumental investigations such as functional MRI that provides information on the cortical representation of the eloquent area and DTI fiber tracking that allows us to view the bundles of connecting fibers between the eloquent cortical area and the white matter subcortical. Also, we have completed the preoperative planning through the 3D reconstruction using the neuronavigation system (BrainLab) that allows us to obtain a three-dimensional representation of the AVM inside the skull and to center the opening of the bone operculum exactly in the site of interest.

During the AVM exclusion, ultrasound images about the lesions were obtained at the beginning in B-mode. The ultrasound acquisitions were oriented in the three planes of the space, according to the sagittal, axial and coronal planes through the integrated navigation system with which the ultrasound equipment is equipped. This step is not of secondary importance, as it allows a more immediate understanding of the spatial relationships of the lesion according to the reference planes of navigation, known and easier to recognize by the neurosurgeon.

Case	Gender	Age	Location	Side	Symptoms	Spetzler	mRS pre-op	mRS 6m FU	mRS last FU	Eloquent area
1	F	23	Temporo-occipital	L	Bleeding	3	3	2	1	Vision
2	M	55	Occipital	L	Seizures	3	2	1	1	Vision
3	F	48	Temporal	L	Seizures	3	3	2	1	Language
4	M	35	Temporal	R	Seizures	2	2	2	1	Sensitive
5	M	40	Interhemispheric frontal	R	Seizures	2	2	1	0	Motor
6	M	45	Frontal	R	Motor impairment	2	3	2	1	Motor
7	M	56	Parieto-temporal	L	Dysphasia	1	2	2	0	Language
8	M	54	Parietal-occipital	L	Seizures	2	2	1	1	Language, attention, vision
9	F	50	Frontal	L	Motor impairment	3	3	3	2	Motor
10	F	63	Frontal	L	Bleeding	2	4	2	2	Motor
11	M	49	Temporal	R	Seizures	2	2	2	0	Language
12	F	42	Interhemispheric frontal	L	Bleeding	3	3	2	0	Motor
13	M	68	Fronto-temporal	L	Bleeding	2	4	3	1	Language
14	M	54	Parietal	L	Headache, paresthesia	3	1	1	1	Sensitive
15	M	35	Temporal-parietal	R	Bleeding	1	5	4	4	Vision, neglect, attention
16	M	15	Temporo-occipital	R	Bleeding	1	3	1	0	Memory, vision
17	F	37	Interhemispheric frontal	R	Bleeding	2	2	1	0	Motor
18	F	46	Temporal-parietal	R	Bleeding	2	3	2	0	Language
19	F	63	Parietal	R	Bleeding	2	5	2	0	Language

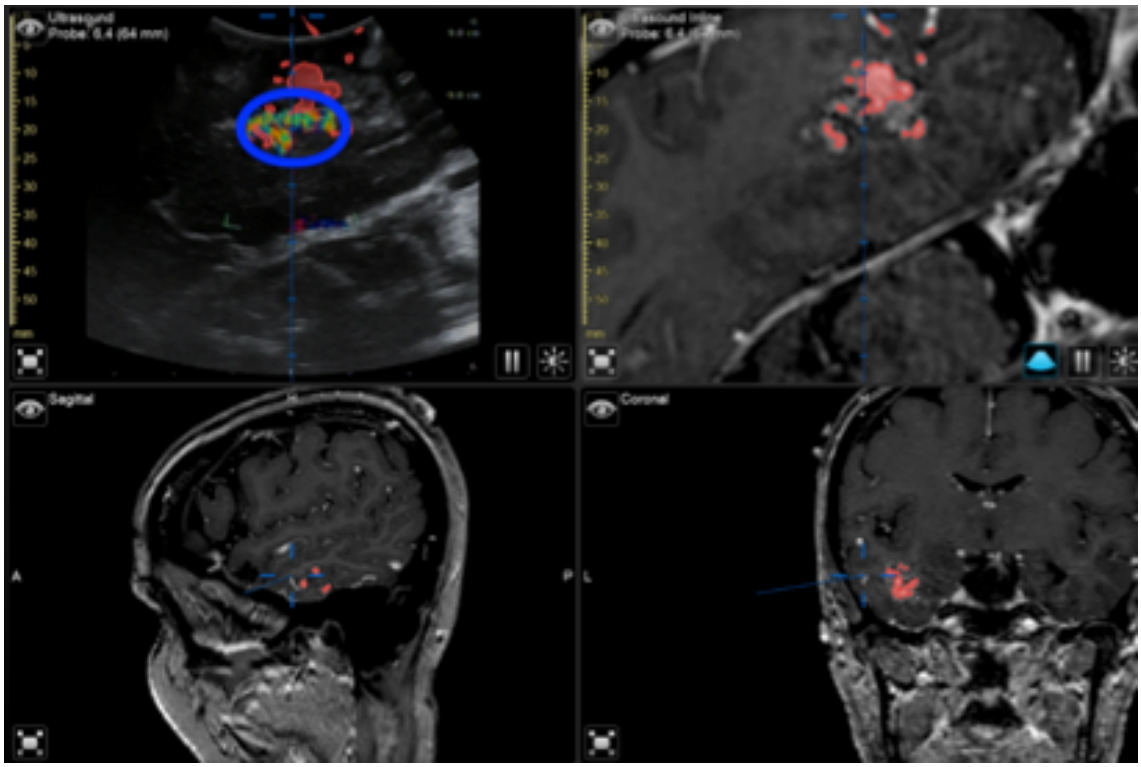
Table 1: Main clinical and AVM characters.

Moreover, neurophysiological monitoring of motor and sensory functions, obtained with evoked potentials (MEP, SEP) or cortical and subcortical stimulation, (directly stimulating the cerebral cortex and the bundles of fibers present in the subcortical white matter) allowed to obtain a mapping of the eloquent area of interest.

The spatial error of the navigation system was found to be less than 5 mm. This discrepancy between the ultrasound image and that of neuronavigation, based on preoperative imaging, has been corrected manually thanks to the possibility of performing an accurate overlayer between the two images. This corrects the trigonometric error of navigation by introducing a new three-dimensional reference (Fig. 21).

After the visualization of the lesion in B-mode, color Doppler US was used in order to evaluate, with better definition, the AVM boundaries from the surrounding parenchyma. This mode allowed neurosurgeon to accurately identify the nidus, the arterial supplies and the venous discharges (Fig. 22). This made possible to choose the safest access route to the AVM by distinguishing the healthy tissue from the vascular tissue and, above all, identifying the afferents that must be closed first and the drainage veins that must be preserved until the last surgical step.

A



B

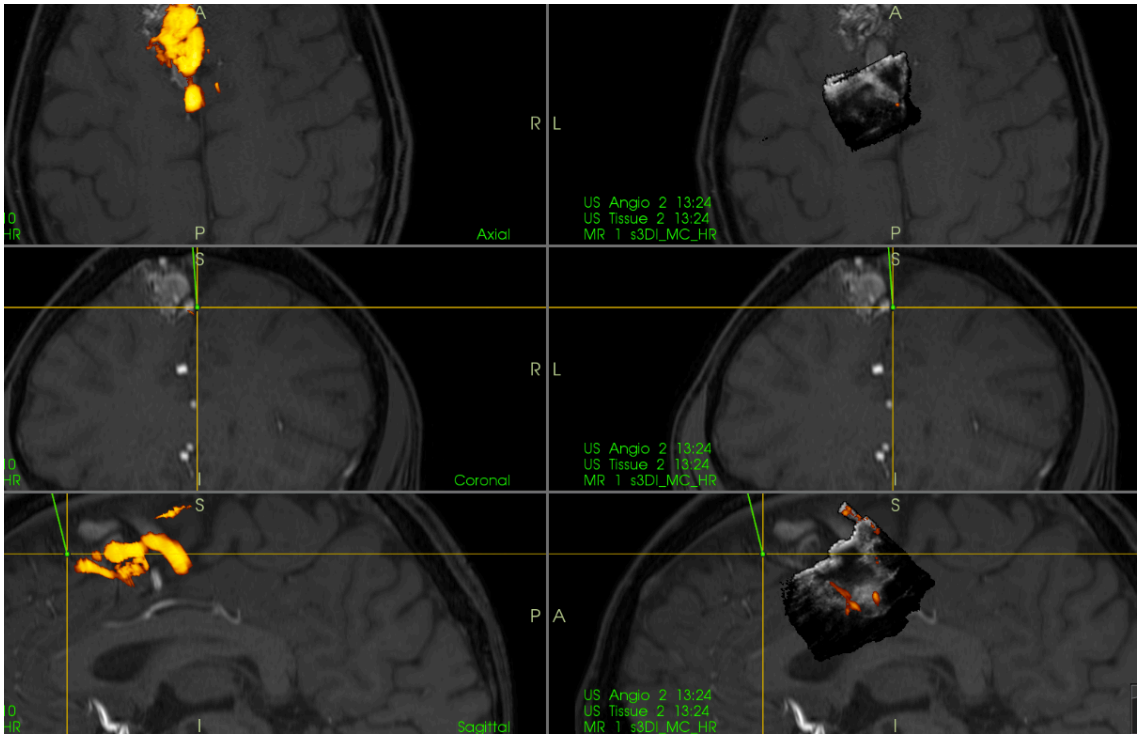
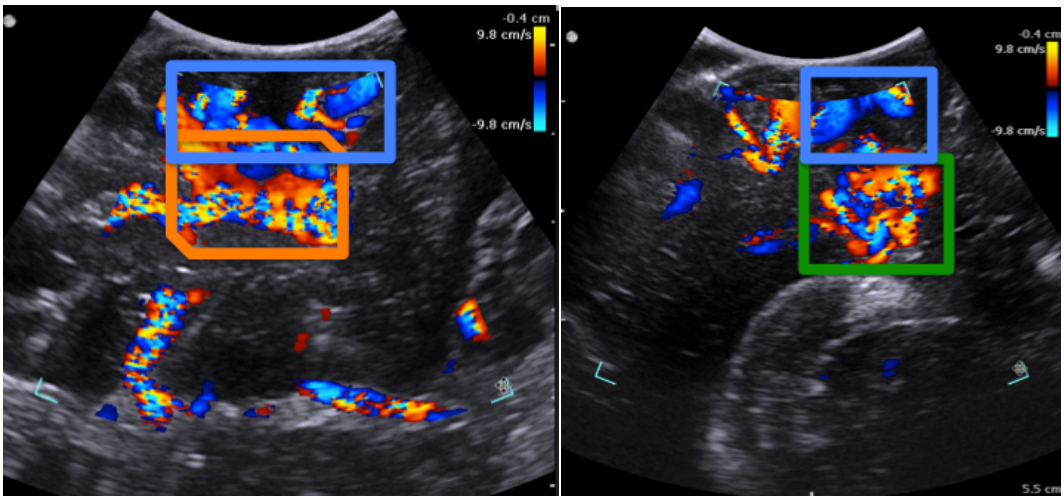
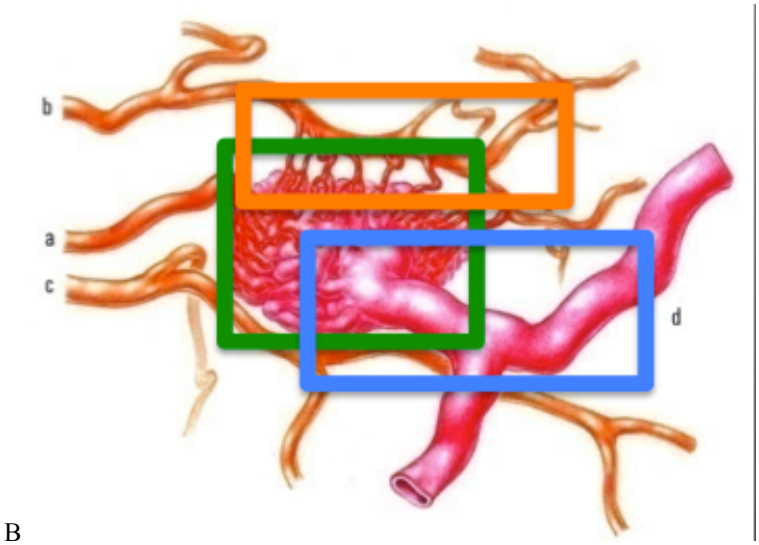


Fig. 21: Spatial orientation of ultrasound images. A. Esaote US probe and BrainLab neuronavigation system. B. Sonowand US probe. Fine tuning between US and preoperative MRI.

A





B

Fig.22: A-B Colordoppler ultrasound acquisition: visualization of the AVM and relationships with the surrounding parenchyma. In green the nidus, in red the arterial afferents and in blue the venous drainage.

Finally, we used intraoperative CEUS. SonoVue is a totally intravascular contrast medium, with no possibility of tissue diffusion. This implies its diffusion and a corresponding contrasting enrichment only in areas with the presence of vascular supply (Fig. 23). During surgery, it is possible step-by-step to check for any bleeding and the interruption of the vascular supply to the malformation, which makes it safer to exclude the AVM. Sometime, if the residual part is deafferentated, even if not removed from the surgical cavity, at the time of ultrasound control with the contrast medium, there will be no possibility of taking the contrast and therefore the residue could be hypoechoic. But, in these cases, the arterial blood flow persists in the venous drainage.

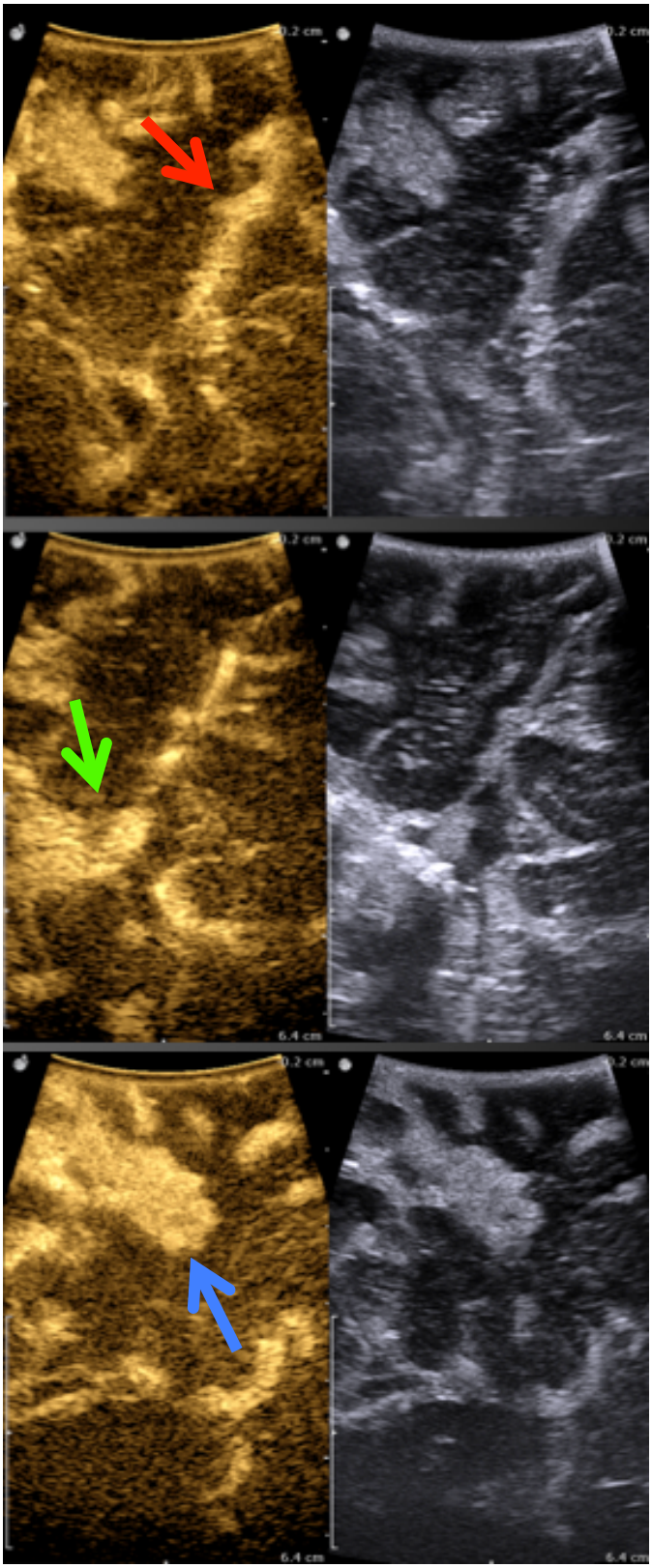


Fig.23: Ultrasound acquisition after administration of the contrast medium: visualization of arterial afferents (red arrow), nidus (green arrow) and venous drainage (blue arrow)

Below, it is showed an example of image in case of the AVM residue. This image was obtained from the scan performed during the deafferentation of the AVM in which we see the last arterials afferent to a minimum portion of the nidus (Fig.24) Subsequently, the exclusion of the residue and the hemostasis were completed; the final ultrasound acquisition of the surgical cavity showed the complete exclusion of the AVM with the preservation of the surrounding parenchyma (Fig.25).

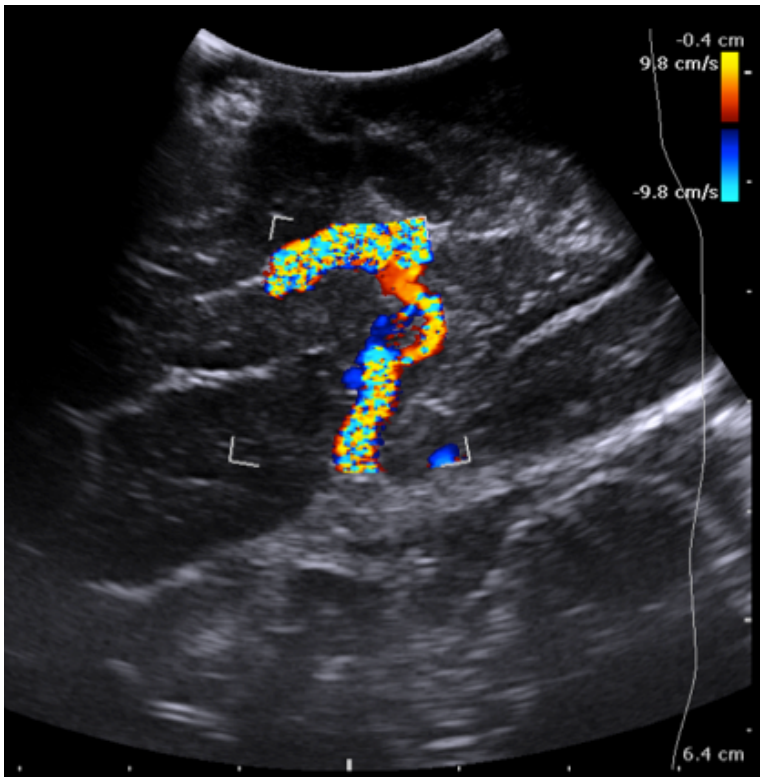


Fig: 24: Visualization of AVM residual

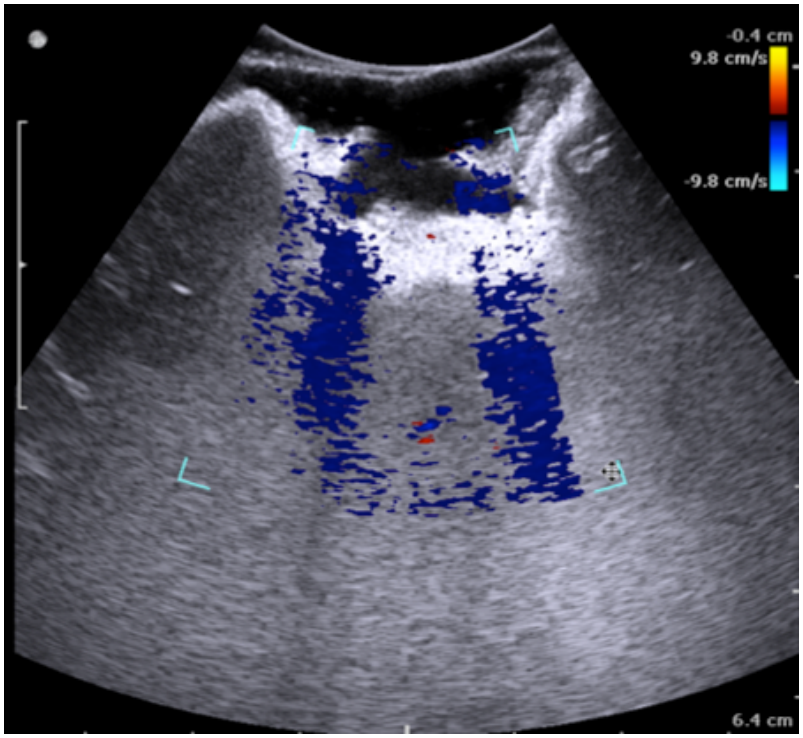


Fig. 25: Operating cavity after complete AVM exclusion

7.1 Complications and technical difficulties

There were no surgical complications. In one case, a previous endovascular treatment was necessary for reducing the high flow of the malformation. It was a patient with AVM grade III, according to Spletzler-Martin score, located in the left parietal lobe, very close to primary sensitive area, with multiple big venous ectasias (Case 14, see Tab.1, pag. 98). In this case, the liquid embolic material used for partial embolization (Onyx) gave artifacts and shadow effects, so much so, that it was not possible to clearly distinguish the arterial afference of the malformation. To stem the problem it was necessary to perform scans in multiple orientations and remove part of the embolizing material (Fig.26).

From the technical point of view, the size of the ultrasound probe plays a fundamental role because it is important for the neurosurgeon to be free to slid the probe on the parenchyma without having shadow cones due to the bony margins of the craniotomy. Finally, the major problem encountered was that the real-time perfusion

process could be observed in only two dimensions, whereas the AVM is a 3D lesion. Thus a single image contains a relatively small quantity of information.

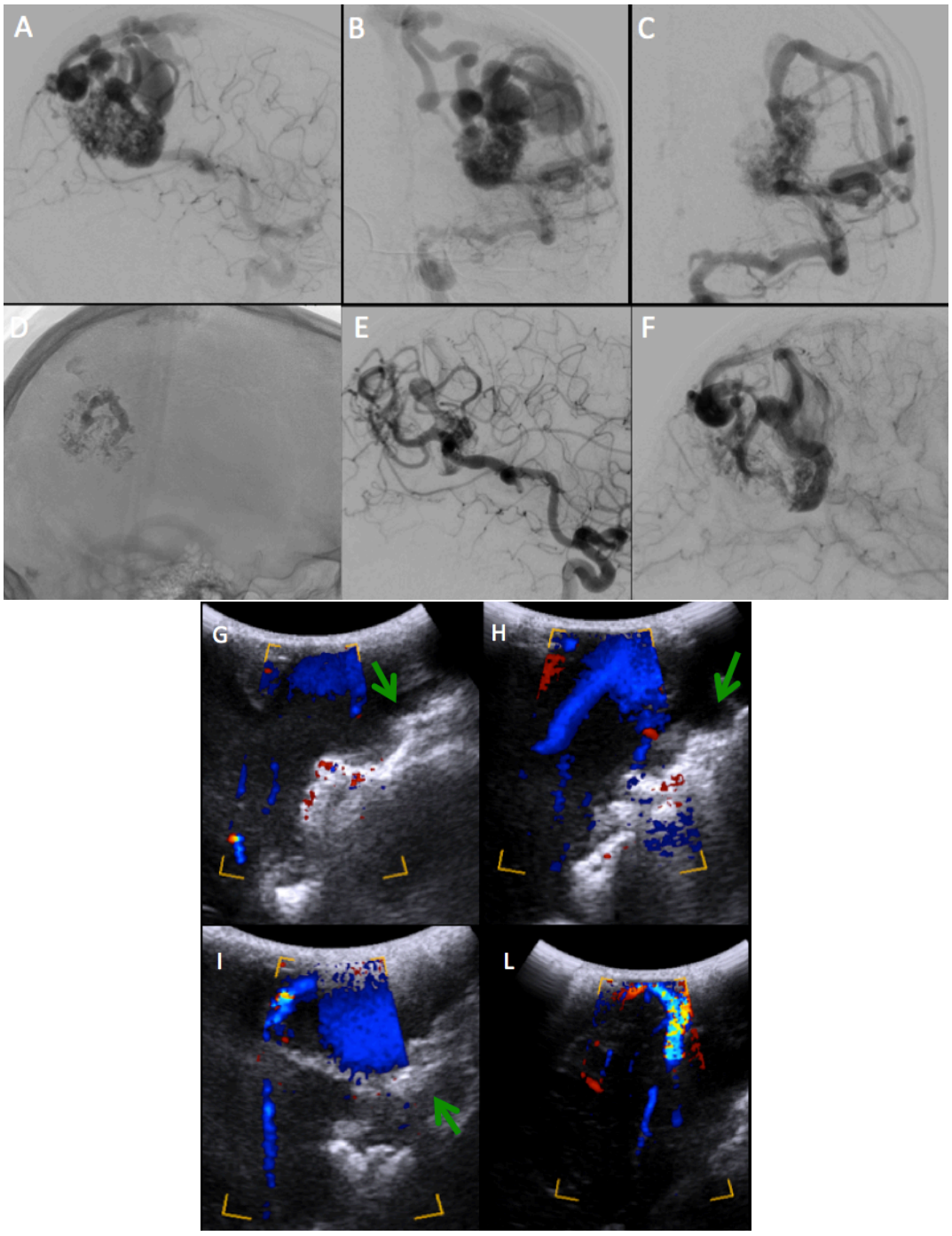


Fig.26 A 54-years-old man. A. Parietal AVM Spetzler-Martin grade 3. C. Arterial afference from parieto-occipital branch of MCA. B. Venous drainage by multiple cortical veins with huge ectasia. D. Onyx injected from arterial afference into the nidus and decrease of AV shunt (E-F). G-H-I Shadow effect and artifact around the hyperechogenic part (green arrow) due to Onyx that covers the arterial afference of the malformation. L. Feeder artery identified after scans in multiple orientations and removal of some embolizing material.

7.2 Clinical and radiological follow-up

Clinical follow up was performed using mRS score and equivalent score of neuropsychological tests at 6 months and at last follow up (average of 37.2 months). The average duration of radiological follow-up was 13.5 months (DSA) and 26.2 months (MRI). A marked improvement in symptoms was observed for all patients, with an improvement in term of mRS from an average score value of 2.8 (values between 1 and 5) in the pre-intervention time to an average score value of 1.9 (values between 1 and 4) at six months and 0.8 (values between 0 and 4) at the last follow-up. In 8 patients a complete resolution of the symptoms was obtained and in 10 cases there was a partial resolution with a marked improvement in the symptoms (95% overall). Only in one case (5 %) did no improvements occur after treatment (see Tab.1, pag. 98). Morover, we could observe an improving trend also from the neuropsychological point of view, according several tests administered to the patients (MMSE, LTM, language, attention, executive functions, vision-spatial functions, emothion-behaviour evaluation), see Tab. 2-3, pp.108-109.

The radiological follow-up included checks in the immediate post-surgical time with CT scan and DSA, at 3-6-12 months with brain MRI with or without Angio-MR examination and at 1 year by angiographic examination. After one year, it was asked to the patients tracking only some changes in clinical conditions to continued the clinical follow up. However, some patients performed MRI also after more than 24 months because they preferred to stay in radiological follow up.

A complete angiographic study was performed in the immediate post-operative period and after one year, in order to avoid any rehabilitation of the shunt. For all cases, DSA showed complete exclusion of the AVM and normal circulation time. The parameters that best convey information on the effectiveness of the treatment were: the exclusion of the shunt, the reduction of venous congestion and the resumption of normal venous outflow. All patients were contacted and clinically re-evaluated. None patient was lost during the follow-up. At the same time it was recommended to contact the ward again in the event of a change in their clinical conditions.

Case	MMSE		Attention		Language		MLT	
	Score pre-op	Score at last FU	Score pre-op	Score at last FU	Score pre-op	Score at last FU	Score pre-op	Score at last FU
1	Normal	Normal	Normal	Normal	Normal	Normal	Deficit	Medium low
2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
3	Normal	Normal	Normal	Normal	Compromise	Selective for verbal task	Semantically unrelated long-term memory deficit	Medium low
4	Normal	Normal	Alternating attention deficit	Medium	Normal	Normal	Normal	Normal
5	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
6	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
7	Normal	Normal	Alternating attention deficit	Normal	Verbal production deficit	Verbal production deficit	Semantically unrelated long-term memory deficit	Medium low
8	Normal	Normal	Selective attention deficit	Normal	Comprehension deficit	Medium	Normal	Normal
9	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
10	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
11	Normal	Normal	Normal	Normal	Compromise	Selective for verbal task	Semantically unrelated long-term memory deficit	Medium low
12	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
13	Normal	Normal	Deficit	Normal	Deficit	Deficit	Deficit	Medium low
14	Normal	Normal	Selective attention and visual alternating deficit	Normal	Normal	Normal	Normal	Normal
15	N/A		N/A		N/A		N/A	
16	Normal	Normal	Deficit	Normal	Normal	Normal	Deficit	Medium low
17	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
18	Normal	Normal	Normal	Normal	Comprehension and verbal production deficit	Verbal production deficit	Normal	Normal
19	Deficit	Normal	Deficit	Normal	Comprehension and verbal production deficit	Normal in production, at limits in writing numbers and words	Deficit	Medium low

Table 2: Neuropsycological evaluations: MMSE, attention, language, MLT.

Case	Executive functions		Visuospatial functions		Emotional-behavior	
	Score pre-op	Score at last FU	Score pre-op	Score at last FU	Score pre-op	Score at last FU
1	Normal	Normal	Associative agnosia	Associative agnosia	Apathy	Normal
2	Complex planning deficit	Complex planning deficit	Agnosia, visual field deficiency	Agnosia, visual field deficiency	Emotional lability	Emotional lability
3	Complex planning at the limit	Medium low	Recognition deficit	Normal	Verbal irritability	Verbal irritability
4	Complex planning deficit	Medium low	Normal	Normal	Normal	Normal
5	Normal	Normal	Normal	Normal	Normal	Normal
6	Normal	Normal	Normal	Normal	Verbal irritability	Verbal irritability
7	Normal	Normal	Normal	Normal	Verbal irritability	Verbal irritability
8	Normal	Normal	Constructive apraxia	Constructive apraxia	Normal	Normal
9	Complex reasoning deficit	Complex reasoning deficit	Normal	Normal	Verbal irritability	Medium
10	Complex reasoning deficit	Complex reasoning deficit	Normal	Normal	Verbal irritability	Medium
11	Complex planning at the limit	Medium low	Normal	Normal	Normal	Normal
12	Normal	Normal	Normal	Normal	Emotional lability	Emotional lability
13	Normal	Normal	Normal	Normal	Normal	Normal
14	Complex planning deficit	Normal	Normal	Normal	Normal	Normal
15	N/A		N/A		N/A	
16	Normal	Normal	Visual field deficiency	Normal	Ideational slowdown	Ideational slowdown
17	Normal	Normal	Normal	Normal	Anxiety	Anxiety
18	Complex planning deficit	Medium low	Normal	Normal	Depression, anxiety, hostility	Depression, anxiety, hostility
19	Deficit in programming/planning	Medium low	Agnosia	Normal	N/A	Normal

Table 3: Neuropsycological evaluations: executive functions, visuospatial functions, emotional-behavior.

CHAPTER VIII

DISCUSSION

Arteriovenous malformations are lesions defined by the presence of arteriovenous shunting through a nidus of coiled and tortuous vessels connecting feeding arteries and draining veins.[10,149,213] Because no capillaries connect these vessels, arterial circulation flow into the venous circulation, producing the characteristic hemodynamic changes of increased blood flow velocity and decreased hemodynamic resistance. Clinical presentations of AVMs, such as hemorrhage, epilepsy, and neurological deficits are based on these pathophysiological mechanisms.

Surgery for AVMs located near eloquent areas is associated with significant risk of neurological deterioration, especially in patients presenting with unruptured malformations with minimal or no neurological deficits. The goal of treatment is to achieve the best possible compromise between the need not to have residual part of the malformation and the need not to cause permanent neurological deficits. To achieve this goal, it is necessary to accurately identify not only the eloquent nervous tissue (or, from the surgical point of view, the tissue whose resection would lead to a permanent neurological deficit), but also where is exactly the vascular malformation.

Although endovascular embolization and stereotactic radiosurgery have been used to treat these lesions for the past 10 years,[76,149,194] microsurgery remains the mainstay of AVM treatment. The exclusion of the AVM proceeds through well-defined stages: the AVM is identified, the superficial feeding arteries are eliminated, the superficial portion of the nidus is circumferentially dissected, the apex is then dissected and the venous drainge(s) is occluded.[194]

A thorough understanding of the vascular anatomy of the AVM and, specifically, the knowledge of the location of feeding arteries and draining veins are essential points for treatment. Unfortunately, in identifying the eloquent areas, the

anatomical data alone are not sufficient. Anatomical data are fairly reliable in identifying the precentral gyrus and the corresponding primary motor area,[64] but extremely unreliable as regards other areas: for example, areas responsible for the expressive function of language are often found beyond the anatomical limits of the frontal operculum, and the temporal linguistic areas are statistically at a distance from the temporal pole varying between 3 and 9 cm. To overcome the anatomical interindividual variability, individualized anatomical information can be obtained through neuroimaging methods, but this does not solve the problem of functional interindividual variability, even more marked than the previous one. Interindividual variability implies that any surgical act in correspondence with the eloquent areas can lead to unpredictable neurological deficits. It is therefore necessary to use an individualized approach, "tailored" for each patient, to anatomically and functionally identify the eloquent areas in that single patient.[64,180]

Consequently, these patients are typically managed conservatively or treated radiosurgically. Eloquent functions may shift in the presence of an AVM from its anatomic location to an adjacent gyrus or even to the contralateral hemisphere. Increasingly, sophisticated neuroradiological imaging (magnetic resonance imaging (fMRI), DTI fiber tracking) can partially detect these shifts in functional localization. Finding an unexpected separation between eloquent cortex and AVM nidus on one of these imaging modalities may encourage more aggressive intervention with surgical resection, but the resolution of these studies is often low because significant shifts in functional localization occur infrequently. Therefore, preoperative functional imaging is usefull only as a screening test for major re-organization of the eloquent cortex.

Electrocortical stimulation mapping is widely used with intrinsic brain tumors, facilitating more extensive resections than otherwise possible and increasing patient survival. However, electrocortical stimulation mapping has not been widely used with AVMs, probably because compact AVMs do not contain brain tissue within the nidus, and they typically have a distinct plane between their borders and adjacent brain. In addition, AVM resections can be more technical, tedious, and prone to bleeding than glioma resections, which makes them more daunting in awake AVM patients than in awake glioma patients. In reality, a significant portion of the dissection around an AVM is not in a subarachnoid plane and instead is in a parenchymal plane beyond pia mater. Further-

more, a significant number of AVMs have a border or borders that are diffuse rather than compact, forcing the dissection into brain parenchyma to completely encircle the nidus. Even minor pial violations and parenchymal invasions can be costly in the eloquent areas.

At this moment, there are fewer intraoperative imaging techniques than sophisticated preoperative ones.

Four concepts seem to represent the options:

- neuronavigation system;
- interventional MR imaging;
- intraoperative DS angiography;
- intraoperative ultrasonography.

Intraoperative ultrasonography has been used for many years and is an efficient imaging adjunct to neurosurgery during the exclusion of brain tumor.[116,147,204]

The main topic of this project is the advantages of using updated intraoperative ultrasound images during AVM's surgery. By recording real-time imaging data intraoperatively, AVMs and additional findings are localized directly and are ready for navigation immediately. Therefore, the neurosurgeon can be guided in real-time during the dissection of AVMs located near eloquent area, in a much more precise and timely manner, even in those area at high risk of consequent neurological damage.

AVM surgery, which is often much more complex than expected, has benefited from neuroimaging guidance and intraoperative monitoring techniques. Although navigation technology has revolutionized many aspects of neurosurgery, brain shifts that occur when opening the patient's cranium and during the resection of AVMs remain to be a serious limitation.[185] Intraoperative imaging is therefore important to allow for navigation based on updated images, and to offer the possibility of observing the immediate effects of surgery for quality control.[184] This goal is obtained using intraoperative US.

During AVM dissection, neurosurgeons require key anatomical details of AVMs seated within the parenchyma to facilitate surgical excision and minimize surgery risks. These details include location of the main body of the AVM in relation to the

craniotomy, the size of AVM, its relation with the brain parenchyma, perivascular changes, location of feeding arteries, the course of arteries "en passant", venous drainage(s) and any accompanying lesions related to the AVM.

Pia mater is an important protective barrier that defined the bounderies of the subarachnoid domain. However, pia transgressions are inevitable requirements of AVM surgery. The pia must be incised to initiate circumdissection into brain parenchyma and advance the resection. Intact pia reassures us that neurological morbidity might ensue. Therefore, pia is the anatomic link to eloquence, and the pial incision forces the neurosurgeon to confront eloquence at this phase of dissection, even though eloquence is a property of brain tissue and becomes a major factor later during parenchymal dissection. Eloquence is not so easy to judge intraoperatively.

Most neurosurgeons deal with eloquence by maintaining a close dissection distance from the AVM. Eloquence is assumed based on structural anatomy and protected during dissection with tight adherence to the AVM. Neurosurgeon begins with a pial incision that closely circumscribes the AVM, and then he develops planes that hug the nidus and pull us in to minimize brain transgression. This tact is crude and works with compact AVMs, but clean planes rarely persist. Margins often become irregular or diffuse and the dissection migrates into parenchyma. In addiction, bleeding from the nidus can push back the dissection. The comfort that comes from tightly adhering to the AVM is replaced with nagging concern about assumed eloquence there is a dynamic between tight AVM adherence on the one hand and wide dissection distance on the other, between aggravating the AVM with the former and the harming the patient with the latter. The end result is a constant, unrelenting tension that comes from uncertain eloquence, beginning with the pial incision and continuing throughout circumdissection. This is the psychology of eloquence that permeates AVM resection when our measures of eloquence are inadequate.

Ultrasonography, which requires only a small, sterile, draped scan head in the field, rendering real-time 2D scanning available when needed.

Our experience with intraoperative ultrasonography over a period of approximately 5 years has shown us the value of its real-time results. The ability to depict real- time anatomical data during a surgical procedure is a valuable surgical

adjunct, one that even affects decisions made during surgery. It is a rapid and effective way to localize and characterize AVM.

Identification of AVM components enabled the preservation of functional area, during AVMs resection, with care during dissection not to transgress pial planes. In case of deep AVM the intraoperative US guided the dissection through overlying sulci down to the nidus because allowed the neurosurgeon to localize exactly where is the nidus and the feeding arteries that could be coagulated. Intraoperative US influenced the attitude toward the extent of dissection. Our patients had AVM borders that were too intimately associated with the functional cortex to complete the resection safely. Some patients had deep, conical extensions of nidus into white matter near cortico-spinal tract. In these cases, AVM was circumferentially dissected in all planes and Doppler US allowed us to disconnect most arterial feeders while preserving arteries "en passant" and the major draining vein until the final step, avoiding to have some damage into the eloquent area.

In all cases, conventional ultrasonography provided rapid localization of the AVM nidus before to open the dura mater. However, it is difficult to distinguish feeding arteries from draining veins. Some authors[51,90,187,222] have reported that duplex scanning can differentiate between lesion-associated arteries and veins or between feeding arteries and peripheral normal arteries by using the resistance index, peak systolic velocity, and directional information.

The echo-color Doppler study allowed to identify more accurately the nidus, arterial afferents and venous drainage (s), even if not exposed in the operating field, proving, in this sense, superior to the study with indocyanine green.[69] Exposure of all feeding arteries may be impossible with large-sized or deep-seated AVMs, which lead special challenges to the surgical resection. The challenges are exacerbated when arterial bleeding from the nidus continues even after major feeders are thought to have been occluded. This means that there are still some unidentified feeding arteries. The key step is to find the feeding arteries behind the nidus and the relatively early occlusion of these arteries in the course of dissection and the echo-color Doppler helped neurosurgeon to perform this step, because he could see the exact position. It also allowed to choose the safest approach to AVM, allowing exactly to distinguish healthy

tissue from pathological vascular tissue and identifying any pseudoaneurysms or venous ectasias AVM's related.

The distinction of feeder arteries from "en passant" arteries is fundamental in the preservation of these vessels during surgical operations, thus guaranteeing the protection of the functional vascularization of the areas surrounding the AVM. So it is possible to preserve from ischemic damage the tissue around the malformation, resulting in a better clinical outcome.

In our study, the use of ColorDoppler and CEUS were seen to be of great help to distinguish the draining veins from arterial supply, the nidus, pseudoaneurysm, and the residual component. Feeding artery can be skeletonized with greater precision to preserve normal "en passant" arteries directed to distal territories.

Owing to the emergence of contrast agents and the ease with which we could administered, we can now try this technique in seeking and identifying feeding arteries intraoperatively. Microbubbles of encapsulated gas possessing strongly nonlinear properties led to the introduction of harmonic imaging, which differentiates echoes of microbubbles in the capillary bed from those in avascular tissue. Although insonated tissue responds primarily at the fundamental frequency, resonating microbubbles cause the scattering of echoes at multiples of fundamental frequency called harmonic frequencies. By selecting the ultrasound frequency required to preferentially detect echoes from microbubbles while suppressing those from solid tissues, we achieved specialized harmonic imaging, known as contrast agent–specific imaging. Furthermore, a new harmonic imaging method, the pulse-inversion harmonic perfusion-imaging technique, was developed to improve image quality while reducing contrast agent–specific artifacts. [70,82] This method can provide an angiogram-like view of AVM vessels in real-time imaging. Fortunately, this real-time angiospecific imaging enabled us to observe the microbubble perfusion process and to distinguish feeding arteries from draining veins.

Results obtained in these 19 cases indicate that the microbubble perfusion process in the brain is the same as that of contrast-enhanced computed tomography scanning proceeding from artery to tissue to vein. Although the AVM displays a unique characteristic hemodynamic change, infact microbubbles do follow this perfusion pattern. Because ultrasonography provides results in real time, is always readily

available, and presents no radiation danger, it is an optimal intraoperative guidance tool. Moreover, it is appropriate for intraoperative application, even when used in combination with contrast agents. In situations in which surgeons have doubts after an ultrasound examination, they can review the video records stored on the hard disk and review and analyze the vascular anatomy carefully.[231,233]

The major problem encountered with the method described here was that the real-time perfusion process could be observed in only two dimensions, whereas the AVM is a 3D lesion. Thus a single image contains a relatively small quantity of information. This is a serious problem in contrast agent–specific imaging. To counter this issue, we used one of two options:

1) repeating the bolus injection whenever observation of a new section was required;

2) using the burst–refill technique. The former method is a time- consuming process; whenever we wanted to observe a new dynamic perfusion process, we had to wait until most of the microbubbles in the tissues disappeared. [90]

In addition, although this method apparently requires lesser amounts of contrast medium with each bolus injection, the overall cumulative amount is significant and possibly harmful to the patient.

To overcome this limitation, we took advantage of another characteristic of microbubbles. Above a certain pressure threshold, microbubbles burst or collapse and are destroyed on sonication. We could thus send a pulse of high-pressure sound waves to clear the microbubbles within the insonation field. The difference in the concentration of contrast agent would then bring about a new refill process of microbubbles, allowing us to observe the perfusion process in multiple sections. By contrast, although this method required a great amount of contrast agent in one bolus injection, it actually saved the overall consumption and scan time of the contrast agent.

Pulmonary circulation, nitrous oxide anesthesia, and positive-pressure ventilation do not appear to be significant limiting factors for the harmonic imaging of intravascular microbubbles. Further, SonoVue can persist intravascularly for approximately 3 to 5 minutes, depending on the weight of the patient and the frequency at which the burst–refill technique is applied; this is a sufficient time to complete a multidirectional sweep.[70,82,181,182]

One should bear in mind that this technique also has some shortcomings. The ultrasonograms are hard to interpret and that inability to demonstrate precise spatial localization can be confusing during surgery, even though professional examiners could interpret them. Even if the resolution of images obtained with intravenous contrast-enhanced ultrasound angiography is lower than that of DS angiography, CEUS could be useful to increase the probability of overlooking an arterial aneurysm within a lesion.

The detection rate for malformations on intraoperative US (B-mode) in this study was very high (94,7%).

The only lesion not detected was a micro-AVMs (<1 cm), that in B-mode was very difficult to be localized because it was inside a huge intraparenchymal hematoma. In addition, the malformation was too small to show typical imaging characteristics on real-time US. At first, the feeding artery was only segmentally visualized on B-mode because of the limitation of scanning angle, tortuosity, and deep location. Colordoppler and CEUS were ideals for locating exactly the shunt.

The localization and the identification of numbers of draining veins are very important for evaluating the risks of rupture of arteriovenous malformations. We delineate the draining veins in all our cases.

Especially, in case of intraparenchiaml hemorrhage, intraoperative US helps the neurosurgeons to make intervention plans and guide them to locate and to resect arteriovenous malformations.

We have clearly appreciated that colordoppler US and CEUS had high detectability for small and deeply located arteriovenous malformations. Furthermore, the scanning method is very important for optimizing visualization of malformations in specific anatomical site. Indeed, multiple scanning, proved to be particularly useful for identifying malformations in interhemispheric or deep site. Multiple scanning can provide good images of lesions in the frontal, parietal, and occipital lobes without being obscured by surrounding highly attenuated bony structures. However, attenuation may be increased by the increase in depth through contralateral scanning. This factor can be solved by using a low scanning frequency to improve the penetration and administrating a contrast agent to enhance the contrast between a vascular lesion and normal brain tissue.

We routinely injected contrast agent for ultrasound angiography at the surgery of complex AVMs to find missing feeding arteries or to identify the real-time hemodynamic status of the lesion. We found that real-time contrast-enhanced ultrasound angiography assisted planning of the route of approach to the surgical target to reduce surgical time and trauma. It can also help to distinguish between arteries supplying the AVM and normal vessels during assessing the collateral circulation.

Incomplete surgical resection markedly increases the risk of postoperative rebleeding. Microscope is not a reliable way to determine the completeness of extirpation of a cerebral AVM. The incidence of a residual nidus reached up to 15% in the hand of experienced neurosurgeons who thought that the AVM had been completely eliminated.[165] We have integrated intraoperative ultrasound imaging as a less invasive method for detecting the residual nidus.

In our study, post-resection ultrasound localized a residual portion of the malformation in two patients, for them the resection of the residual lesion was ultimately accomplished. The postoperative angiogram confirmed that all the intended resection had been performed. Ultrasound may be also an alternative to DSA for quality control after an assumedly complete resection.[226-228,231]

In our series, the incision site was planned by MRI and MRA neuronavigation. For all patients the AVM pre-surgical information were obtained by DSA. In the context of AVM surgery, ultrasound image guidance must be measured against the "golden standard" of image guidance and intraoperative angiography. Expectations regarding intraoperative MRI or DSA systems are significant, but these systems require a large investment as well as a special operating room and surgical equipment and require a relatively long time for image acquisition.[161]

Contrast-enhanced intraoperative ultrasound may be an alternative to DSA for quality control.[34] Compared with intraoperative DSA, contrast-enhanced intraoperative ultrasound did not have special requirements for the construction of operation room. Moreover, this approach is free of radiation and characterized by real-time and simple operation. In addition, contrast-enhanced intraoperative ultrasound could detect AVM from different angles. It could define vascular components of AVM and residual part after resection. In the present study, we have integrated intraoperative ultrasound image guidance into a strategy of navigated AVM resection located near eloquent area.

The main benefit of ultrasound image guidance was the improved precision and accuracy of planning surgical procedures. The ultrasound image made it easier to understand the vascular architecture during the operation and is useful to map the size of the nidus, to detect the degree of brain shift, the components of AVM distinguishing arteries that supply healthy parenchyma and reducing parenchymal trauma right in those areas at high risk of neurological damage.

Finally, it is useful to identify residual part of AVMs, in order to eliminate the risk of bleeding related to a partial exclusion of the malformation. Intraparenchymal hemorrhage located so closed to eloquent areas can result in a devastating neurological imparement.

At last clinical follow up, all patients but one reported a good outcome (mRS 0-2), even in neuropsychological testes, and the angiographic study confirmed complete resection of all malformations.

At the end, we should consider the ultrasound is a highly operator dependent method: the same exploration area can be completely soundproofed by two different operators. Ultrasound parameters (gain, power and depth) must be adjusted every time you explore an area, based on what you want to see.[34] Moreover, the angle of soundproofing varies continuously during the exploration maneuvers of the area of interest as the probe is held in the hand by the operator. Also, you need to choose the type of probe suitable for the exam you are going to do (more superficial or deeper exploration, anatomical detail).

The ultrasound image is the result of the return echoes reflected by the surfaces that are crossed by the ultrasound beam. This continuous passage from one surface to another, with a continuous change of the mechanical index of the crossed medium, can lead to the formation of image artifacts.

In particular, the formation of the artifacts at the time of the ultrasound evaluation of the residue is due to several factors:

- at the time of acquisition, a large part of the malformation was deafferented and therefore the resulting surgical cavity must be filled with saline solution (physiological solution) in order to allow for the insonation. This means that there is a sudden change in the means

crossed by the ultrasound beam, with the consequent passage between two different mechanical indices and the formation of areas of hyperreflection and tissue echoes.

- presence of blood clots that appear hypereogenic and that can mimic the presence of a residue where not present or distort its size
- presence of hemostatic material: causes the formation of hyper-reflective areas that distort the formation of the ultrasound image. before acquiring new ultrasound data, it is advisable to remove all traces of hemostatic material from the walls of the surgical cavity in order to obtain an image that is as correct as possible.
- US images that are obtained are exclusively two-dimensional: during the acquisition one of the three floors of the space is systematically lost. The spatial plane that is not represented is the one that is perpendicular to the explorer probe.[134]

However, even if simple to use, ultrasound still requires adequate preparation to be able to solve the problems deriving from the limits set forth so far by this method and to obtain information that can be quantitatively and qualitatively relevant for the operator. It is therefore appropriate to have adequate training for the neurosurgeon who wants to use the ultrasound correctly.

The improvement of imaging definition combined with the possibility of using the contrast medium allow the neurosurgeon to have a precise and reliable intraoperative investigation tool. Preliminary data showed that the intraoperative colordoppler US study improves the exact definition of the components of the AVM, allowing a safer and accurate dissection of the pathological tissue from the healthy cerebral parenchyma and thus allowing the preservation of the eloquent functions.

For neurosurgeon to know exactly the course of feeders arteries, the location of the nidus, which are the arteries “en passant” to preserve and the venous drainage to coagulate at the end of the AVM exclusion is mandatory for those malformations especially when localized near to eloquent areas. Intraoperative US allows to avoid the violation of pial planes in search of the vessels because it becomes possible to identify them in a specific way. Thanks to this methodology is possible to preserve healthy parenchyma in eloquent areas.

CHAPTER IX

CONCLUSIONS

Arteriovenous malformations still represent a demanding challenge for all the figures involved in the therapeutic path of the patients who are affected.

We used intraoperative ultrasound, as demonstrated by the medical literature,[34,142,143,181,182,231] has proven to be a valid tool in the hands of the neurosurgeon to be able to perform the exeresis of brain tumor but we do not have much data for the exclusion of brain AVM. The knowledge of the specific AVM anatomy before and during surgery is mandatory to minimize the risk of neurological deficits.

This project is focus on the employment of a new methodology as US for the intraoperative evaluation of blood flow during surgery to understand and to recognize exactly every component of AVM. Moreover, the improvement of the definition of the images combined with the possibility of using the contrast medium allows neurosurgeon to have a precise and reliable intraoperative investigation tool.

Also, we used intraoperative ultrasound in combination with neuronavigation system integrated to the operative microscopy as guidance in AVM resection and we established that is a reliable and useful method for intraoperative localization expecially for those malformations localized closed to eloquent area. This technique has shown a very high complete resection rate with extremely low associated morbidity and mortality. This technology also has several other applications in aiding the acute surgical management of AVMs and represents an alternative to on-table angiography, which is not available at many institutions. [70,82]

Preliminary data showed that the intraoperative colordoppler US study improves the exact definition of the components of the AVM, allowing a safer and accurate dissection of the pathological tissue from the healthy cerebral parenchyma and thus allowing the preservation of the eloquent functions. Furthermore, the evaluation of intraoperative blood flow offered an advantage in terms of post-operative neurological

outcome to the patient who underwent surgical excision of a cerebral AVM located near an eloquent area.

The improvement of imaging definition combined with the possibility of using the contrast medium allow us to have a precise and reliable intraoperative investigation tool. The ultrasound contrast medium is an effective and specific tool in identifying the residue.[142,160] Therefore, it plays a decisive role in the maximization process of the AVM exeresis in that it makes the residue and its location within the operative cavity clearly evident, allowing its removal.

Moreover, the definite advantages of ultrasonography over other imaging modalities are its availability, utility, and low cost.

Using ultrasound and intraoperative contrast enhancement in AVM surgery is currently pioneering. For this reason, to fully understand the potential of intraoperative ultrasound, color-doppler, contrast enhancement and the integration of them with the other instruments, are needed further clinical studies in order to guarantee the widest possible dissemination of this method of investigation and to obtain the best possible results for our patients.

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