GUIDELINES

Consensus Document of the International Union of Angiology (IUA)-2013
Current concepts on the management of arterio-venous malformations

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Arterio-venous malformations (AVMs) are congenital vascular malformations (CVMs) that result from birth defects involving the vessels of both arterial and venous origins, resulting in direct communications between the different size vessels or a meshwork of primitive reticular networks of dysplastic minute vessels which have failed to mature to become 'capillary' vessels termed "nidus". These lesions are defined by shunting of high velocity, low resistance flow from the arterial vasculature into the venous system in a variety of fistulous conditions. A systematic classification system developed by various groups of experts (Hamburg classification, ISSVA classification, Schobinger classification, angiographic classification of AVMs,) has resulted in a better understanding of the biology and natural history of these lesions and improved management of CVMs and AVMs. The Hamburg classification, based on the embryological differentiation between extratruncular and truncular type of lesions, allows the determination of the potential of progression and recurrence of these lesions. The majority of all AVMs are extra-truncular lesions with persistent proliferative potential, whereas truncular AVM lesions are exceedingly rare. Regardless of the type, AV shunting may ultimately result in significant anatomical, pathophysiological and hemodynamic consequences. Therefore, despite their relative rarity (10-20% of all CVMs), AVMs remain the most challenging and potentially limb or life-threatening form of vascular anomalies. The initial diagnosis and assessment may be facilitated by non- to minimally invasive investigations such as duplex ultrasound, magnetic resonance imaging (MRI), MR angiography (MRA), computerized tomography (CT) and CT angiography (CTA). Arteriography remains the diagnostic gold standard, and is required for planning subsequent treatment. A multidisciplinary team approach should be utilized to integrate surgical and non-surgical interventions for optimum care. Currently available treatments are associated with significant risk of complications and morbidity. However, an early aggressive approach to elimiate the nidus (if present) may be undertaken if the benefits exceed the risks. Trans-arterial coil embolization or ligation of feeding arteries where the nidus is left intact, are incorrect approaches and may result in proliferation of the lesion. Furthermore, such procedures would prevent future endovascular access to the lesions via the arterial route. Surgically inaccessible, infiltrating, extra-truncular AVMs can be treated with

endovascular therapy as an independent modality. Among various embolo-sclerotherapy agents, ethanol sclerotherapy produces the best long term outcomes with minimum recurrence. However, this procedure requires extensive training and sufficient experience to minimize complications and associated morbidity. For the surgically accessible lesions, surgical resection may be the treatment of choice with a chance of optimal control. Preoperative sclerotherapy or embolization may supplement the subsequent surgical excision by reducing the morbidity (*e.g.* operative bleeding) and defining the lesion borders. Such a combined approach may provide an excellent potential for a curative result.

Conclusion. **AVMs are high flow congenital vascular malformations that may occur in any part of the body. The clinical presentation depends on the extent and size of the lesion and can range from an asymptomatic birthmark to congestive heart failure. Detailed investigations including duplex ultrasound, MRI/MRA and CT/CTA are required to develop an appropriate treatment plan. Appropriate management is best achieved via a multi-disciplinary approach and interventions should be undertaken by appropriately trained physicians.**

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Key words: **Arteriovenous malformations - Central nervous system vascular malformations - Classification - Angiography - Sclerotherapy.**

The International Union of Angiology (IUA) has established an expert panel to formulate guidelines for physicians and health care professionals for the evaluation and treatment of arterio-venous malformation (AVM) based on the best currently available scientific evidence in the world's literature and the sound opinions of clinicians with many years experience in this area of congenital vascular malformations.

The guidelines in this document are broad and incorporate proven concepts and new discoveries. In the last decade, rapid progress in both diagnostic techniques and minimally invasive catheter technology has been significant in this challenging field. Imaging studies to include radionuclide scintigraphy, ultrasound, computed tomography (CT), CT angiography (CTA), and magnetic resonance imaging (MRI) technologies have largely been improved. The endovascular therapy revolution has transformed the way clinicians treat patients with vascular disorders in many anatomic locations which includes AVM management.

Patients are now best treated in referral centers where patients with vascular malformations are regularly seen and managed by a group of physicians participating in a specialized care team organized for "centralized" management.

The various endovascular specialists, surgical and medical specialists, pediatricians, and anesthesia specialists function together based on a new concept of a multidisciplinary team approach. Each physician brings his needed experience to the table. Treating patients on a regular basis allows experience to be gained, rational decisions made, judgment advanced, thus, optimizing patient care. It cannot be emphasized enough that vascular malformations constitute one of the most difficult challenges in the practice of medicine. A cavalier approach to their management may lead to significant complications and poor patient outcomes.

It is the sincere hope of the panel and the IUA, that these guidelines will serve its purpose: general guidelines based on scientific evidence to assist clinicians and patients in the diagnosis and treatment of AVMs. The panel recognizes that some guidelines may be impractical in certain parts of the world with limited access to advanced technology or special expertise. To this end, the panel has incorporated the most important advances in this field to formulate the most up-to-date and sound guidelines based on the best available scientific evidence.

Definitions

AVMs are one of various CVMs that result from birth defects involving the vessels of both arterial and venous origins resulting in direct communications between the different size vessels or via a meshwork of abnormal vessels termed a "nidus". These lesions are defined by shunting of high velocity, low resistance flow from the arterial vasculature into the venous system in a variety of fistulous conditions.[1-4]

Irrespective of the presence or absence of a nidus, all AVMs demonstrate high flow through micro- or macro-fistulous communications between the arterial and venous systems. Due to this unique condition of AV shunting, AVMs have vastly different clinical presentations compared to VMs and other CVMs, with a wide range of presentations, unpredictable clinical course, complicated anatomical, pathophysiological, and hemodynamic status. Altered cardiovascular hemodynamics occurring centrally, peripherally and locally, involve arterial, venous and lymphatic systems. These characteristics make

the AVM the most hemodynamically complex type of CVM with a significant hemodynamic alteration to both the arterial and venous systems: cardiac failure, arterial insufficiency (gangrene), chronic venous insufficiency distally, and lymphatic overload due to venous hypertension. These lesions also have a mechanical impact on the surrounding tissues and organs and are associated with high morbidity related to treatment and high recurrence rates following treatment.[5-8]

Terminology

The terminology found in the general medical literature has been non-specific and confusing. The term 'AVM' is not infrequently used by non-vascular specialists to refer to all CVMs.[9, 10] But not all CVMs are AVMs. In addition, AVMs may also be confused with hemangiomas, which are vascular malformations but tumors as clearly defined by Mulliken et al. and properly classified through ISSVA[i] Classification.[11-14] Hemangiomas and other vascular tumors have a distinctly different clinical behavior, etiology, histology and pathophysiology and hence should not be grouped together with CVMs.

AV fistula vs. *AV malformation*

All AVM lesions are 'fistulous' whether they have a "nidus" or not. Due to the subclassification of the AVM by ISSVA Classification [15] into "AV fistula (AVF) and AV malformation (AVM)", many mistakenly identify the AVM as a "non-fistulous" lesion.

Based on this misconception, many may interpret "fistulous" to describe a "direct" communication with no nidus, while the term "non-fistulous" to describe a lesion with a detectable nidus. But there is NO AVM lesion without a fistulous connection between the artery and vein to allow a free "high flow" shunting.[16-19]

Due to the unique embryological nature of the AVM as a consequence of defective development through various stages of embryogenesis, there are NO "non-fistulous" AVMs. All AVMs are "fistulous" by nature.[20-23]

The "AVF" lesion defined by ISSVA Classification is equivalent to the "truncular" AVM lesion with no nidus (e.g. Ductus Botalli, pulmonary AVM) defined by the Hamburg Classification. The "AVM"' defined by ISSVA Classification is equivalent to the 'extra-truncular' AVM lesion with nidus defined by the Hamburg Classification.

"Nidus" versus «*non nidus" AVM*

The term of 'nidus' (breeding place, breeding ground) is a clinical term created by the radiologists to describe the bundle/cluster of small sized AV connections/fistulae, filled with contrast on arteriography and other tests. This is NOT a histological term. Naturally, "nidus" is not an anatomic/pathologic term but a descriptive term of a conglomerate of blood vessels constituting the AVM.[24-27]

A "nidus" is always present in an extratruncular lesion and only "extra-truncular" AVM lesions will have a nidus, often appearing as a net of dysplastic pulsating, tortuous vessels between the artery and vein. The 'nidus' of the lesion retains its 'diffuse, multiple small fistulous' condition (in contrast to the truncular lesion as with large, individual AV fistulas).

In contast, truncular AVM lesions will have a nidus on arteriogram but instead will have a direct connection between the artery and vein. Further detailed explanation is included in the section on arteriographic classification of extratruncular AVM lesions.

Classification

Old nosology and terminology of the congenital vascular defects failed to provide appropriate differentiation and classification of anatomic, pathophysiologic, and clinical presentations of various CVMs that are required for precise diagnosis, evaluation, and therapeutic implementation (*e. g.* Klippel and Trenaunay syndrome).[28-31]

Malan and Puglionisi proposed a new classification to distinguish the different venous, arterial and other associated malformations for the first time (1964),[32, 33] which became the basis of the subsequent Hamburg Classification [15] and ISSVA Classification.[15] They also described the

[i] ISSVA: International Society for the Study of Vascular Anomalies

morphological difference between lesions involving the main vessel trunks, often with a direct communication ("truncular" form) and the lesions occurring peripherally as separate defects (arteriovenous angiomas).

To avoid the confusing term of "angioma" (c.f. hemangioma), Belov [34-37] re-introduced an old embryologic term: "extratruncular", described by Sabin F.R.(1917), for these "angiomatous" AVM lesions based on their distinctively different morphology from "truncular defects" [38] during the Hamburg Consensus meeting in 1988.

This new term "extratruncular" successfully replaced the often misleading old term "angioma" and stopped the confusion involving the "angioma hemangioma".

The origin of this morphological difference between both groups has been explained on the basis of an embryological mechanism as an outcome of the arrest or disturbance in development of the vascular system during various stages of angiogenesis, from the earlier stage where the primitive vascular structures are still in the "reticular network stage" before evolving into mature structures in the later stage of vascular trunk formation.[21, 39]

Extratruncular forms have a high tendency to progress/worsen and to recur after treatment, while the truncular lesions do not. According to the embryologic concept, the worsening of CVM lesions would depend on the type of the (endothelial) cells present as remnants of the primitive capillary network that maintains its ability to proliferate and with an often unpredictable biological behavior.[23, 40]

This new definition later became the base of "modified' Hamburg Classification led by S. Belov based on embryological characteristics of the CVMs (Table I).[34, 41, 42]

Mulliken as well introduced a new classification system of vascular anomalies where hemangiomas are considered to be separate from the vascular malformations. Hemangiomas are true vascular tumors of an often benign nature and clearly different from CVMs. They also proposed a new classification of vascular malformation based on the Hamburg Consensus/Classification and lesion flow characteristics: fast-flow and slow-flow lesions as in the ISSVA Classification (Table II).[5, 11-15]

These two new classification systems based on the Hamburg Consensus, became the basis of a new system to replace the old name based eponyms and to meet the mandate for the contemporary management of the CVMs.[43] Recently, two more classifications were proposed to improve the AVM management: Schobinger Classification and Arteriographic Classification.[44-46] The Schobinger Classification (Table III) was designed to assess AVM lesions in different clinical stages and clinical conditions more accurately based on the patient's clinical status and to select

TABLE I.—*Modified Hamburg Classification of CVM.*

Main classification based on its predominant vascular component:
– Predominantly arterial defects
– Predominantly venous defects
– Predominantly AV (arteriovenous) shunting defects
– Predominantly lymphatic defects
– Predominantly microvascular/capillary malformation
– Combined vascular defects
Subclassification based on its embryological stage of the defect:
– Extratruncular forms - former A-V "angioma"
– Infiltrating, diffuse
– Limited, localized
– Truncular forms - direct A-V connection
– Deep A-V fistulas
– Superficial A-V fistulas

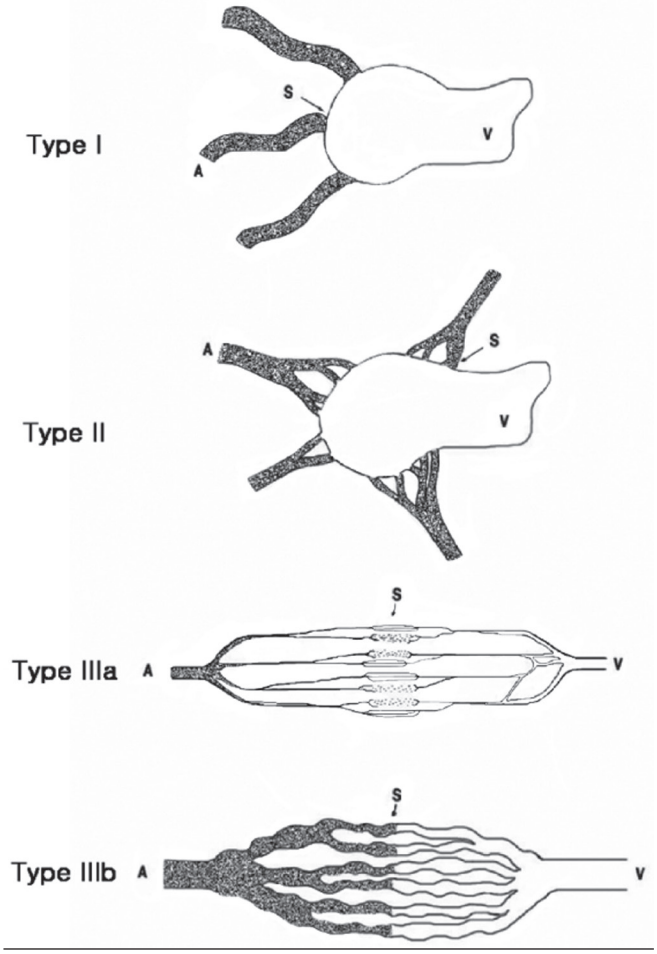
TABLE II.—*ISSVA Classification of CVM.*

VASCULAR MALFORMATIONS:
– Fast-flow
– Arterial malformation (AM)
– Arteriovenous malformation (AVM)
– Arteriovenous fistula (AVF)
– Slow-flow lesions:
– Capillary malformation CM (port wine stain, telangiectasia, angiokeratoma)
– Venous malformation (VM)
– Lymphatic malformation (LM)
– Combined vascular malformation (CVM, CLM, CLVM, CAVM, CLAVM)
VASCULAR TUMORS:
– Infantile Hemangioma
– Congenital Hemangioma
– Other

TABLE III.—*Schobinger Classification of AVM.*

– Stage I - Quiescence: Pink-bluish stain, warmth, and arteriovenous shunting are revealed by Doppler scanning. The arteriovenous malformation mimics a capillary malformation or involuting heamangioma
– Stage II -Expansion: Stage I plus enlargement, pulsations, hrill, bruit and tortuous/tense veins
– Stage III -Destruction: Stage II plus dystrophic skin changes, ulceration, bleeding, tissue necrosis. Bony lytic lesions may occur
– Stage IV -Decompensation: Stage III plus congestive cardiac failure with increased cardiac output and left ventricle hypertrophy

TABLE IV.—*Arteriographic Classification of AVM.*



– Type I (arteriovenous fistulae): at most 3 separate arteries shunted to a single draining vein.
– Type II (arteriolovenous fistulae): multiple arterioles shunted into a single draining vein.
– Type III (arteriolovenulous fistulae): multiple shunts between the arterioles and venules.

the best-suited time for management as a practical guideline.[44]

Arteriographic Classification of AVMs (Table IV) was proposed exclusively to classify the "extratruncular" AVM lesions located in the torso and extremities based on the arteriographic findings/morphology of the "nidus". The lesions were classified into 3 types: Type I (arterio-venous fistulae), Type II (arteriolo-venous fistulae), and Type III a & b (arteriolo-venulous fistulae).

All three types of lesion have radiological findings of the "nidus", represent the primitive reticular networks of dysplastic minute vessels which failed to mature into "capillary" vessels. Hence, this arteriographic classification provides data for better management of extratruncular AVM lesions, together with an embryological classification.

It is also helpful in predicting outcome of endovascular treatment. The rate of complete occlusion or obliteration is highest for arteriovenous and arteriolovenous fistulas and lowest for arteriolovenulous malformations.

Generally, arteriolovenulous fistulae should be treated via the arterial route or by direct puncture of the "nidus", whereas arteriovenous and arteriolovenous fistulae can be treated via a transarterial or transvenous approach.

Incidence and epidemiology

Most of the current data available regarding the incidence and prevalence of AVMs are based on cerebrospinal AVMs. They are rare and usually go undetected until clinical symptoms appear in the usual age range approximately 20-40 years. AVMs are known to affect approximately 250,000 people in the U.S. with a male to female ratio believed to be equal or Female>Male (2:1).[47, 48]

Nevertheless, the peripheral AVMs are the least common type of CVMs representing 5-10% to 15-20%.[49, 50] The majority of CVMs are VMs,[51, 52] LMs [53, 54] and mixed lesions.

The "extratruncular" AVM (formerly angiomatous AVM) comprises the majority of AVM cases. The "truncular" AVM lesions are extremely rare and occur as a direct communication between the pelvic vessels, or between the femoral artery and vein for example. They are genuine fistulous lesions without a nidus such as a patent Ductus Arteriosus (PDA) or pulmonary AV fistula.

To date, no racial, demographic, or environmental risk factors for AVMs have been identified.

Etiology - molecular/genetic evidence

There has been significant progress in genetic research of CVMs, where several gene mutations have been shown to be responsible for the etiology/ pathogenesis of CVMs.[55-66]

Studies are in progress that may help a better understanding of the pathological process that

leads to the development of defects on main vessels resulting in AV shunts with dysplastic high-flow vessels in the tissues. Hopefully these studies also provide additional evidence for a more advanced and logical classification of the CVMs in the future.[67]

The growth tendency of extratruncular AVMs can also be explained with the most recent genetic theory, based on gene mutations occurring in the tissues. Identification of the causative genes in several defects has allowed a more precise diagnosis. Further studies are necessary to better understand these mechanisms.[56, 68, 69]

There are some rare inheritable genetic mutations that predispose patients to developing vascular malformations affecting subsequent generations. Osler-Weber-Rendu syndrome, also termed Hereditary Hemorrhagic Telangiectasia, Blue Rubber Bleb Nevus syndrome, also termed Bean's syndrome, RASA 1 mutations, PTEN mutations, etc., all contribute to a genetic basis for acquiring vascular malformations.

While the exact mechanisms are not yet clear, several mutations have been found to be responsible for AVMs.

Hereditary hemorrhagic telangiectasia (HHT) is the best studied inheritable condition that is caused by loss-of-function mutations in the genes encoding activin receptor-like kinase-1 (ACVRL1) and endoglin (ENG), TGF beta vascular growth factors. The condition is autosomal dominant where affected individuals have mucosal and cutaneous telangiectasias. AVMs may also be present, particularly in the brain, lungs and liver. Vascular lesions develop progressively over time, with most AVMs being diagnosed in adults. While the angio architecture of the AVM is variable, a high percentage of AVMs are arteriovenous fistulae with a saccular varix of the immediate draining vein. Some positive results have been seen treating these patients with angiogenesis inhibitors such as Avastin.[59, 61]

RASA1 mutations are responsible for CM-AVM, another autosomal dominant condition. Affected family members can have capillary malformations, which tend to be round or oval, pink or red, sometimes with a pale halo, AVM, or both. The most common sites for the AVM are brain, spine, face and extremities. Intracranial AVMs can be typical arteriolovenular malformations or pial arteriovenous or arteriolovenous fistulae. The latter typically have a large varix draining the arterial connections and include aneurysmal malformation of the vein of Galen.[56, 64]

Parkes Weber syndrome (PWS) is also associated with the RASA1 mutation. In these patients, the AVM is typically a diffuse small vessel lesion affecting some of the muscles and subcutaneous tissue of the limb with dilated draining veins and relatively proportional marked tissue overgrowth. Affected muscle, bone and subcutaneous fat tend to be proportionally or symmetrically enlarged. Cardiac volume overload is common. Lymphatic channel abnormalities can also be seen. Individuals with PWS without multiple additional capillary malformations generally do not carry this mutation. Patients with CVM-AVM also have an increased incidence of some tumors, including basal cell carcinoma and neural tumors.[60]

PTEN mutations are responsible for overgrowth syndromes including Cowden and Banyan Riley Ruvalcaba syndromes. The term PTEN hamartoma has been applied to the focal tissue overgrowth that frequently contains AVMs. The condition can be recognized by the presence of macrocephaly, penile freckling and asymmetrical overgrowth, with ectopic fat deposits. The most common locations for the AVM are intramuscular affecting the limbs and paraspinal muscles, and cranial (dural). A high percentage of patients have multiple AVMs. The angio-architecture is usually arteriolovenous with irregular dilatation of the draining veins. These AVMs behave aggressively, typically being difficult or impossible to control by embolization.[57, 58, 63]

A genetic theory would explain the morphogenesis of both groups of AVMs and the tendency to worsen as well. In near future we will better understand on the mechanism of genetic mutations to cause the CVMs/AVM with no doubt.

Pathophysiology and clinical course

Abnormal endothelial cell turnover rate among the AVM compared to other CVMs with normal cell cycle/ECTR

Differences in the expression of various structural proteins and angiogenic factors are seen in different vascular anomalies.

Mulliken and Glowacki [13] classified pediatric vascular malformations based on endothelial cell characteristics, specifically the rate of endothelial cell turnover (ECTR).[70] They differentiated between hemangiomas that are characterised by endothelial cell hyperactivity during the proliferative phase followed by diminishing cellularity during the involuting phase later in life, and vascular malformations that are characterised by a normal ECTR (compared with normal blood vessel ECTR).

In the last 10 years, research on the ECTR and the role of endothelial progenitor cells (EPC) have improved our molecular vision of AVM.

First, the ECTR has been found to be significantly greater in AVMs than in normal blood vessels (the mean Ki-67 index is higher for AVM vessels than control vessels, with an approximately seven-fold increase in the number of non-resting endothelial cells).[71]

Additionally, it has been also found that increased expression of stromal cell-derived factor-1 (SDF-1) is present in the AVM nidus, whereas SDF-1 expression is rarely identified in normal vessels. It shows that EPCs may play a role in maintaining active vascular remodeling within the AVM nidus.[72]

Finally, mRNA expression of factors that recruit EPCs VEGF, SDF-1α, hepatocyte growth factor (HGF) and hypoxia-inducible factor-1 (HIF-1) have been demonstrated to be different in Schobinger stage II and III AVM's. Higher-staged AVMs exhibit increased expression of EPCs and factors that stimulate their recruitment so that neovascularization by EPCs can be then considered as a factor promoting evolution of AVM.[73]

Different evolutional/clinical course based on the different genetic expression of endothelial progenitor cells activity

While the early work of Mulliken indicated that vascular malformations do not grow by cellular proliferation, more recent data indicates that there is an element of cellular proliferation and up regulation of matrix metalloproteinases, especially in symptomatic AVMs. This new understanding may lead to the development of pharmacotherapy strategies for treating symptomatic AVMs.[62, 66]

Different evolutional/clinical course between the sporadic and familial/syndrome-based AVM

AVM without documented genetic mutations are considered to be sporadic, but it is possible that the future will demonstrate that many of them are also caused by genetic abnormalities. AVMs in patients with RASA1 mutation (CM-AVM) appear to be relatively stable, although symptomatology is based on the anatomical location of the AVM. Those of the central nervous system (CNS), however, can produce significant mass effect and occasionally hemorrhage.[56, 64]

Patients with Parkes-Weber syndrome experience a slow progression of their AVM when compared to children with sporadic lower limb AVM. In fact, the amputation rate in the second or third decade of the life is more frequent in the group of patients with sporadic lower limb AVM even considering that they usually present with a smaller size of the malformation lesions.[74, 60, 75-77]

Similar considerations could be addressed for the visceral AVM in the context of the patients with Rendu Osler syndrome. Although bleeding is by far more frequent in patients with HHT, the need for a surgical intestinal resection is exceedingly rare. Nevertheless, the need for surgical approach to control the intestinal bleeding is higher in patients with sporadic anomalies than the group of children with HHT.[59, 61]

The most aggressive AVMs appear to be those caused by PTEN and mutations. Not only do the individual AVMs recur very rapidly after embolization or resection, but patients tend to develop new sites. Symptomatology is also significantly related to be associated PTEN hamartoma, which is invariably in the same location as the AVM.[57, 58, 63]

Hemodynamic consequences affecting clinical course

The human circulatory system between the heart and tissue is directly connected in the normal state, but indirectly through the capillary system. When this capillary system breaks down, or is no longer present due to a variety of reasons, these three uniquely different hemodynamic components of the circulatory system -artery, vein, and lymphatics- affect each other in a negative manner.16-19, 78-82).

When an abnormal connection between the ar-

terial and venous system bypasses the normal capillary system, the pivotal function of the capillary system to maintain a delicate balance between high-pressure (arterial) and low-pressure (venous) systems, is no longer present. Venous pressure increases, and tissue perfusion decreases.

Nevertheless, there are naturally occurring AV connections in the human circulation that are not pathological. Naturally occurring fistulas are found in the finger tips, dura, and the tongue. These AV connections do not produce any pathology and are assumed to be part of the "normal" state.

The AVM is a unique, complex, vascular structure that is able to "short circuit" the normal circulation between the high-pressure arterial system and the low-pressure venous system. This abnormal connection (AVM/AV fistula) between the high and low pressure systems forces these two circulatory systems to respond in a compensatory manner to minimize the hemodynamic effects.

Depending on the location and/or degree (size and flow) of the fistulous connection, the arterial and venous systems produce a compensatory hemodynamic response that occurs in two distinct phases that are known as the compensation period and the decompensation period:

— Peripheral effect; arterial ischemia and venous hypertension

— Central effect; heart failure

— Local effect; degenerative change in the vessels leading to and draining the AV fistula.

Compensation period

— Increased pump function by the heart can assist the failing arterial system to maintain arterial flow as before in response to the newly established low peripheral resistance by the AV fistula.[16-19, 18, 83-86]

Hence, peripheral tissue ischemia can be prevented during this compensatory period. However, the compensatory effect on the arterial system by increased heart pump function results in increased load on the venous system and subsequently on the heart itself.

The venous system will have to respond to this increased pressure and increased volume produced by the AV fistula. The negative impact of increased heart function on the venous system is partly compensated by the lymphatic system. The lymphatic system is limited in its capacity to assist the failing venous system, due to its unique lymphodynamic mechanism based on autoregulated peristaltic circulation from low resistance to high resistance, in contrast to the venous system hemodynamics.

Decompensation period

Once these compensatory mechanisms involving the arterial, venous, and lymphatic systems and the heart, are in place, the decompensation period begins where each circulatory system including the heart, begins to produce abnormal physiology.

The arterial system can no longer maintain adequate arterial blood flow to the peripheral tissues distal to the AV fistula resulting in tissue ischemia. The venous system distal to AVM/fistula (affecting the peripheral tissues) is also no longer able to maintain normal valvular function. This results in venous valvular failure, retrograde blood flow and continuous reflux, further impeding normal antegrade venous flow from the peripheral tissues, resulting in chronic venous insufficiency and severe venous hypertension.

Conclusions

The hemodynamics of the AVM affects every component of the arteriovenous communication, resulting in local, peripheral and central effects. Therefore, precise hemodynamic information regarding the close relationship among three pairs of proximal, distal and collateral arteries and veins at the different stages of the disease with dynamic change is most critical for the proper management of various pathophysiologic effects of the AVM on the entire vascular system.

Proper understanding of these crucial biomechanical factors in particular, from a hemodynamic standpoint, is mandatory for proper assessment of the biomechanical impact of the AVM, either congenital or acquired.

Diagnosis

General overview

Presenting symptoms are protean and can include, but are not limited to pain syndromes, neuropathy, dermatological manifestations, tissue ulceration, tissue hypertrophy, infections,

hemorrhage, pulsatile tinnitus, high-output cardiac state and even death.

In neonates, AVMs can present as a macular pink or red stain similar to a CM.[87, 88] There is currently no imaging study that can diagnose an AVM at such stage but special immuno-histochemical stains can be used on tissue samples to exclude an AVM (see below- Diagnosis- New Born cases- Immunohistochemical Analysis). Large lesions, however, may be detected on routine duplex ultrasound .

The differential diagnosis for such high flow lesions in a neonate includes a vascular tumor or an AVM. As described below (see Differential Diagnosis- Infantile/ Congenital hemangioma), the diagnosis may be established by duplex ultrasound or MR. A biopsy is rarely needed. Children presenting with an AVM may complain of pain and warmth in the affected area or limb.

Symptoms and subsequent sequelae of AVM are related to the body tissue or organ system infiltrated by the lesion.[89-92] An early sign may be excess warmth felt on the affected region but with time most lesions result in soft tissue and bony hypertrophy.

Therefore, an AVM typically manifests itself as a pulsating mass associated with swelling of the surrounding tissues, both because of the increased size of the arteries and veins and because the affected tissue grows faster and larger than the normal tissue.

Hemorrhage can be a presenting sign of an occult AVM. This is seen in AVMs of the CNS or lesions that cause skin or mucosal ulcerations. CNS lesions may also present with significant mass effect.

There is an associated soft tissue hypertrophy and the affected side will be larger and warmer than the contralateral side. AVMs involving the limbs may present with bony and soft tissue hypertrophy. The soft tissue hypertrophy involves the subcutaneous fat. The muscle is usually hypertrophied, as opposed to VM or KTS.[93, 94]

AVMs of bone can cause pain syndromes, but frequently cause overgrowth of the involved bone due to stimulation of the epiphysis. Such condition known as "angio-osteohypertrophy / hypotrophy" would result in pelvic tilt, and resultant scoliosis in addition to the leg length discrepancy. Corrective management of the AVM lesion itself is a more logical way to prevent this "vascular bone syndrome" than old fashioned epiphyseal stapling.[95-97, 98-101] However, the cases with a complex AVM or with a condition that makes the treatment difficult, not indicated, or overgrowing still persists after the treatment, may benefit from the epiphyseal stapling, which is today performed with a less invasive technique.[102-104]

Large AVMs can result in significant morbidity and even mortality. Severe changes of chronic venous hypertension and the consequent lymphatic failure and the associated pain has required amputations of the affected limbs.

High-output cardiac failure may be caused by AVMs involving the Vein of Galen or dura in neonates or large truncal lesions involving the shoulders, chest, abdomen, liver, kidneys, pelvis or buttocks.[60, 105-107]

Paradoxical emboli and a subsequent ischemic stroke may be facilitated by pulmonary AVFs (with or without HHT syndrome) with fistulas larger than 3 mm.[108, 109]

Bleeding from an AVM of the CNS may result in a hemorrhagic stroke and death.

Dermatological manifestations

Subtle dermatological manifestations may be one of the earliest signs of an occult AVM. Such lesions may present with a cutaneous pallor with a stellate pattern.[110-112] This is due to shunting of arterial blood directly into the venous system bypassing the cutaneous vascular plexi resulting in a cutaneous 'steal syndrome'. In this situation, the cutaneous vascular supply is denied of its arterial input and the corresponding area(s) of skin appear paler than the surrounding tissues.

Larger AVMs involving skin-supplying arteries affect larger surface areas and may present with a reticulate pattern. This is referred to as and presents with incomplete cyanotic rings that contain central pallor. The overlying skin may present with dilated and tortuous draining veins and overlying capillary or microcystic lymphatic malformations.

One particular cutaneous manifestation of AVMs is acroangiodermatitis (pseudo-Kaposi's sarcoma:KS). In contrast to KS, this condition is not associated with human herpes virus 8 (HHV-8). Acroangiodermatitis can present with circumscribed pigmented, violaceous or dusky

macules, plaques or nodules of the skin overlying or distal to the AV anomaly

Chronic changes such as lichenification and ulceration can be seen in some lesions. Confluence of such lesions can present with pigmentary changes affecting large areas of skin and can be easily confused with pigmentation associated with chronic venous insufficiency.

Histology would demonstrate a collection of dilated vessels within a thickened papillary dermis, a peri-vascular lymphocytic infiltrate, red cell extravasation and haemosiderin deposition. Acroangiodermatitis may be due to a range of underlying conditions including severe chronic venous hypertension seen in patients with Klippel-Trenaunay syndrome. When secondary to an underlying AVM, the condition is referred to as Stewart-Blufarb syndrome.

Investigations

Due to its complicated hemodynamics, AVM lesions often lead a high rate of progression with significant destructive potential based on:

— High flow

— Venous hypertension distally

— Lymphatic overload due to venous hypertension

— ALWAYS progressive (flow related) nature

— Truncular AVM – very high flow, low resistance connection

— Extratruncular AVM – high flow, proliferative potential, nidus in microfistular & macrofistular conditions

Therefore, the history and physical examination should be followed by non-invasive diagnostic imaging in order to distinguish AVMs from other CVMs based on these unique conditions. Given the serious prognosis and inherent difficulties encountered in the management of such lesions, a complete systematic approach to the evaluation is required. Although most AVMs present as a single lesion, the investigations should rule out the co-presence of other CVMs.[113-116]

In addition to the assessment of the primary AVM lesion, assessment of the secondary impact on the non-vascular organ systems, especially to the musculoskeletal system, is warranted. Early detection of vascular-bone syndrome with long bone length discrepancy is essential for appropriate management.[95-97, 98-101]

The aims of the investigations should be to cover the following:

1. Diagnosis- to make a diagnosis of an AVM using various non- to minimally-invasive imaging modalities. Differential diagnoses such other forms of CVMs and NICH (Non-involuting congenital hemangioma) should be excluded.

2. Extent- The extent and size of the lesion and its location with respect to surrounding normal structures should be established. The affected side should be compared with the contralateral side. Presence of other AVMs in the affected limb or organ should be excluded. This is especially important in bony AVMs where multiple lesions may be found. Evaluation for the presence of other AVMs at distant sites also should be considered whenever indicated especially if there are associated symptoms present. In same token, the presence of other CVMs, such as those found in complex malformations (Parkes-Weber syndrome) should be excluded as well.[75-77]

3. Associations- Associated abnormalities, whether they are caused directly by the AVM (acroangiodermatitis, soft tissue hypertrophy, etc) and the syndromic features should be investigated. This may include tissue sampling, genetic analysis, nerve conduction studies and specific investigations of the organs involved.

4. Treatment- Particular investigations such as arteriography will be required to plan the treatment strategy.

The initial diagnostic evaluation should include a combination of baseline non- to minimally-invasive investigations. Such investigations include:

— CW-Doppler;

— Duplex ultrasonography (arterial and venous);

— MRI with T1 & T2 weighted imaging; MRA using dynamic contrast enhancement technique (dceMRI);

— CT angiography with contrast enhancement, with 3-D CT reconstruction;

— Whole body blood pool scintigraphy (WBBPS)- optional;

— Trans-arterial lung perfusion scintigraphy (TLPS) -optional;

— Superselective catheter arteriography - Gold standard as road map.

CW-Doppler and Duplex Ultrasound

These investigations should be considered the first line of evaluation. CW-Doppler is a simple bedside investigation that can quickly determine the type of flow (high pulsatile flow versus low or no flow) within the lesion. CW-Doppler is best used during the initial consultation. VMs and LMs will contain low or no flow, whereas AVMs and active vascular tumors will present with pulsatile flow.

Duplex ultrasound sonography (DUS) remains the first choice study amongst various non-invasive modalities for the initial clinical assessment and the subsequent follow–up.[117-120] DUS differentiates a vascular tumor from an AVM based on B-mode and Doppler findings: Vascular tumors as a highly vascular, relatively homogeneous soft tissue mass that contains pulsatile blood flow and varying low flow draining veins, whereas AVMs are formed of multiple vascular channels with a honeycomb appearance.

DUS also readily differentiate AVMs from VMs and LMs. While AVMs and most LMs are non-compressible on B-mode ultrasound, patent (non-thrombosed) VMs are compressible. LMs present with multiple cystic structures that contain no flow whereas AVMs would demonstrate pulsatile flow.

Spectral, color and power Doppler are very helpful to further define the flow characteristics in the feeding arteries, within the nidus and in the draining veins. These Doppler modalities allow a real time analysis of arterial and venous flow and measurement of flow characteristics such as flow velocities, amplitude and volume. AVFs present with a low resistance high amplitude waveforms. Aliasing is a typical Doppler feature noticed within the nidus and represents turbulent flow.

DUS in the investigation of vascular anomalies has a number of limitations. Firstly, DUS is an operator-dependent investigation which requires extensive training in vascular ultrasound and a comprehensive understanding of vascular anomalies. Secondly, although duplex is an excellent modality in determining flow characteristics, it does not provide a comprehensive understanding of the spatial positioning of the lesion and its extension and infiltration into various surrounding tissues. These B-mode limitations can be further limited by the ultrasound system used, the transducer frequency and design and the software technology. Finally, DUS is limited in the assessment of deeper structures and those adjacent to interfering air or bone.

Magnetic Resonance Imaging (MRI) and Computerised Tomography (CT)

MRI remains the major diagnostic study for the entire group of CVMs including the AVMs.[121-124] MRI is able to provide basic information of lesion extent, severity, and anatomic relationship to the surrounding tissues/structures/organs. Unlike slow flow vascular malformations which usually appear bright on T2 weighted or fluid sensitive sequences, AVM is usually represented by the presence of dilated fast flow vascular channels.[187-189]

Quantitative MRA techniques can also be used to determine the shunt volume or relative flow through an AVM and represent a noninvasive technique to follow the response to treatment. These techniques however are mainly available in tertiary care medical centers.[125]

Standard MRI is not a good technique for precisely demonstrating the nidus or arteriovenous connection. Instead, CT angiography (CTA) provides much better anatomical information, sometimes showing the arterial and venous anatomy in excellent detail, but is inferior in all aspects to the newer technique of dceMRI (see below).

Especially, CT (CTA) can be very useful to evaluate AVMs of bone as MR images bone poorly. CTA with reconstructions can be useful in place of diagnostic arteriography in the evaluation of many cases of AVM, reserving arteriography for when requirements for treatment is established.[126-129]

However, CT angiography is usually avoided in children and young adults because of the radiation exposure. Despite reports of the mean radiation dose in children undergoing x-ray imaging procedures vary widely, radiation dose for contrast-enhanced 64-slice multidetector computed tomography in children is greater than that received by angiography. Even considering that CT angiography may give more precise anatomical detail than MRI, particularly in small blood vessels, the benefits of clinically justified CT examinations should always outweigh the risks for an

individual child, and referral to a center that performs dceMRI [130, 131] should be considered as well.

No amount of radiation should be considered absolutely safe and the highest quality images that require the most radiation are not usually required to manage an AVM. MRI should remain as the option of choice in the diagnosis of high flow vascular anomalies for this special group. Only when dealing with a specific AVM in a critical area difficult to treat, CT is indicated though extremely rare.

Scintigraphy

Scintigraphy is not an essential examination necessary for the diagnosis of AVM but remains an option for a secondary investigation only in selected cases. Transarterial lung perfusion scintigraphy (TLPS) [132, 133] has a unique role in determining the degree of arteriovenous shunting by the AVM lesion within an extremity. TLPS has a special value to detect and assess a micro-AV shunting lesion, which is often difficult with conventional techniques. Micro-AVMs frequently exist in the combined form of CVM, the hemolymphatic malformation (HLM), and its delayed if not overlooked diagnosis to allow its progress beyond the optimum time for the interception can be avoided with TLPS alone. TLPS also provides quantitative measurement of the shunting status during therapy. TLPS may replace the substantial role of traditional arteriography as a follow-up assessment tool for extremity AVMs.

Whole body blood pool scintigraphy (WBBPS) [134, 135] utilizing radio-isotope tagged erythrocytes, is also an excellent optional test for the AVM evaluation as well. But it is rather more useful for the screening of hidden CVM lesions throughout the body and also for a qualitative analysis of the AVM lesion along the course of the multisession therapy as a cost-effective measure. It is an excellent tool for the routine follow up on the progress of treatment and its natural course as well when TLPS is not feasible/available.

However, both TLPS and WBBPS are underutilized throughout the world and not commonly available in the U.S. yet although every nuclear medicine laboratory is capable to perform based on current equipments. Not because of a lack of technology but a lack of knowledge and of request is the main reason why many laboratories never perform these examinations.

Angiography

Basic diagnosis of the AVM as one of the CVMs is generally sufficient with proper combination of the non- to minimal invasive tests as suggested as above. But the final diagnosis of the AVM should be confirmed with this invasive study as a road map to further define the lesion and plan proper treatment. To minimize radiation exposure, these techniques are usually performed at the time of treatment in young patients.[136, 137]

These studies include:

— selective & superselective arteriography;

— percutaneous direct puncture arteriography;

— percutaneous direct puncture phlebography.

Contemporary diagnostic test: dynamic contrast enhanced magnetic resonance imaging (dceMRI)

Dynamic contrast enhanced magnetic resonance imaging (dceMRI) yields more information, including flow characteristics, soft tissue involvement, and the relationship to normal anatomy, as a new generation of radiographic technologies.[130, 131]

dceMRI is not only capable of diagnosing vascular malformations but more importantly, able to differentiate high flow from low flow.[131] The presence or absence of early venous return from veins draining the lesion or true immediate arterial venous shunting through the lesion can also be identified. If the lesion is not apparent on the dynamic gadolinium enhanced images until the capillary phase or more typically the venous phase as determined by comparison with visualization of normal vessels, the lesion is considered to be a low flow abnormality.

dceMRI provides the most critical information, especially regarding a lesion that will be treated surgically. dceMRI not only determines hemodynamic quality, but also demonstrates the true extent of the lesion as well as soft tissue compartments involved, all of which becomes important in planning the surgical approach.

The hemodynamic and anatomical characteris-

tics determined by dceMRI allow for implementation of either catheter-based embolization for high flow lesions, or transcutaneous sclerotherapy for low flow lesions, with or without surgical resection, depending on the extent of the lesion, cystic quality, and involvement of vital structures.

As with the majority of sophisticated imaging techniques, dceMRI requires the use of sedation or general anesthesia in the pediatric population due to the length of time required to perform the study, the need to hold still, and the noise of the magnet.

Differential diagnosis with acquired AV fistula

Acquired arteriovenous fistulas (AVF) in the peripheral vasculature (non-CNS) are largely secondary to some form of trauma. Post-catheterization groin AVF, post-penetrating trauma AVF (knife injury, bullet injury, shrapnel injury, etc.), postsurgical iatrogenic AVF (post lumbar spine disc surgery, etc), spontaneous aorto-caval fistula (due to aortic aneurysm rupture into the IVC), are the most commonly published entities.

Iatrogenic or traumatic AVFs are different from congenital AVMs and need to be differentiated as treatment differs. One percent of AVF were reported due to blunt trauma, while penetrating trauma, stab wounds, and gunshot wounds accounted for the vast majority of these lesions (63% and 26%, respectively).[138, 139]

Iatrogenic and traumatic AVF are characterized by a single direct communication between an artery and a vein without an intervening vascular nidus. Significant variability in clinical presentation and subsequent potential clinical consequences of AVF depend on the nature of the arterial trauma, the anatomic location, and duration of the AV communication.

Differential diagnosis- capillary malformation in new born cases- immunohistochemical analysis

Differential diagnosis between AVM and capillary malformations (CM) can be challenging in newborns and debate continues regarding the need for and type of diagnostic imaging for patients who present with an isolated macular stain in the neonatal period.

Early accurate diagnosis of this birthmark either as AVM or CM is not easy but the AVM is needed to be firmly dismissed as the prognosis dramatically changes. Recently, Wilms Tumor 1 (WT1) antibody has been presented as an ancillary test that can be helpful to differentiate AVM from most capillary malformations.[140, 141] All vascular malformations in a study were completely negative for WT1 except in arteriovenous malformations, where WT1 expression was positive.

Hopefully in a not too distant future immunohistochemical analysis of WT1 expression will be a useful tool in differentiating both capillary and arteriovenous malformations, allowing an earlier diagnosis and consequently preventing misdiagnosis and inappropriate therapy.

Management: general overview

The AVM, regardless of its type (extratruncular or truncular), remains the most challenging malformation among various CVMs due to its extensive impact on the entire cardiovascular system and the subsequent profound hemodynamic consequences. The clinical manifestations associated with the AVM are dependent on the anatomical location, where centrally and peripherally located lesions may produce cardiac failure, local venous hypertension, and arterial/venous insufficiency, respectively. In addition, local effects of AVMs may include ulceration and gangrene.[142]

Indications for treatment of (extratruncular) AVM lesions are listed in Table V based on its urgency. These indication criteria were formulated based on the extratruncular AVM lesions since the absolute majority are extratruncular lesions while the truncular AVM lesions are extremely rare.[1, 4, 143]

Among the lists of criteria, the first 4 indications although very rare, often reflect a condition that is 'too late' to be handled safely with a high risk of morbidity as well as mortality. But in general, the latter 5 indications are common conditions clinicians will encounter.

TABLE V.—*Multidisciplinary Team for the Contemporary Management of the AVM*

Vascular Surgery, Pediatric Surgery, Plastic and Reconstructive Surgery, Orthopedic Surgery, Neurosurgery, Oral-Maxillar-Head and Neck Surgery, Anesthesiology, Pathology, Physical Medicine and Rehabilitation, Cardiovascular Medicine, General Medicine, Pediatrics, Interventional Radiology, Diagnostic Radiology, Nuclear Medicine, Dermatology, Neurology, Psychiatry.

Progression of AVM varies slightly from patient to patient, with some patients remaining asymptomatic until adulthood while others develop symptoms early in childhood. Development of symptoms is caused by increased shunting that results in arterial steal and venous hypertension, both of which reduce tissue perfusion. Tissue ischemia is manifested by the development of pain, ulceration, and bleeding.

Factors known to trigger progression include elevation of systemic vascular growth factors such as are seen with generalized growth, during and after puberty/menarche or pregnancy and following tissue trauma including surgery and proximal occlusion of feeding arteries. Patients with early-stage AVM should be counseled to minimize these risks, by avoiding the use of estrogen containing contraceptives and unnecessary surgery. The Schobinger classification is an important aid in defining the level of clinical progression in AVM diagnosis and treatment.

An ill planned and improper treatment strategy (incomplete resection, ligation or proximal embolization of the feeding arteries) only stimulates the extratruncular AVM lesion to transform from a dormant state to a proliferative state, resulting in massive growth with uncontrollable complications. Aggressive control of the lesion nidus itself is therefore warranted to prevent recurrence and eventual deterioration of the AVM lesion.

The main goal of treatment should be to eliminate the "nidus" by occlusion or removal. Simple occlusion or ligation of feeding arteries, leaving the nidus intact, and will result in an almost sure recurrence by opening and development of new feeding vessels. Every treatment of AVM should be centered on the complete occlusion of the "nidus".

Recommendation

Occlusion or removal of the AVM "nidus" should be the main goal of treatment. Simply occlusion or ligation of feeding arteries is an incorrect treatment and should be avoided.

General principles

Management of truncular AVM lesions (patent ductus arteriosus) is relatively simple and straight forward compared with extratruncular lesions, because of NO risk of recurrence and/or progress/growth. Surgical or endovascular occlusion/removal of the AV shunting hole between the artery and vein will be able to provide a permanent "cure" (covered stent).

However, a controlled, aggressive approach must be performed in the management of extratruncular AVMs in general where the benefit of treatment must always exceed the risk of the associated morbidity. Only in situations where treatment morbidity and mortality are exceedingly high, should a palliative approach be considered. For example, when no invasive treatment is indicated, it's possible to improve swelling and discomfort related to an AVM of the arm or leg by wearing a graded elastic compression sleeve or stocking.

A relatively new multidisciplinary team approach to the treatment of AVMs has resulted in significant improvements in the work up, diagnosis, and treatment of these lesions. Reductions in morbidity, mortality and recurrence rates associated with the treatment of AVMs have been reported with the multidisciplinary approach that utilizes new CVM lesion classification, advanced diagnostic and therapeutic technology, and full integration of the latest treatment modalities.[144-147]

A fully integrated specialty team for advanced diagnosis and treatment of AVMs will provide the full spectrum of endovascular and surgical therapy. The multidisciplinary team approach will allow maximum coordination among the various CVM-related specialists (Table V).

Therefore, the management strategy for the treatment of AVMs is fundamentally different from other CVMs [148-153] due to the difficulties encountered in treating a high-flow lesion versus a low-flow lesion. The agent of choice, the route of application and the general treatment frequency and strategy is vastly different for different types of CVMs.[154-157] For instance, while direct percutaneous puncture may be used for most VMs, the combined endovascular /percutaneous route is utilized for AVMs.[144, 146] Surgical management of high-flow malformations and low-flow malformations do have their distinctive issues for resection.[158-161]

Management: surgical therapy

General overview

Surgical resection has long been the only means of eradicating the AVM nidus and has re-

mained the gold standard for the treatment of "extratruncular" AVMs for many decades.[162-165] Complete eradication of the 'nidus' of AVM is required to achieve an effective cure despite high rates of complication, and morbidity. But, incomplete resection in many cases is unavoidable due to the prohibitively high morbidity associated with radical surgical therapy to prevent recurrence.

The role of surgical resection has changed with the development of endovascular therapy over the last decade. Open surgical resection outcomes have significantly improved with the use of adjunctive endovascular therapy.[166-169] For most AVMs, the goal of embolization is to reduce AVM nidus size to the point where surgery would be possible. Preoperative embolo/sclerotherapy has improved the safety and efficacy of subsequent surgical resection, resulting in significantly reduced morbidity and mortality (minimizing intraoperative bleeding). Postoperative supplemental endovascular therapy has also been shown to be of benefit in the surgical treatment of AVMs.

Excisional therapy

The most difficult decision in the surgical management of extratruncular AVM is the right 'timing' of the surgery. A localized AVM in the anatomically non-critical area can be excised at any time but most of the occasions the surgeon has to face the problem with a "correct" timing. Early surgery can be unnecessary and also can exacerbate the residual lesions if the procedure is not radical and complete.

Severe complications existing at the time of surgery is a sign of inappropriate delay in the treatment. A thorough knowledge of the AVM pathophysiology is mandated for the proper selection of the best suited surgical option.[170, 171] Most of all, a strong interaction and frequent communication with the interventional radiologist is critical for the surgeon to achieve successful outcome in this complex and difficult patient group.

Nevertheless, advances in endovascular techniques and materials through the decades has reduced the need of aggressive surgical procedures significantly.[172-175]

From the technical point of view the surgeon would need an accurate evaluation of the involved anatomic areas to choose the best surgical approach. Four different groups of the (extracranial) AVM: head and neck, visceral, upper limb, and lower limb, have different characteristics related to their own specific approach, excisional options, and reconstructive options.

In general, the dissection of the tissue plane at a considerable distance from the lesion ("en block" resection) is advisable with adequate amount of surrounding soft tissues unless preoperative embolotherapy is combined.

Furthermore it is appropriate to underscore the benefits gained from the use of skin expanders in the reconstructive phase. A silicone balloon expander is inserted under the skin near the AVMs area and then gradually filled with saline over time, allowing the skin to stretch. In this manner it is much easier to perform a reconstructive procedure after removing the malformation lesion. Tissue expansion is very useful in reconstructing almost any part of the body; it produces excellent results expecially in the face and neck, but also in the hands, arms, and legs.

Unfortunately, the AVM lesions are very often poorly localized and are often diffuse infiltrating lesions where surrounding tissue structures make obtaining free margins difficult even with the help of intraoperative histological examination. Residual lesions will be the cause of undesirable additional surgical procedures. Removal of viable unaffected tissue as a security margin is often an unnecessary sacrifice but only increases the morbidity in functional or cosmetic areas.

Special issue involved to the excisional therapy of upper extremity & hand AVM

Hand/finger AVM has a unique condition of frequent involvement of the skin to cause ulceration and bleeding. Endovascular treatment of AVM of the hand/fingers has a significantly higher risk of complications including fingertip ischemia and necrosis.[186]

Indeed, the surgical treatment of AVMs in the upper extremity requires a sound working knowledge on the clinical course of this high flow vascular malformation lesion in addition to such unique reconstructive techniques involved to the upper limb lesions. The anatomy of the neuro-vascular bundle in the digits is a difficult surgical hurdle to successfully manage.

The surgeon who will manage the AVM among children and adults should be familiar with the issue on "when to resect an AVM of the hand and how to properly reconstruct the defect".

The aim of reconstructive surgery following the resection of hand and/or forearm AVM is to preserve function and optimize the cosmetic outcome. However, the arm, forearm and hand contain limited soft tissue and and narrow compartments such that the soft tissue reconstruction following AVM resection can be as simple as allowing the wound to heal by itself, which is less ideal, or as complex as the coverage of the defect with a microsurgical osteocutaneous free flap.

Nevertheless, the principles of surgical management include the restoration of vascularity, stable bone fixation, and if needed, repair of specialized tissue such as muscle, nerve and tendon, followed by a definitive soft tissue coverage.

Exposure of nerves, tendons, blood vessels, and bone will often require free tissue transfer. Occasionally, after a massive AVM lesion excision, the tendon transfers are not available necessitating muscle flap closure.

Finally, common postoperative complications are associated with soft-tissue failures (e.g. skin graft contraction, fascial adhesions causing restricted tendon motion, and diminution of muscle function), infection, and AVM recurrence. The surgeon therefore, would need a solid knowledge of the nature of these complications as well as the means for their prevention and treatment.

RECOMMENDATION: Surgical management of AVM requires the cooperation of different surgical specialities depending on the age of the patient, involved anatomical area and the frequently sophisticated reconstructive procedures to be performed

Management: endovascular therapy

General overview

Endovascular therapy with various embolization and sclerotherapy modalities, is now fully accepted as the 'preferred' therapeutic option in the majority of "extratrucular" AVM lesions. Endovascular/Embolo-sclerotherapy alone as an independent therapy is the treatment of choice for surgically "inaccessible" lesions or the lesion with prohibitive surgical risks as independent therapy, such as AVM lesions that extend beyond the deep fascia and involve muscle, tendon and bone – the diffuse infiltrating type of extratruncular form of AVMs in particular.[177-180]

Precise delivery of the embolo/sclerosants directly into the nidus of the extratruncular AVM lesion is required for successful endovascular therapy. The outdated approach with the coil embolization or proximal ligation of AVM feeding arteries should be abandoned.

A combination approach utilizing all three routes of delivery (transarterial, transvenous, and direct puncture) should be considered to destroy the AVM lesion nidus as much as possible.

Multi-session endovascular therapy is preferred and every effort should be exercised to minimize the risks of embolo-sclerotherapy during each session. The most appropriate embolic agents for primary control of AVM include: absolute ethanol, Onyx, N-butyl cyanoacrylate (NBCA), and venous coils. The use of nBCA or Onyx alone is generally inadequate to "cure" or provide long-term control for AVM.[181-184]

Embolic agents

Almost every known embolic agent has been used in the treatment of AVMs. Particular agents, which include polyvinyl alcohol particles, microspheres, gelfoam and collagen powders, have been used to treat these types of lesions. Their use, alone or in combination with other agents, is well documented in the literature.[173-175, 181-184] Unfortunately, these agents do not possess properties that are well suited for treating AVMs. The particles are often either too large, and occlude the vessels proximal to the nidus, or too small traveling through the AV shunt causing non target embolization. Since they are not well suited to treat AVMs their primary purpose is to alter the hemodynamics of the lesion to improve the effectiveness of other therapies.

Coils

Coils are designed to focally occlude larger vessels and have no way of penetrating into the lesion nidus.[185, 186] Another major disadvantage of coil embolization therapy is that its mechanism of action is limited to the occlusion and subsequent thrombosis of the artery or vein in which it is placed.

Permanent damage to the blood vessel endothelium does not occur allowing for subsequent regeneration or recovery of the endothelium. This can result in recanalization with recurrence of the lesion. This is especially true with extratruncular AVM lesions where the potential for subsequent proliferation is significant.

In extratruncular type AVMs, where the propensity for lesion regeneration is high and the complexity of the nidus is great (Table IV) - review the section of arteriographic classification of the AVMs-, it is never clinically appropriate to use coils to occlude the primary arterial path to an AVM. When this is done, effective treatment with an appropriate agent is severely hindered with significant clinical consequences. In these situations coils are typically used as secondary devices or on the venous side of the lesion.

Coils can be placed in the outflow veins to assist in definitive treatment. This is particularly effective where multiple arteries connect to a single draining vein (arteriographic type II lesions). In this subtype of AVM, occlusion of the venous outflow with coils can be very effective and reduces the risk of tissue injury from arterial embolization.

In extratruncular AVMs that have an aneurysmal dilatation along the draining vein, with multiple outflow veins arising from it (Arteriographic type II), coil embolization can be used in combination with ethanol to secure definitive treatment. Once flow has been slowed in the outflow veins by the placement of the coils, the injection of absolute ethanol can then reflux into the many vein fistulae in the wall of this aneurysmal vein to allow permanent occlusion of the AVM.[187, 188]

Coils are appropriate and very effective in treating "fistulous AVMs" as the primary treatment. Indeed, such truncular lesions are often amenable to successful treatment with coils or other mechanical occlusive devices (Amplatz device). However, these truncular (fistulous) type lesions often require many coils for successful obliteration of the lesion and treatment of the associated hemodynamic problems (cardiac failure, arterial insufficiency, and venous insufficiency).

Liquid agents

Liquid agents all have the ability to penetrate into an AVM nidus and as such are ideally suited for the treatment of these types of lesions.[180-184] Liquid agents can be divided into two groups; slerosants and polymerizing agents. The two most commonly used polymerizing agents are N-butyl cyanoacrylate (nBCA) and Onyx. Among the sclerosants, the most commonly used agents to treat vascular malformations are ethanol, sodium tetradecol sulfate, polidocanol and bleomycin. Of these sclerosants, ethanol is by far the most commonly used agent in the treatment of high flow arterial lesions. The rest of the agents are primarily used in low flow venous and lymphatic lesions.[189-192]

nBCA (n-Butyl Cyanoacrylate)

nBCA is a clear free flowing adhesive liquid that will polymerize on contact with any ionic solution. nBCA must be combined with eithiodized oil to reduce the polymerization time and to add radiopacity. The more eithiodized oil used the slower the polymerization time.[193-196]

In addition to its immediate mechanical effect, nBCA also induces an acute inflammatory response likely related to heat generated during the polymerization process and a chronic inflammatory response related to a chemical effect. This inflammatory response is believed to play a role in the long-term success of the occlusion obtained. In addition to the inflammatory reaction, the homogeneity of the glue cast may play a role in the long-term success of vascular obliteration.

However, many consider nBCA to be "palliative at best". It is clear that only in very small AVMs (therefore also resectable AVMs), has nBCA been curative. The vast majority of AVMs causing significant symptoms requiring therapy are not of this type. Furthermore, nBCA has been documented to being "resorbed" and disappearing on long-term follow-up causing AVM recurrence and symptoms.

Onyx

Onyx is a new less adhesive liquid polymerizing embolic agent that can be injected very slowly for embolization of AVMs. Its active component is a copolymer of ethylene and vinyl alcohol (EVOH) dissolved in dimethyl sulfoxide (DMSO). It is known to be extremely effective in reaching a large part of the nidus with macro

shunting. However this effectiveness is not universal, and in some patients, onyx embolization results in extensive arterial occlusion without penetration of the nidus of the extratruncular AVM lesions.[196-199]

Onyx has several advantages over glue (nBCA). For one, the ability to inject more slowly transforms the embolization procedure from a rather unpredictable intervention into a controlled procedure. Additionally, since Onyx is less adhesive and polymerizes more slowly, microcatheters are rarely glued in the nidus and consequently a prolonged (>60 minutes) and controlled intranidal injection is possible with less risk of propagation through the vessels away from the malformation. This usually results in penetration of different portions of the nidus until a satisfactory result is obtained. Another advantage of this agent is its much lower risk of pulmonary embolism compared to the other particulate emboloagents.

In peripheral AVM use, Onyx has not been shown to be a curative agent. It is a palliative or pre-operative embolic agent like nBCA. With extensive Onyx embolization, as with extensive nBCA embolization of large AVMs, over time the neovascular stimulation that occurs as new collaterals form to re-supply the AVM with arterial flow, can create a "massive network of small arteries/arterioles" that are by any means.

This neo-vascular stimulation can lead to symptom recurrence without any endovascular or surgical treatment option remaining for these difficult patients.

Sodium tetradecyl sulfate

Sodium tetradecyl sulfate (STS) is a long-chain fatty acid salt with detergent properties. It is a very effective venous sclerosing agent causing vascular injury by altering the surface tension around endothelial cells. It is not nearly as potent a sclerosant as ethanol so that its use as an intra-arterial agent is limited despite its popularity for the treatment of venous malformations.

Unfortunately, occasional anecdotal experience with intra-arterial use of STS to treat AVMs reported severe complications associated with the intra-arterial administration of STS. These complications may be related to STS's propensity to cause extensive vascular thrombosis that may extend beyond the region of the injection and cause subsequent vascular occlusion and tissue necrosis.

Doxycycline and bleomycin

Both agents are considered mild sclerosing agents and have been used in the treatment of lymphatic and venous malformations.[191, 200] These agents have not been used in the treatment of AVM lesions due to their mild properties as a sclerosant which are unlikely to cause any significant vascular injury when administered in a high flow vascular bed. In low flow lesions where the contact time with the endothelium is much greater, their effectiveness is greatly increased.

These agents can also cause unwanted systemic side effects. Bleomycin is known to cause pulmonary fibrosis, hair loss and pigmentation and therefore the quantity of this drug used must be carefully limited.

Polymethlmetacrilate

Polymethlmetacrilate (PMMA) is a dual component substance composed of a non–organic element (aluminium hydroxide) and an acryilc polymer (PMMA). The combination of both products activate a polymerisation process which produces a stable, inert and solid material. The substance has been used in percutaneous vertebroplasty. Recently, it has been reported to be successful in the treatment of intraosseous AVMs by direct percutaneous injection into the affected bone. However, larger experience is necessary to evaluate the real efficacy on intraosseous AVM.[201]

Factors effecting embolo-sclerotic agent choice

It is a common misconception that there is only one "gold standard" embolic agent that should be used when treating AVMs. Selection of the right embolic agents is often determined by three factors; lesion location, lesion morphology and the clinical circumstances.

Lesion location is often the most important factor in determining which embolic/sclerosant agent to use. If a lesion is located near neurologic structures, then the use of ethanol may very well be contraindicated. Ethanol can cause extensive soft tissue and nerve injury and severe neurologic complications have been reported with

the use of this agent. In these instances the use of a different liquid embolic, such as nBCA or Onyx may be preferable. In addition, peripheral skin lesions are also problematic. When treating these lesions with ethanol, skin breakdown and ulceration are not uncommon, increasing the morbidity substantially.

The clinical circumstances in any individual case may impact the choice of embolic/sclerosant agents. If the primary goal of treatment is to reduce severe vascular shunting, then the use of a large embolic agent may be preferable. As an example, an infant that is born in heart failure from an extensive extremity AVM may be best treated with coil embolization of the iliac artery. This embolization agent, although far from ideal, will rapidly correct the hemodynamic problem and save the infants life to allow more definitive future therapy.

Similarly, in situations where the goal of therapy is to devascularize the lesion to aide in surgical resection, it is not necessary to be as concerned about the long-term cure potential of the agent. This is often the case with cerebral AVMs. If a lesion is small with minimal clinical symptoms, then the risk of using a strong sclerosing agent such as ethanol may outweigh the potential benefit of obtaining a cure. This is commonly the case with low flow venous malformations.

Lesion morphology will also play a crucial role in the choice of embolic/sclerosant agents. The fistulous AVM defined as "truncular" lesion, such as the pulmonary AVM, can be best treated with a large embolic device such as coils or other mechanical occlusion devices with no risk of recurrence. But for the "extratruncular" AVM lesions with more complex conditions of the nidus, the nuances of the venous and arterial anatomy will determine which combinations of embolic/sclerosant agents are used. Coils, sclerosants and polymerizing agent may all need to be employed to address the anatomy of a specific lesion.

Absolute ethanol therapy

Absolute ethanol's curative potential as an AVM embolic/sclerosant agent lies in the fact that it is a powerful sclerosant.[202-206] The endothelial cell is denuded from the vascular wall, its protoplasm precipitated, and the vascular wall is fractured to the level of the internal elastic lamina. Platelet aggregation occurs on the denuded vascular wall surface. This thrombotic process progressively occludes the vascular lumen from the vascular wall surface to the central lumen. There will be no more "chemotactic cellular factor" and "angiogenesis factor" since the endothelial cell is completely destroyed.[202-206]

However, the risk of cardiopulmonary complications during the ethanol sclerotherapy administration is significant therefore, appropriate measures should be taken which include administration of general anesthesia and close cardiopulmonary monitoring. Use of a pulmonary artery catheter during ethanol sclerotherapy will allow continuous pulmonary artery pressure monitoring. [207, 208]

Pulmonary hypertension is a potentially fatal complication associated with ethanol sclerotherapy and occurs when a significant dose of ethanol is allowed to reach to the lungs. The etiology of pulmonary hypertension is felt to be related to either pulmonary arterial spasm or extensive micro-thromboembolization. The development of pulmonary hypertension can lead to subsequent cardiopulmonary arrest if not controlled effectively.

A total dose of ethanol which is less than 1 ml/kg is the maximum volume that can be safely given during a procedure since the volumes higher than this can result in toxicity. As advocated by Do YS and Lee BB,[209] limiting ethanol injections to 0.14 ml ethanol/kg ideal body weight every 10 minutes, will be able to obviate the need of a pulmonary artery catheter when anticipating large injections of ethanol in large lesions.

By adhering to these principles, the risk of ethanol flowing to the pulmonary circulation, thus causing spasms with subsequent acute right heart failure, is negligible.

Absolute ethanol is therefore, associated with various complications and morbidity. Safe use of ethanol in AVM embolization requires accurate delivery into the nidus by precise placement solely in the AVM nidus vasculature that is nonnutritive and without capillaries. Proximal injection of ethanol into a feeding artery would cause severe tissue necrosis.

It may be diluted when used to treat superficial AVMs which carry a high risk of skin necrosis and AVM lesions in close proximity to nerves. Administration of smaller volumes in divided doses also

minimizes the risk of surrounding tissue injury. The residual ethanol may be drained prior to removal of needles. Direct compression of the vein draining the AVM during treatment, may prevent early drainage during ethanol injection.

In order to enhance the denaturating or "sclerosing" effect on the endothelial cells, lowering the flow in the AVM itself is a highly effective technique to allow the injected ethanol to remain in longer contact with the cells. Decreasing the flow through the lesion can be achieved in different ways.

1. An arterial approach. This approach makes use of occlusion balloons.

2. Direct nidal injection of the sclerosing material. Occlusion balloons are also used in this technique.

3. A venous approach. A venous occlusion is created distal to the puncture point in the outflow vein. This occlusion can be achieved by means of manual compression, placement of coils if a dilated venous pouch is present, or use of pneumatic compression bands.

In a situation with high outflow it is an advantage to compress the outflowing veins either by applying suitable devices or simply by manual compression, thus redirecting the blood flow in a retrograde fashion towards the nidus.

If the draining veins are aneurysmal it is an advantage to apply embolisation using coils or J-guide-wires to slow down the venous outflow first so that ethanol can achieve not only thrombosis, but also to denude the vascular endothelium - a critical step towards achieving permanent obliteration of the AVM.

Multiple sessions are often required in order to minimize the risk for ischemic complications of normal surrounding tissue, and at the same time obtaining a cure of the AVMs. Sometimes in situations with micro-fistulous type AVMs, where there are diffuse infiltrative patterns of the nidus, it is an advantage to deliver the ethanol in a 50/50% diluted form with a non-ionic contrast medium.

An additional way to decrease the severe effect of alcohol in terms of swelling followed by pain in the treated area is a routine use of hydrocortisone as well as non-steroid anti-inflammatory drugs, thus preventing, or at least minimizing, the risk for development of compartment syndrome with subsequent possible nerve injuries.

Nevertheless, many concerns regarding the routine use of ethanol for all AVMs are due to its significant risks of complications and morbidity (pulmonary vasospasm, nerve damage or skin necrosis), which requires discrimating use to the AVM lesions with the risk of serious local or systemic complications (acute bleeding).[210, 211]

Endovascular therapy - covered stent implantation

Endovascular placement of covered stents mainly in subclavian, iliac and femoral arteries to control the 'acquired' AV fistulas has been reported in the literature with good results. Covered stents have also been utilized in the treatment of AVMs. They are effective in excluding arterial aneurysms that often develop in the afferent arteries of the AVM. Covered stents are effective in treating direct communicating, truncular AVM lesion. Use of a covered stent in the treatment of an extratruncular AVM will have the same disadvantages/risks associated with surgical ligation or endovascular occlusion of the feeding artery, leaving the "nidus" intact, and will ultimately which result in recurrence.

Therefore, covered stents should not be used in the treatment of extratruncular AVMs.

However, in the rare occasion in which surgical removal or endovascular occlusion is not possible and the patient has a severe complication (cardiac failure, bleeding or others), covered stents may be considered as a last-option of a life-saving procedure.[212-215]

Laser therapy

There has been substantial improvement on the management of the CVMs with the laser through last decades.[216-227] The treatment of VMs with 1470 nm diode laser is now known to be very effective espe¬cially in small children to avoid the toxic side effects of sclerosing agents.[216-220] The diode laser also produces good results when treating superficial VM lesions by direct contact with the luminal surface. Experience for photocoagulation of AVMs have been also reported with satisfactory responses with the use of three types of lasers: Nd-YAG, pulse-dye, and diode laser.

Two more techniques have been reported in the treatment of AVMs: a percutaneous ap-

proach with the laser fiber guided to the nidus fluoroscopically, and an intraoperative approach with the laser fiber introduced under direct vision into dilated afferent arteries and efferent veins in a previously resected malformation. The experi¬ence is still limited and large series are needed in order to establish its indications for independ¬ent use and/or combined use with standard em¬bolization techniques.

However, the endovascular laser remains to be further proven for the efficacy in the treatment of AVM lesions although the laser effectively produces occlusion of the lesion resulting in reduced risk of bleeding. Therefore, the lasers should be used in the treatment of specific cases with appropriate indication either intravascularly (by catheterization) or percutaneously (by puncture and echo-guided approach of the fiber to the malformation).

At present, the first choice therapy for the management of AVM lesions is embolization, either alone or following laser therapy. For extensive lesions, interstitial Nd:YAG laser coagulation may help by obliterating all microfistulas to collapse the AVM permanently, or collateral vessels can develop very slowly.

Truncular av fistula

In general the pure truncular AVM lesion is successfully treated with embolization. However, some cases with the peripheral smaller vessels remained, are an indication for laser therapy. Depending on the size and origin, the pulsed dye laser, the KTP laser, the pulsed Nd:YAG laser, or the CW Nd:YAG laser chopped with the fluid cooling chamber can be used. For the fistulas which are not treated by embolization, a paravasal or intraluminal Nd:YAG laser coagulation can be performed. The surrounding pathological vessels are treated in the same session with high power transcutaneous ice cube-cooled Nd:YAG laser. Depending on the size of the lesion, multiple punctures with the afterloading technique and several sessions are necessary.

Combined truncular/extratruncular avm

Beside the case of the CMs, the most important malformation for laser therapy is the hamartous AVM lesion ("angioma racemosum"). Even though the first choice of the therapy is embolization, it is not always possible and even after successful embolization small AV fistulas remain in the periphery. In such occasion, an interstitial laser therapy or a transcutaneous ice cube-cooled Nd:YAG laser therapy can be tried.

Rendu-Osler-Weber Syndrome (Hereditary Hemorrhagic Telangiectasia)

For gastrointestinal bleeding spots, argon beamer electrofulguration is easier to handle endoscopically than side fire laser fiber. However, for all other manifestations Nd:YAG laser therapy is the treatment of choice.

For nasal or endoral spots, including tongue mucous membrane, CW Nd:YAG laser with 600 µ bare fiber either in near contact with 12-15 W at 300-400 ms in the repetition mode is effective.

For skin lesions including the face, finger or subungual areas, the pulsed Nd:YAG laser with intermittent ice cube cooling is the first choice. The parameters vary depending on the laser system, mainly between 50 and 100 J/cm^2.

For micro AV shunts, CCDS guided interstitial coagulation with 5W and in CW mode is necessary. In larger AV shunts with life threatening bleeding on the face, additional arterial embolization is indicated.

Other telangiectasias

Widespread telangiectasies as a component of other syndromes should also respond to pulsed dye laser treatment. Patients with diffuse telangiectasies as a component of the Rothman-Thompson syndrome or Telangiectasia Macularis Eruptiva Perstans demonstrate effective clearing following treatment with the pulsed dye laser. Other spider vascular lesions with a central artery show better results with pulsed Nd:YAG laser treatment.

So from the standpoint of the lesions general one can say the more smaller vessels like capillaries the shorter the wavelength and the pulse duration, the larger the diameter the longer the wavelength and longer exposure time. Due to these biophysical rules one can say the more extratruncular malformation the more a Laser indication the more truncular the more surgical and other intraluminal techniques.

Pharmacologic treatment

Pharmacotherapy of AVM is in its infancy.[229-231] In a small number of children treated at Children's Hospital Boston, Marimostat, a matrix metalloproteinase inhibitor, appeared to be effective in controlling progression of AVM. In one patient, subsequently reported, the drug clearly led to involution of an intraosseous AVM and bone healing. This patient is dependent upon the drug and has been taking it for 13 years. Unfortunately, marimostat is no longer available.

Doxycycline [200] has been used to treat patients with brain AVMs, where it may be associated with a reduced rate of bleeding. It is a matrix metalloproteinase inhibitor with mild antiangiogenesis effects. Clinically, it usually does not lead to any significant change.

Thalidomide [232] has also been used to treat symptomatic AVMs. In the experience of physicians at Children's Hospital Boston, the drug led to significant improvement in swelling and pain, especially for patients with AVM associated with PTEN hamartoma syndrome. Unfortunately, the AVM usually does not diminish with this medication.

Avastin/bevacizumab [233] has been used to treat several patients with HHT and has shown a significant reduction in epistaxis as well as arteriovenous shunting. Unfortunately it can also lead to bleeding.

Two children with AVMs were treated with Sorafenib, a multi-kinase inhibitor taken orally (unpublished data, P Burrows). These patients appeared to worsen so the medication was given for only a few months and then stopped.

Rapamycin has been shown to be highly effective in shrinking the painful hamartomas in PTEN hamartoma syndrome. Unfortunately, the lesions recur when the drug is stopped, and the AVM does not regress on this medication.

Prognosis of AVM lesions

The prognosis of an AVM is dependent on two major aspects: age at diagnosis and appropriate management. Children experiencing AVM exacerbation early in life will have a worse prognosis, will require a significantly higher number of surgical procedures, and have higher morbidity and sequellae, when compared with adult patients presenting with AVM exacerbations at 40-50 years of age.

In fact, the therapeutic objectives in children with large and incurable AVMs are generally are aimed at stabilizing their clinical course, preventing ulceration and bleeding, and managing the AVM lesion in order to minimize progression without significant disturbances on their quality of life.

Unfortunately, mismanagement of the AVM remains the principal cause of avoidable complications, which are mainly pain, skin necrosis, infection and bleeding. Once again, preventive medicine plays a key role as soon as possible. Patients with AVMs should undergo thorough evaluation by an experienced multidisciplinary team in order to avoid ineffective and potentially harmful treatments.

Hopefully, simple and useful blood markers will soon be discovered for patients with AVMs, as is the case with patients with VMs where D-dimer levels are useful for following the progression and activity of their lesions.

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