AVMS – HOW I TREAT THEM: ALCOHOL

ARTERIOVENÓZNÍ MALFORMACE – JAK JE LÉČÍM JÁ: ALKOHOLEM

review

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SUMMARY

Wayne F. Yakes, M.D. AVMs – how I treat ther: alcohol

AVMs are congenital vascular lesions typified by hypertrophied in-flow arteries and shunting through a primitive vascular nidus and into tortuous dilated out-flow veins. No intervening capillary bed is present. Symptoms are usually referable to the location of the AVM. The larger and more centrally located AVMs have a greater likelihood for cardiac overload. Other presenting symptoms include pain, progressive nerve deterioration or palsy, disfiguring mass, tissue ulceration, hemorrhage, impairment of limb function and, limiting claudication.

As catheter delivery systems and embolic agents improved, embolization has since emerged as a primary mode of therapy in the management of AVMs. In many cases, vascular malformations are in anatomically and surgically difficult or inaccessible areas; this has led to increased reliance on interventional radiology to manage these lesions.

Since ethanol completely destroys the endothelial cell, the phenomenon of recanalization and neovascular recruitment are noticeably absent. The permanence encountered with ethanol is unusual with other agents.

Because cure is possible by endovascular procedures, the role of surgery for AVMs has diminished. If cure is not possible by embolization, then either repeated transcatheter procedures and/or surgery may still have a role. With current fluoroscopic systems, vessels smaller than 1 mm can be imaged. This allows planning to spare normal structures and embolize the AVM nidus superselectively.

Vascular malformations are best treated where these patients are seen on a regular basis.
Key words: AVMs, embolization, ethanol.

SOUHRN

Wayne F. Yakes, M.D. Arteriovenózní malformace – jak je léčím já: alkoholem

Arteriovenózní malformace (AVM) představují jedno z nejtěžších diagnostických a terapeutických dilemat v medicíně. Klinický obraz může kolísat od symptomatického mateřského znaménka po život ohrožující srdeční selhání. Díky tomu se stává jejich léčba výzvou pro nejzkušenější z kliniků. Problém je dán tím, že AVM jsou relativně vzácné. Pokud se s takovou lézí setkává lékař jednou za několik let, je obtížné získat potřebné zkušenosti s diagnostikou a optimální léčbou. Typicky pak dochází k návštěvám mnoha odborníků, vznikají komplikace, rekurence potíží a často i zhoršení vlastních symptomů. V práci je prezentován vlastní přístup k diagnostice a léčbě pomocí aplikace etanolu.
Klíčová slova: arteriovenózní malformace, embolizace, etanol.

INTRODUCTION

Arteriovenous malformations (AVMs) constitute some of the most difficult diagnostic and therapeutic dilemmas in the practice of medicine. The clinical can range from an asymptomatic birthmark to life-threatening congestive heart failure. Attributing any of these varied symptoms to a vascular malformation can be challenging to the most experienced clinician. Compounding the problem is the relative rarity of these lesions. If a physician encounters one patient with this condition every few years, it is difficult to develop sufficient experience for diagnosis and optimal treatment. Typically, these patients seek help from a number of physicians, only to experience disappointing outcomes, complications, and recurrence or deterioration of their presenting symptoms. Here we present our approach to the diagnosis and their treatment with ethanol endovascular therapy.

INITIAL EVALUATION

A thorough clinical exam and history can usually establish the diagnosis of pediatric hemangioma or vascular malformation. Hemangiomas are usually not present at birth and have a bright scarlet color that gradually deepens. Vascular malformations have a persistent color depending on the dominant arterial, capillary, venous or lymphatic component. Evaluating for skeletal abnormalities, abnormal veins, arterial abnormalities, pulsatility or non-pulsatility of a lesion, dependent swelling or flattening upon elevation and disparity of limb size, along with neurologic evaluation and a good history can frequently enable diagnose and even categorization of a vascular malformation. The Nicoladoni-Branham test of in-flow arterial occlusion, if positive, will result in a reflex bradycardia if the AVM is of such a high flow that it is causing cardiac consequences.

Color Doppler Imaging (CDI) is an essential tool in the diagnostic workup of AVMs. Accurate measurements of flow volumes (a calculated physiologic parameter) and resistive indexes can be very helpful not only in the initial evaluation but are important noninvasive parameters for follow-up after therapy. Documentation of decreased arterial flow volumes and normalization of the resistive indexes are very specific and may obviate the need for repetitive follow-up arteriography (1).

Magnetic resonance (MR) imaging has replaced CT in the evaluation of vascular malformations. It has proven to be a mainstay in the initial diagnostic evaluation as well as in assessing the efficacy of endovascular therapy. MR can distinguish accurately between high-flow and low-flow malformations as well. And the relationship to adjacent anatomic structures, such as muscles, nerves, organs, is easily determined. High-flow malformations typically demonstrate signal void on most sequences. On gradient-echo sequences, increased signal within the vascular structures is present. At follow-up, MR can accurately determine residual areas of AVM as well as those areas that have been treated (2).

After the diagnosis has been established, the next major decision is to determine whether therapy is warranted. The interventional radiologist should plan and direct the patient's care with surgical specialists who are familiar with AVM management and the problems they present with must be available. It is extremely important that appropriate surgical, medical, pediatric, and anesthesiology specialists and subspecialists be involved for optimal patient care.

PAIN CONTROL

With the use of intravascular ethanol, pain control is a significant problem. Anesthesiologists can greatly aid in solving this problem and determine whether general anesthesia or intravenous (IV) sedation is required for the procedure. This leaves the interventional radiologist free to concentrate on the case at hand. For children, general anesthesia is required.

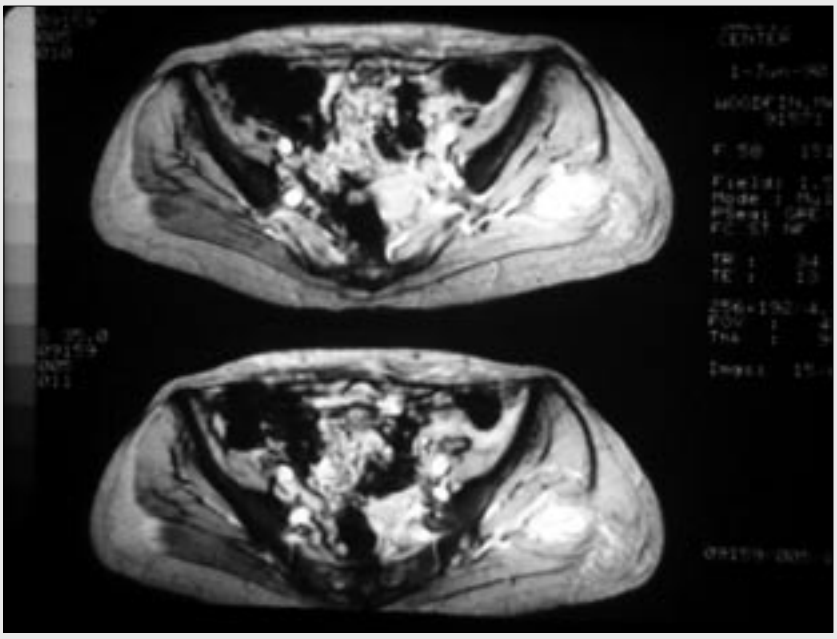
In patients with large AVMs and it is anticipated that larger amounts of ethanol will be used, Swan-Ganz and arterial line monitoring may be performed. Pulmonary artery pressures are consistently monitored during the injection of absolute ethanol. Decadron (dexamethasone sodium phosphate, USP, Merck & Co., Inc., West Point, PA, USA) is given IV to all patients prior to the procedure, usually 10 mg for adults and 3 to 10 mg for children depending on body weight.

ETHANOL ENDOVASCULAR THERAPY

The area of vascular access, whether it is the groin, the arm, or other points of percutaneous catheter access, is prepped and draped in sterile fashion. If the ethanol volume of injection is limited to 0.1 ml/kg every ten minutes, then Swan-Ganz monitoring may not be required. The area of the AVM that is to be treated percutaneously is also prepped and draped in sterile fashion. Fluoroscopy and/or CDI imaging techniques are used in those patients that require percutaneous access. Detailed arteriography is performed to determine the angioarchitecture of the AVM, the major compartments and endovascular access to those compartments are delineated. If the patients have had prior therapy, such as surgical ligations, partial resections, intraarterial coil placement, NBCA/IBCA embolization, etc, direct puncture techniques may be required to circumvent catheterization obstacles. Superselective placement of the catheter tip or the needle tip is a requirement, only then can ethanol be injected into the malformation and all normal vascular structures spared.

In the extremities, external pneumatic blood pressure cuffs as well as hand tied tourniquets may be useful and necessary to cause vascular stasis within an AVM. In the chest, abdomen, pelvis, and head and neck area, intravascular occlusion balloons may be necessary to achieve some element of flow arrest. Arteriograms must be performed in both the nonocclusive and occlusive state to determine exactly the flow characteristics of the AVM so that an appropriate volume and an appropriate rate of ethanol injection may be determined. The amount of ethanol used is equal to the flow-volume characteristics of the malformation compartment being treated.

After an injection of ethanol vascular occlusion is usually maintained for 10–15 min. After this time, vascular occlusion is released and arteriograms are performed to determine if therapy is complete or further embolization is required. Frequently additional compartments of AVM will then fill as others become thrombosed. Meticulous repetition of the previously described technique is then required.



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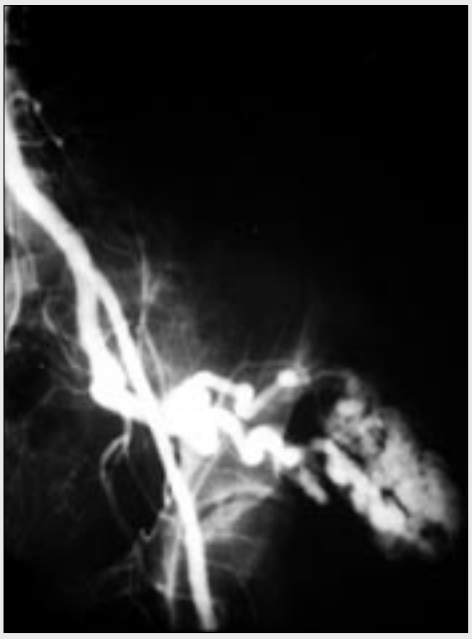

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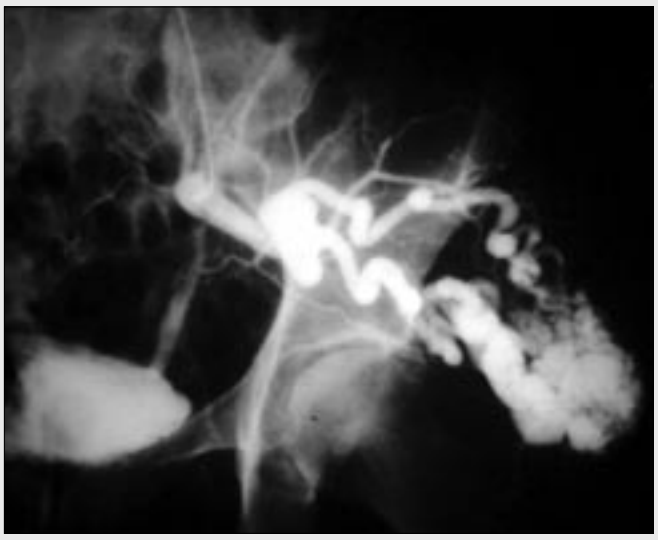

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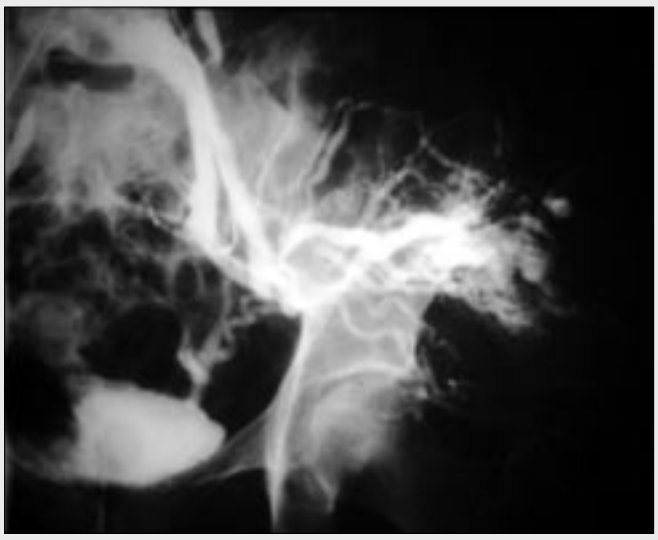

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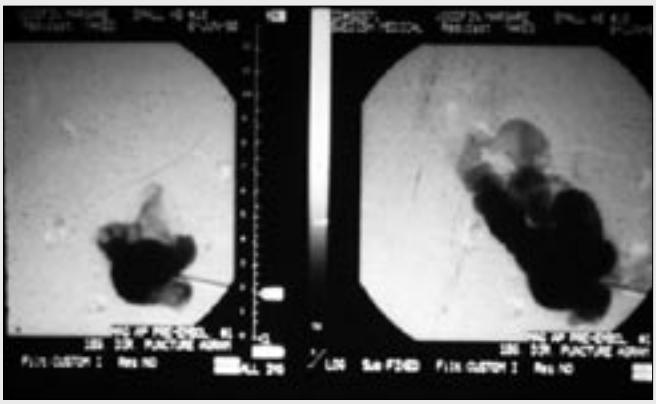
Fig. 1. ***A– 40-year old female with enlarging, painful left buttock mass. Axial gradient echo MR of the pelvis demonstrates a high flow AVM in the left gluteus medius and gluteus maximus muscles; B – AP pelvis arteriogram documenting large AVM of left buttock with arterial supply primarily from left superior gluteal artery branches of the left internal iliac artery. Note that the arterial supply proximally to the left Sciatic Nerve arises from the left superior gluteal artery branches as it exits the left pelvis; C1,2 – AP left superior gluteal arteriogram, arterial and venous phases. Note the venous drainage is into the left internal iliac vein; D – AP direct puncture arteriogram through 18 gauge needle percutaneously placed through the left buttock muscles and into the inferiormost compartment of the left buttock AVM. This access site allows filling of all the AVM compartments with ethanol as demonstrated by the total filling of the AVM on this direct puncture arteriogram; E – AP direct puncture arteriogram after injection of 31 ml of ethanol into the AVM nidus. Note the stasis of contrast on this injection due to thrombosis within the AVM nidus; F – AP pelvis arteriogram immediately post endovascular direct puncture embolization of the AVM nidus with ethanol. Note that there is normal contrast filling of all normal branches. The thrombosed AVM no longer has arterial supply. No further contrast filling of the AVM nidus is noted. No further arteriovenous shunting is present; G – AP pelvis arteriogram at three year follow up. Note total absence of the left buttock AVM. Only normal branches and normal vascularity is present. The AVM remains cured. The patient has no further symptoms that brought to seek treatment.***

Obr. 1. ***A – 40letá žena s bolestivým zvětšením levé hýždě, axiální obrazy MR ukazují vysokoprůtokovou arteriovenózní malformaci (AVM) levého velkého a středního hýžďového svalu; B – předozadní pánevní arteriografie dokumentující rozsáhlou AVM s arteriárním zásobením z levé horní gluteální arterie, větve vnitří pánevní tepny. Je zřetelné, že větve zásobující AVM odstupují z horní gluteální arterie proximálně od ischiadického nervu v místě, kde tepna vystupuje z pánve; C1, 2 – předozadní projekce arteriografie horní gluteální tepny – arteriální a venózní fáze. Venózní drenáž AVM směřuje do vnitřní pánevní žíly; D – předozadní projekce přímé arteriografie punkcí jehlou 18 gauge zavedenou přes hýžďové svaly do nejspodnější části AVM. Tento přístup umožní naplnění všech oddílů AVM etanolem, jak je ukázáno úplným naplněním AVM při přímé arteriografii; E – předozadní projekce přímé arteriografie po aplikaci 31 ml etanolu přímo do nidu AVM. Kontrastní látka stagnuje uvnitř kvůli trombóze malformace; F – předozadní projekce arteriografie bezprostředně po endovaskulární embolizaci AVM přímou punkcí etanolem. Je patrné normální naplnění všech obvyklých větví pánevních tepen. AVM již nemá žádné zásobení, není přítomno ani plnění nidu ani arteriovenózní zkrat; G – předozadní projekce arteriografie pánve po 3 letech. Kompletní absence AVM v oblasti hýždě, přítomné pouze normální cévní struktury. AVM zůstává vyléčena, nemocná nemá žádné přetrvávající příznaky, které by vyžadovaly další léčbu.***



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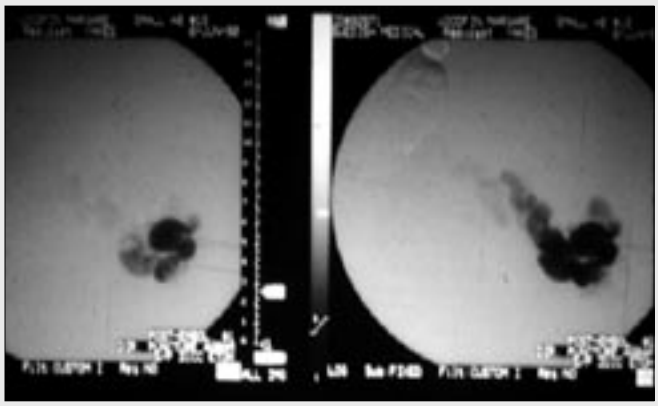

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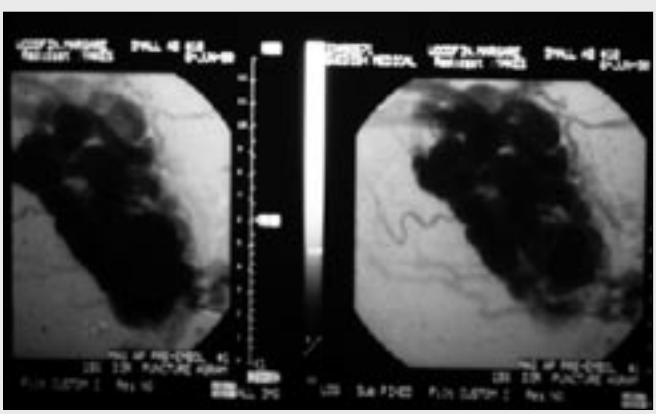

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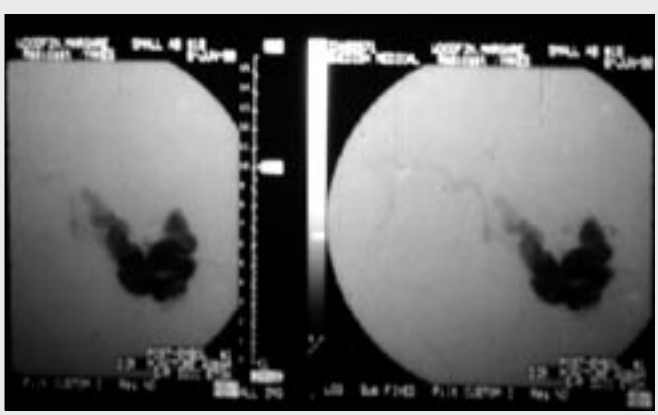

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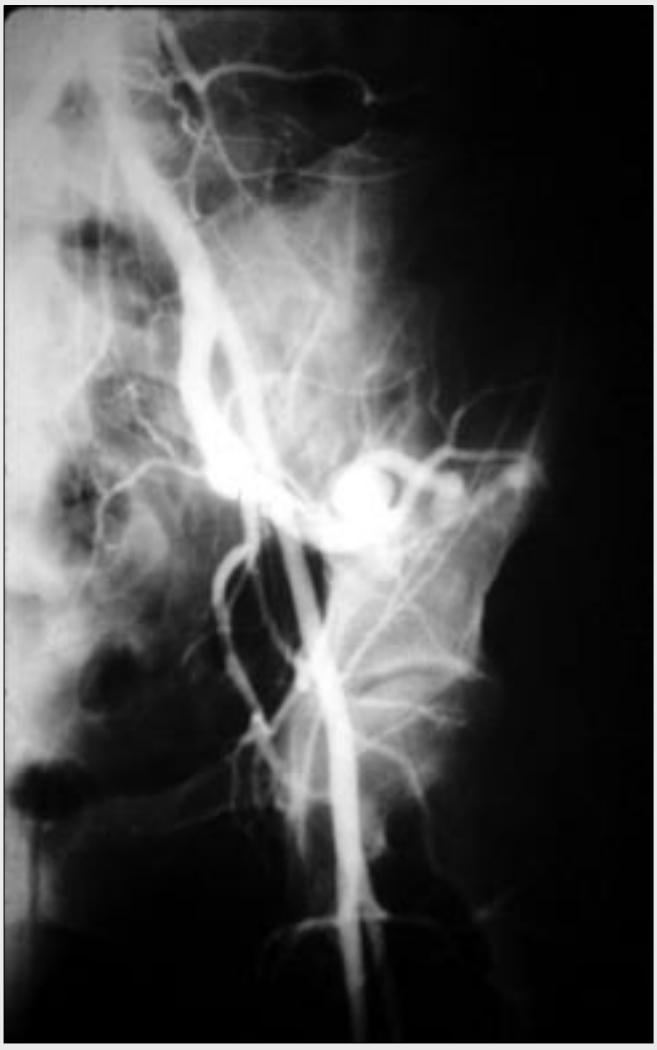

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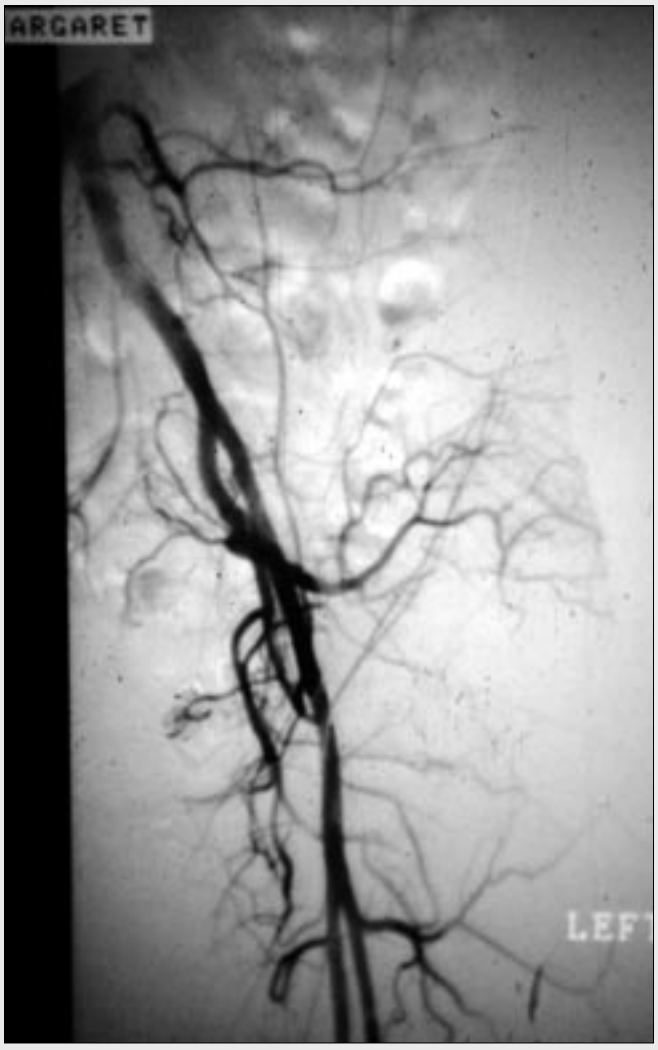

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The maximum total volume of ethanol used in treating patients with AVMs rarely exceeds 0.5–1.0 ml/kg body weight total dose. Most patients will tolerate these total ethanol volumes very well. Exceeding these doses can lead to ethanol toxicity. Cardiopulmonary collapse is a very rare but dreaded sequela and pulmonary artery Swan Ganz line and arterial line monitoring may be necessary to minimize the possibility of this event occurring. Once pulmonary artery pressures begin to rise, it is best to wait and not inject any more ethanol until the pulmonary pressures begin to normalize. If pulmonary artery pressures become pathologically high, the infusion of nitroglycerin, adenosine, or prostaglandin E-1 through the Swan-Ganz line can lower the intrapulmonary pressures; we favor adenosine. We have determined that increased pressures related to ethanol injection reaching the pulmonary artery capillary bed may cause, in some patients, pre-capillary spasm, which is a transient phenomenon. However, the infusion of these drugs through the Swan-Ganz line is very helpful in reducing the elevated pulmonary artery pressures. Nitroglycerine not only reduces pulmonary pressures, but may cause unwanted systemic blood pressure to drop. Adenosine infusion does not reduce the systemic blood pressure.

After the procedure and recovery from anesthesia, patients are sent to the general hospital ward. It is unusual for patients to require intensive care. Post-operative management consists of IV Decadron, fluids, Inapsine (Droperidol injection, Janssen Pharmaceuticals, Inc., Titusville, NJ, USA) as needed to control nausea. Oral or intramuscular (IM) Toradol (Ketorolac tromethamine, Syntex Laboratories, Inc., Palo Alto, CA, USA) by body weight is very helpful to control pain and swelling in adult patients. Pain is unusual, however oral and IV pain medications may be given additionally, if required. Patients with GI sensitivity to steroids can also be placed on Zantac (Ranitidine hydrochloride, Glaxo Inc., Research Triangle Park, NC, USA) to protect against gastric or duodenal ulcer development. Patients are usually observed four hours and discharged. Discharge medications usually include a tapering dose of steroids over 5 days, Zantac management to prevent ulcer development, and pain medications, if required. All patients are usually seen 7–10 days post-discharge or sooner if any problems develop.

Patients usually exhibit focal swelling in the area of the AVM, which in most patients will resolve within one to two weeks. In patients with lower extremity and foot AVMs, swelling may last longer due to the fact that the leg and foot are not only dependent organs but are weight-bearing structures as well. Usually after 4 weeks all swelling is resolved and the patient is ready for follow-up therapy as required.

FOLLOW-UP

After serial therapy, MR and CDI can be used to document the efficacy of therapy. CDI spectral analysis gives very accurate information in treated and untreated high-flow AVMs. AVMs demonstrate high velocity and low resistance waveforms. As the malformation serially becomes ablated, the waveform will normalize and the resistive indexes and the flow volumes that can be calculated will become normalized as well. MR is also an important investigative follow-up modality (1–2).

One of the most important aspects in AVM management is the determination of whether a patient's symptoms have been alleviated. In those patients who have no symptoms other than an increased cardiac output, Swan-Ganz line placement and calculation of cardiac output, cardiac index, and systemic vascular resistance will be important parameters to follow. Current non-invasive technologies used by cardiologists to evaluate these parameters are not as accurate as placement of a Swan-Ganz line and direct measurement. Our patients are evaluated with non-invasive and arteriographic studies annually. After several years of a persistent AVM closure, non-invasive imaging modalities will usually be sufficient for longer-term follow-up.

COMPLICATIONS

Various complications can occur with any interventional procedure. In patients with AVMs, complication rates around 5% occur in our institution. In our initial series, we reported a total complication rate of 30%, of which 10% were major and 20% were minor complications (3). With more experience, our complication rates have dropped to around 5%. Complication rates are related to the tissues that are being embolized. Non-target embolization with ethanol will lead to tissue necrosis, as capillary beds of normal arteries will be totally destroyed. Therefore, it is essential that superselective catheter positioning be achieved before ethanol can be used. Direct puncture techniques may need to be performed in the event that the catheter cannot reach the desired position to treat only malformation and not embolize normal tissues.

Vascular spasm, edematous tissues, and venous thrombosis can lead to complications as well. Localized skin blisters may occur. This is usually a minor annoyance that heals uneventfully. Injury to adjacent muscles, organs or other tissues is possible. In the pelvis, the colon is the most sensitive organ and great care must be taken against non-target embolization to avoid localized infarction. In only 1 patient in our series has this occurred, where a patient had to have a diverting colostomy to put the injured segment at rest. The AVM was intimately involved with the superior hemorrhoidal artery.

Motor or sensory nerve injuries may occur as well. We have found that most injuries have been related to the swelling involved with resultant nerve compression, rather than non-target embolization of the vasa nervorum. Again, aggressive Decadron therapy will be essential to minimize the effects of this swelling and to allow the nerve to recover more quickly. It is unusual for nerve injuries to become permanent.

Involvement of the appropriate clinical specialist in the management of complications is essential to minimize the morbidity of that complication. Those patients who present with tissue necrosis, whether related to arterial steal phenomenon or venous hypertension must be counseled that treatment of the AVM may not reverse their necrotic process. In those patients who develop ischemic complications, particularly of the digits, this process can be halted, but may come too late to save that digit. What is important therefore is to treat the malformation to prevent further tissue loss.

Bleeding is an uncommon complication of AVM's, unlike those of the brain and spinal cord, whose propensity to bleed is their main presenting symptom. In the periphery, AVMs will cause bleeding only if they involve the alimentary canal or if they cause superficial tissue ulceration. In this situation,

the malformation requires primary treatment. Only then will the tissues become normal, heal, and discontinue the hemorrhagic process. Attempts at skin grafting without treating the underlying malformation are usually doomed to fail.

COMMENTS

AVMs are congenital vascular lesions typified by hypertrophied in-flow arteries and shunting through a primitive vascular nidus and into tortuous dilated out-flow veins. No intervening capillary bed is present. Symptoms are usually referable to the location of the AVM. The larger and more centrally located AVMs have a greater likelihood for cardiac overload. Other presenting symptoms include pain, progressive nerve deterioration or palsy, disfiguring mass, tissue ulceration, hemorrhage, impairment of limb function and, limiting claudication.

Vascular anomalies were first treated by surgeons. The early rationale of proximal arterial ligation proved totally futile as neovascular recruitment reconstituted arterial inflow to the AVM nidus. Micro-fistulous connections became macro-fistulous feeders. Complete extirpation of an AVM nidus proved difficult and extremely hazardous ending in many suboptimal partial resections. Partial resection could produce initial clinical improvement, but over time the patient's symptoms recurred or worsened (3–8). Because of the significant blood loss that frequently accompanied surgery, the skills of interventional radiologists were eventually employed to embolize these lesions preoperatively. It was hoped that a more complete resection could result. However, AVM surgery still proved extremely difficult and total removal was rarely possible. As catheter delivery systems and embolic agents improved, embolization has since emerged as a primary mode of therapy in the management of AVMs. In many cases, vascular malformations are in anatomically and surgically difficult or inaccessible areas; this has led to increased reliance on interventional radiology to manage these lesions.

According to D. Emerick Szilagyi, M.D., former editor of the (USA) Journal of Vascular Surgery, "... with few exceptions, their (AVMs) cure by surgical means is impossible. We intuitively thought that the only answer of a surgeon to the problem of disfiguring, often noisome, and occasionally disabling blemishes and masses, prone to cause bleeding, pain, or other unpleasantness, was to attack them with vigor and with the determination of eradicating them. The results of this attempt at radical treatment were disappointing" (4). Indeed, of 82 patients seen in this patient series, only 18 patients were deemed operable. And of these 18 patients operated upon, 10 patients were improved, 2 remained unchanged and 6 were worse at follow-up.

Many endovascular occlusive agents (embolic agents) are currently in use to treat AVMs. Agents include autologous clot, gelfoam, polyvinyl alcohol particles (PVA), the various metallic coils with or without fibers, tissue adhesives (IBCA/NBCA), detachable balloons, Ethibloc, Sotradecol and ethyl alcohol (9–18). It is well known that gelfoam, PVA, coils, or detachable balloons rarely cure peripheral AVMs. Ethibloc has primarily been used for venous malformation management and is uncommon for high-flow AVM's. The tissue adhesives (IBCA/NBCA) were initially thought to be permanent occluding agents. However, there is difficulty in their use and it is now well documented that recanalizations do occur (12–18). As polymerization occurs, the cyanoacrylates generate heat which may contribute to some level of histotoxicity in the adjacent area and angionecrosis. Once solidified intravascularly, the cyanoacrylates incite a mild inflammatory response. In the head and neck area, undesirable cosmetic results may occur from black tantalum powder used to opacify cyanoacrylates. Furthermore, hard acrylate masses in muscular structures can cause muscular dysfunction, and tissue erosions. Miscalculations with the polymerization time can lead to problems with too distal or too proximal a polymerization and solidification. The literature is very consistent that glue embolizations of AVMs are palliative at best.

Liquid sclerosing agents include sotradecol and ethanol. Sotradecol, available in a 1% or 3% aqueous solution, has a soapy texture and contains 2% benzyl alcohol. Toxicities and complications with larger injections have not been studied. Ethanol is a sclerosing agent whose metabolism and excretion in humans in well known. We have treated many sotradecol failures and were successful in the treatment of AVMs with the use of ethanol. In our opinion, ethanol is the most effective and superior liquid sclerosing agent (3, 19–26).

Ethanol induces thrombosis by denaturing blood proteins, dehydrating vascular endothelial cells and precipitating their protoplasm, denuding the vascular wall totally of endothelial cells, and segmentally fracturing the vascular wall to the level of the internal elastic lamina. Any one of these events, and especially the combination of all these factors, causes an acute thrombosis. Again, extreme caution and superselective placement are required when using ethanol as an endovascular occlusive agent. In the treatment of AVMs, ethanol has demonstrated its curative potential, as opposed to palliation, which is commonly seen with all other embolic agents. One of the factors that may lead to the permanence demonstrated by ethanol on long-term follow-up is the fact that the endothelial cell of the vascular wall is totally obliterated. It has not been unequivocally proven but we have much indirect evidence, that endothelial cells mediate vascular recanalization by activating a cellular response to remove thrombus and embolic debris. Endothelial cells then line the new channels in the recanalization process. With regards to angiogenesis factors and neovascular recruitment/stimulation, it is also felt that endothelial cells mediate this response by the release of angiogenesis factors. Again, these concepts are theoretical at this point.

Since ethanol completely destroys the endothelial cell, the phenomenon of recanalization and neovascular recruitment are noticeably absent. The permanence encountered with ethanol is unusual with other agents.

Because cure is possible by endovascular procedures, the role of surgery for AVMs has diminished. If cure is not possible by embolization, then either repeated transcatheter procedures and/or surgery may still have a role. With current fluoroscopic systems, vessels smaller than 1 mm can be imaged. This allows planning to spare normal structures and embolize the AVM nidus superselectively.

Vascular malformations are best treated where these patients are seen on a regular basis. The interventional radiologist who occasionally evaluates a few patients every year or so will never gain enough experience to manage these challenging lesions effectively. All too frequently, the patient

ultimately pays for the interventional radiologist's initial enthusiasm, inexperience, folly, and lack of necessary clinician back up. To optimally manage these patients, a dedicated team should be in place. Interventional radiology and the various surgical and medical specialties function together, much like the tumor board team of specialists. When patients are seen and treated regularly, then experience can be gained, rational decisions can be made, complications can be appropriately managed, and patient care is optimized. It cannot be emphasized enough that, as a group, vascular malformations pose one of the most difficult challenges in the practice of medicine. A cavalier approach to their management will always lead to significant complications and dismal patient outcomes.

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