Review Article

The Use of Cyanoacrylate Adhesives in Peripheral Embolization

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Although liquid adhesives or glue have been used as embolic agents for nearly three decades, experience with them outside of neurointerventional indications is generally limited. Cyanoacrylates are the main liquid adhesives used in the vascular system and have an important role in managing vascular abnormalities, especially arteriovenous malformations. Vascular occlusion results as these agents polymerize on exposure to the ions in blood. A description of the properties, biologic interactions, techniques of use, and indications for acrylic embolization in the peripheral circulation is especially pertinent at this time because of the recent approval of n-butyl cyanoacrylate by the United States Food and Drug Administration.

EMBOLIZATION agents can be categorized by their physical and biologic properties, which in turn affect their level of occlusion and tissue response. Most interventional radiologists are quite familiar with the use of mechanical agents, primarily coil emboli and, less commonly, detachable balloons, and with particulate agents such as gelatin sponge and polyvinyl alcohol particles. Although many interventionalists have likely had some exposure to the use of 95% or absolute ethanol, experience with liquid agents for embolization is generally much more limited, especially adhesives or "glues." This is particularly true in the United States, where, until recently, no Food and Drug Administration (FDA)-approved glue had been available for more than a decade. Nevertheless, this type of agent has an important role in managing vascular abnormalities, especially arteriovenous malformations (AVMs), as is well known to interventional neuroradi-

ologists (1–6). Despite their limited availability, we have had the opportunity to use cyanoacrylate tissue adhesives in a number of patients when we believed that this type of agent was uniquely indicated.

CHEMICAL PROPERTIES OF CYANOACRYLATES

The main liquid adhesives used in endovascular procedures are cyanoacrylates. The monomeric form of this consists of an ethylene molecule with a cyano group and an ester attached to one of the carbons (Fig 1). The ester can have various hydrocarbons attached to it (the R position). The hydrocarbon in this position also contributes to the name of the cyanoacrylate; eg, isobutyl cyanoacrylate, n-butyl cyanoacrylate (n-BCA) (Fig 2), or 2-hexyl cyanoacrylate. When exposed to an anion, such as a hydroxyl moiety found in water or the various anions found in blood, polymerization is initiated, with bonding of the ethylene units. The longer the hydrocarbon is at R position, the slower the rate of polymerization, the less heat released during polymerization, and the lower the histotoxicity (7,8).

Because of their low viscosity, cyanoacrylates are easy to deliver through microcatheters; however, their lack of

radiopacity and their rapid polymerization when in contact with blood can make precise, safe occlusion difficult to achieve. Modifications to address these problems include the addition of powdered metals, typically tantalum or tungsten, and iodized oils (9). Tantalum has been noted to result in a slow initiation of polymerization, so it should be added to the embolic mixture shortly before its use (10). Iodized oils not only opacify the agent but also slow the polymerization time, although this effect was found to be less pronounced when mixing n-BCA with iophendylate (Pantopaque; Lafayette Pharmacol, Lafayette, IN) than when mixing isobutyl cyanoacrylate with iophendylate (10). Another side effect of the oils is to promote a less uniform, more flocculent polymer (7). The addition of glacial acetic has also been described as a method for delaying polymerization (10,11). Currently, we mix monomeric glue with Ethiodol (Savage Laboratories, Melville, NY) in ratios varying from 1:1 to 1:4.

BIOLOGIC INTERACTIONS

The deposition of cyanoacrylate within a vessel results in an acute inflammatory reaction in the wall and surrounding tissues. This progresses to a chronic and granulomatous pro-

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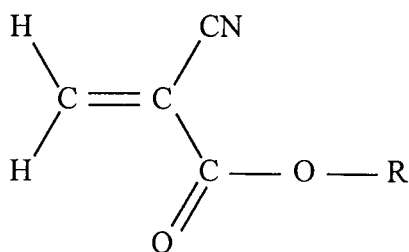
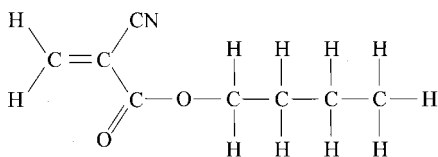**Figure 1.** Monomeric cyanoacrylate. The R represents an alkyl group.

Figure 2. N-butyl-2-cyanoacrylate.

cess after approximately 1 month, with foreign body giant cells and fibrosis (10,12,13). Although the occlusion created by glue may be permanent (14), recanalization has also been observed, especially when only partial embolization was achieved rather than total and solid casting of the nidus of a lesion (10,15,16). Histologically, extravascular extrusion of the glue and the development of capillaries within embolized vessels have been described. Isobutyl 2-cyanoacrylate has been shown to dissipate on long-term follow-up in incompletely occluded AVMs (16).

Whereas sarcomas have been reported to develop in laboratory animals exposed to large doses of isobutyl 2-cyanoacrylate, no malignancies in humans have been clearly demonstrated to be caused by cyanoacrylates (1,7,10,17). Nevertheless, this observation prompted the manufacturer to cease production of isobutyl cyanoacrylate in the late 1980s. Since then, n-BCA has been the principal glue used for embolotherapy.

AVAILABILITY OF ACRYLIC ADHESIVES IN THE UNITED STATES

Until recently, there was no approved tissue adhesive for endovascular use in the United States, leaving the interventionalist in the uncomfortable position of having to obtain an agent

such as Histoacryl (n-BCA; B. Braun, Melsungen, Germany) from outside the country when it was essential for treating a patient. In the latter half of 2000, Trufill n-BCA (Cordis, Miami Lakes, FL) was approved by the FDA for the presurgical devascularization of cerebral AVMs. The Trufill n-BCA Liquid Embolic System has three components: one or two 1-g tubes of n-BCA, 10 mL of ethiodized oil, and 1 g of tantalum powder, which can be mixed together. Although not specifically indicated for use in the peripheral circulation, it is likely that this agent will replace Histoacryl for peripheral applications in the US. Although the legal ramifications of the use of an agent not approved for any indication are not entirely clear, the consensus of courts around the nation hold that off-label use of FDA-approved devices and materials is part of the practice of medicine (18).

Another cyanoacrylate currently undergoing evaluation in the United States is Neuracryl M (Prohold Technologies, El Cajon, CA). It consists of a 2-hexyl-cyanoacrylate compound (Neuracryl M1) that is intended to be mixed with an esterified fatty acid and gold particles to retard polymerization and provide radiopacity (19). This agent is not far along in the FDA approval process.

INDICATIONS FOR ACRYLIC EMBOLIZATION IN THE PERIPHERAL CIRCULATION

The principal pathologic process benefiting from treatment with an acrylic adhesive is an AVM. The ability of a liquid agent to penetrate and occlude at the level of the nidus of this lesion is critically important. Because embolization coils and detachable balloons occlude large vessels, they generally have no role in the embolization of complex AVMs outside the lungs. Polyvinyl alcohol particles have been used, but determining the appropriate size to use is problematic, leading to the risk of paradoxic embolization to the lungs (20). Although 95% or absolute ethanol has been used by some (21), many interventionalists find alcohol to have great risks, including injury to adjacent normal tissues, particularly mucosal surfaces, skin, and neurologic tissue (22–24), and cardiopulmonary collapse caused by escape

to the right side of the heart and pulmonary bed. Our practice is to limit the use of ethanol to organs in which the potential for nontarget tissue injury is minuscule, such as the kidney. We also use ethanol as a sclerosing agent for direct puncture therapy of venous malformations.

Because complex, multichanneled systemic AVMs are difficult (if at all possible) to eradicate, therapy should be considered only when significant symptoms are present. Patients need to be aware that treatment is often palliative and should be prepared for the possibility of future procedures. It is best to approach these patients in a multidisciplinary fashion, with the input of a variety of other physicians. For extremity and superficial lesions, we work closely with plastic surgeons and occasionally with orthopedic and vascular surgeons, especially when treating larger, more extensive abnormalities.

Simple arteriovenous connections, as exemplified by the classical acquired arteriovenous fistula (AVF), are generally best managed by embolization with a mechanical agent if it can be placed directly across the origin of the fistula and the segment of artery being occluded is not critical. The use of glue in large, high-flow AVFs carries a significant risk of paradoxic embolization, although the initial placement of coils to slow flow may enhance the safety of this (25). Small lesions in which a catheter or microcatheter cannot be placed across the AVF may be successfully occluded with use of glue (26,27).

Although aneurysms are generally best embolized with mechanical agents, glue has occasionally been found to be helpful, especially when used as an adjunct to coils (28). Glue is particularly useful when a direct puncture is necessary to approach an aneurysm. This approach has also been described for the embolization of tumors (29,30).

Some other uses reported for glue in the peripheral vasculature include embolization for gastrointestinal bleeding (31), deep dorsal vein embolization for the treatment of impotence caused by veno-occlusive dysfunction (32), internal spermatic vein embolization for the treatment of varicocele (33), in conjunction with iodized oil in the hepatic arteries for hepatocellular carcinoma (17) or neuroendocrine metastases (34), and embolization of en-
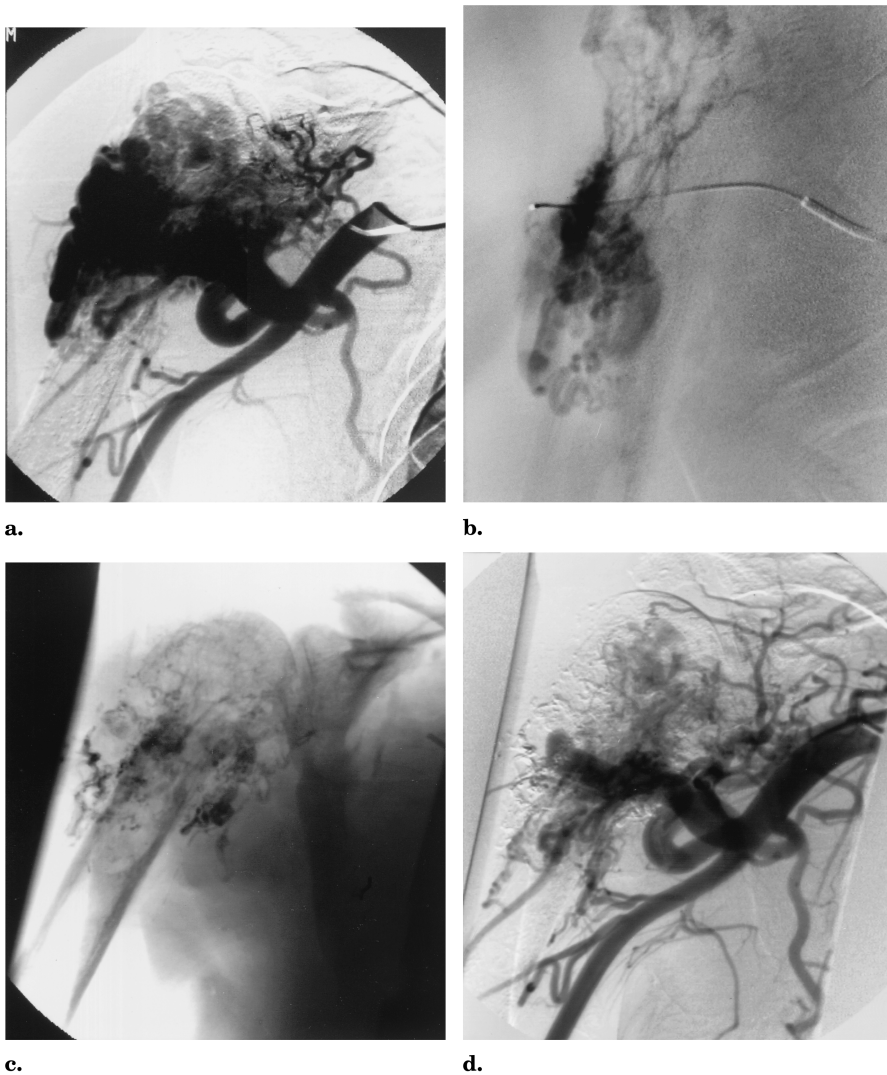
a.

b.

c.

d.

Figure 3. Images from a 34-year-old man with a high-flow AVM in his right shoulder. **(a)** Selective subclavian arteriogram demonstrates the hypervascular AVM supplied by medial and lateral humeral circumflex arteries. **(b)** A 3-F coaxial microcatheter placed through a 5-F catheter is positioned into the nidus supplied by the lateral humeral circumflex artery. A 0.5-mL test injection of contrast material fills the nidus. Two sequential 0.5-mL boluses of a 1:1 n-BCA/iodized oil mixture opacified with tungsten powder were then injected. Each bolus was flushed into the nidus with 3 mL of D5W. **(c)** Radiopaque glue is evident within the malformation after completion of embolization of the supply from the lateral and medial humeral circumflex arteries. **(d)** A completion nonselective angiogram demonstrates preservation of flow in the circumflex humeral arteries and substantial obliteration of the nidi.

doleaks after placement of an endovascular stent-graft (35).

TECHNIQUE

The goal when embolizing an AVM is to occlude at the level of the nidus. When using cyanoacrylate, this means creating a cast of glue within the nidus. Embolization of only the feed-ing arteries will only create greater problems in the future, because the lesion recruits collateral flow through more complex and difficult-to-approach routes. In fact, such measures can result in a larger, more symptomatic AVM and are justified only in certain preoperative situations. The technique of glue embolization for an AVF is similar to that used for an AVM,

keeping in mind the ability to sacrifice the arterial segment of the lesion being occluded.

Acrylic embolization is always performed through a microcatheter that is positioned as close as possible to the nidus (**Figs 3a,b**). Proper placement is confirmed by contrast injections and comparison to earlier diagnostic angiograms. The microcatheter is typically placed through a less-selective 5- or 6-F catheter. This can be a guiding catheter if injections through the outer catheter are desired. The outer catheter provides a stable position in the proximal vessel and allows rapid exchange of microcatheters occluded by glue and angiography of the embolized circulation. Evaluation of the territory supplied by the microcatheter as well as estimation of the volume of glue needed for embolization is performed by test injections of contrast material through this catheter. Although provocative testing with an injection of amobarbital is typically performed for intracranial AVMs to assess the possibility of causing a significant neurologic deficit, it has not been our practice to inject lidocaine to assess for potential supply to a peripheral nerve when treating peripheral AVMs.

The method used for the test injections of contrast material should precisely identify the anatomy and simulate the conditions of the planned embolization. In an extremity, we will often use a tourniquet or blood pressure cuff inflated central to the lesion to slow flow during diagnostic injections. This will more readily identify the arteries supplying the nidus and filling of nonpathologic branches. Alternatively, an occlusion balloon can be used in a more proximal artery to accomplish this or the microcatheter may be wedged in the feeding artery to restrict pericatheter flow. Although we will occasionally use a tourniquet or occlusion balloon to slow delivery of the glue, the glue is usually injected without these. If the microcatheter is sufficiently close to the nidus (generally within 1 cm), the glue should be suitably deposited within it. For peripheral lesions in the extremities, small orthodontic bands can be placed around the digits just before the embolization to limit the risk of nontarget digital artery embolization.

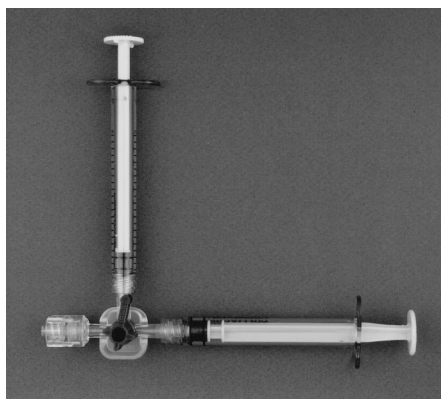A three-way stopcock is attached to the microcatheter. A 1-mL Luer lock

Figure 4. A three-way stopcock with 1-mL and 3-mL Luer lock syringes attached. For test injections and determinations of the volume of glue and rate of injection, the 1-mL syringe is filled with varying amounts of contrast material. The volume of glue/iodized oil mixture is simulated by injecting contrast material and the rate of injection is simulated by flushing D5W with the 3-mL syringe. When the volume and rate of injection are selected, a new stopcock is used and fresh 1-mL and 3-mL Luer lock syringes are filled with the glue mixture and 5% D5W solution, respectively. Approximately 50% of the time, a second glue application can be performed through the 3-F microcatheter before the catheter occludes.

syringe is used on one end of the stopcock for the delivery of varying volumes of contrast material and a 3-mL syringe is attached to the other end for the delivery of a 5% dextrose (D5W) flush (**Fig 4**). Several digital angiograms are then obtained with use of volumes of contrast between 0.1 and 0.6 mL, followed by a D5W flush (**Fig 3b**). It is important to have two operators for this procedure: one to inject the contrast material and the other to inject the D5W. Strict attention should be paid to the opacification of any draining veins from the nidus, in which case the flush should be stopped. Performing this maneuver several times will allow for the determination of the volume of contrast material (and therefore the maximum amount of glue) that will fill the nidus and just start to appear in the venous outflow. Additionally, it will allow for a smooth interaction between the two operators. The volume of glue needed is usually less than the volume of contrast material because thrombosed blood elements will be incorporated in

the occlusion (10,36). Typical volumes of glue will be from 0.1 to 0.6 mL.

Any contact with an ionic substance must be avoided when handling cyanoacrylate. The monomer should be aspirated in a clean 3-mL syringe and kept on a separate embolization table. Because polycarbonate can be destroyed by cyanoacrylate (7), polypropylene syringes should be used or contact with polycarbonate syringes and stopcocks should be brief, and the equipment should then be discarded. In addition to appropriate sterile and protective attire, personnel in the room should wear eye protection to avoid potential contact with the glue. The acrylic is then added to a glass receptacle containing the desired volume of Ethiodol (Savage Laboratories). Although, in the past, we occasionally added tantalum or tungsten powder to the oil to further increase the final mixture's radiopacity, we currently do not use any powdered metals. The ratio of n-BCA to Ethiodol will vary from 1:1 to 1:4. The speed with which the contrast material reaches the nidus and first appears in the draining veins will determine the appropriate dilution for the glue. The longer this takes, the more diluted the glue should be; however, in vitro, the glue can be diluted with iodized oil to a concentration of only approximately 30% before the polymerization time becomes excessively long (9). If the time to reach the nidus seems too long (more than 3–4 sec), concern should be raised whether the microcatheter is sufficiently close to the nidus. If the time is too short, with the test injections of contrast material difficult to visualize on digital angiograms, more aggressive methods to arrest flow may be beneficial, such as increasing the pressure on a cuff around an extremity, using an occlusion balloon, or wedging of the catheter in the vessel. Because the in vivo polymerization time for n-BCA appears to be more rapid than the in vitro time, one needs to make the dilution slightly greater than might be expected (37). This phenomenon may be a result of a faster polymerization speed of cyanoacrylates at body temperature than at room temperature and the greater availability of anions intravascularly, especially when the glue is forced into contact with the endothelium at vessel bifurcations and areas of acute angu-

lation or marked vessel narrowing (10,37). The estimated in vivo polymerization times for glue:oil mixtures between 1:1 and 1:4 are 1–4 seconds, with a linear relationship to the mixture.

Clean towels are placed about the hub of the microcatheter and a fresh three-way stopcock is attached to it. The catheter is flushed several times with the dextrose solution to clear it of any residual saline or blood. Another clean towel is then placed under the hub of the catheter. The estimated volume of glue is drawn up in a 1-mL Luer lock syringe and connected to one injection port of the three-way stopcock while a 3-mL syringe of D5W is connected to the other port. The glue is then injected by one physician. The switch of the three-way stopcock is immediately opened to the other port and the D5W injected by the other physician, advancing the glue completely out of the microcatheter and into the nidus. When the glue fully exits the catheter and no longer passes distal to the catheter tip, the catheter is retracted proximal to the trailing edge of the glue to avoid the possibility of it adhering to the intraluminal glue. Decreased catheter adhesion by cyanoacrylates has been shown in vitro with hydrophilic-coated microcatheters and with certain preparations of 2-hexyl cyanoacrylate as compared to n-BCA (19,38). The delivery is carefully monitored fluoroscopically. If the body region prevents easy visualization of the opacified glue, a roadmap image can be used.

Angiography is then performed, with injection performed through the microcatheter or the outer coaxial catheter if the microcatheter was completely removed. This will determine the need for further embolization. It is safest to use a new microcatheter for each injection of glue. It may be difficult to inject through the microcatheter after the first deposition, presumably because of the adherence of small amounts of glue in its lumen. This makes subsequent acrylate administration more difficult and less controllable. However, if the specific branch being treated was difficult to catheterize, we occasionally will reuse the same microcatheter if it remains easy to inject through. Angiography of the main arterial feeder is performed at the end to demonstrate the degree of

embolization of the nidus and the presence of any residual feeders (**Figs 3c,d**).

If a 3-way stopcock is not used, the microcatheter should be flushed multiple times with D5W after the test angiograms. A 1–3-mL syringe containing the desired volume of glue mixture is attached and the injection is performed under careful fluoroscopic monitoring. When no further distal passage of the cyanoacrylate is observed, the microcatheter is rapidly removed while aspirating with the syringe.

Although we have minimal experience with direct puncture and embolization of AVMs, it has been described for craniofacial lesions with use of acrylic (4) and for peripheral lesions with use of a variety of other agents (39). We have used acrylic adhesive to occlude aneurysms and AVFs by direct puncture of the lesion or a feeding artery. This method is typically needed when conventional catheterization of a lesion is difficult or impossible, such as when the feeding arteries have previously been inappropriately embolized without occlusion of the actual lesion. Embolization can be performed through either the puncture needle or a catheter, with the latter preferred if it is a feeding artery punctured to achieve a more distal location, closer to the lesion. Still, the site of puncture will usually be included in the embolization. This has the added benefit of avoiding bleeding when the access is removed. Alternatively, the access track may be embolized with a coil or gelatin sponge pledget.

Although endoaneurysmal filling with glue may be sufficient, it is technically difficult to accomplish this with complete coverage of the origin of the aneurysm. When treating an aneurysm by direct puncture, we try to reflux the glue for a short distance into all its connecting arteries, assuming all these can be sacrificed. When treating an AVF, care must be taken to avoid paradoxical embolization to the lungs. If the fistula or its origin can be catheterized, it is probably preferable to use mechanical agents, whereas glue is preferred when such a selective position is not reached. After several test injections with contrast material to determine the appropriate amount and dilution of glue, the acrylic is injected under fluoroscopic guidance in the same manner as previously described.

A third alternative for approaching vascular lesions is retrograde venous catheterization (39,40). This option may be feasible if there are sizable veins draining the lesion (preferably a single large vein) that can be entered. Glue may be injected while a flow occlusion technique (eg, occlusion balloon, compression) is used to promote reflux into the lesion.

SIDE EFFECTS, PITFALLS, AND RISKS OF ACRYLIC EMBOLIZATION

As with other agents, a postembolization syndrome can occur after occlusion with glue. Nausea and vomiting can be treated with antiemetics and fever can be treated with antipyretics. Pain can be treated with analgesics; a patient-controlled analgesia pump can be used if needed. Additionally, corticosteroids may limit local edema caused by thrombosis after the embolization of AVMs.

Complications related to acrylic embolization can be minimized by careful attention to the specific vascular anatomy and the information obtained from the test injections with contrast material. When concern exists about the precise volume of glue needed, the interventionalist should err to the side of using too small a volume. Ischemic injury from regional nontarget tissue embolization may be caused by the glue entering a branch distal to the catheter tip or refluxing proximal to the planned site of occlusion. Reflux can occur from the use of too large a volume of glue and/or an inappropriate speed of injection of the glue or D5W flush. If a small piece of glue becomes adherent to the catheter tip, it could be stripped off in a more proximal artery during retraction of the catheter (especially when reaching the outer coaxial catheter) and could embolize to a nontarget location.

Gluing of the catheter tip in place may be related to reflux, early polymerization, or delayed retraction of the microcatheter. If this occurs, it may be necessary to break the catheter and leave the distal fragment in place—hopefully, the level of the break will be quite distal to avoid the presence of the proximal end of the microcatheter fragment in a major

vessel. If there is concern that traction on the catheter may result in rupture of the vessel, it may be preferable to cut the catheter at the level of the arterial entry site and secure it to the groin. A role for anticoagulation will depend on the whether the catheter can be removed surgically, the degree to which it occludes flow in any critical vessels, and the risk of bleeding from the AVM.

Paradoxical embolization of glue results from late polymerization, after passing through the nidus of an AVM. Occlusion of the venous outflow may occur, which can lead to elevated pressure in the nidus or remaining draining veins. This increases the risk of rupture and bleeding with CNS lesions (41); however, this does not seem to be a major issue with peripheral lesions. As the volume of glue is usually quite small, pulmonary embolism is usually asymptomatic (42).

RESULTS OF ACRYLIC EMBOLIZATION FOR NONNEUROLOGIC AVMS

The reported experience with cyanoacrylate embolization outside of the central nervous system and head and neck is small. Our own experience indicates that localized AVMs may be curable or controllable with embolization and/or resective surgery. This is especially true if they are well circumscribed and not intrinsically involved with critical structures. Our review of the outcome of embolotherapy and occasional adjunctive surgery for 20 high-flow extremity AVMs showed good long-term palliation when the lesion was limited (43). However, diffuse, infiltrating lesions involving critical structures and all major arterial trunks in a region have a high likelihood of eventually requiring amputation. Although we were able to palliate malformations in the lower extremities that involved all three trifurcation arteries for several years, many of these patients eventually underwent an amputation.

CONCLUSIONS

Cyanoacrylate embolotherapy requires careful assessment of patients and their vascular anatomy, meticu-

lous attention to technical details, and a reasonable degree of experience. Although they are more demanding to use than many other embolic agents, they do have a unique role in treating complex AVMs and, occasionally, other abnormalities. With the recent approval of a cyanoacrylate for endovascular indications in the United States, interventionalists should become more familiar with these agents outside the neurologic system.

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