Review Vascular Occlusive Agents

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The authors have reviewed the experimental literature about the different agents used for endovascular embolization: clots, tissues, duramater, Gelfoam, oxydized cellulose, Ivalon, beads, microspheres, cyanoacrylates, silicone, barium. Each occlusive agent was studied in regard to its physical properties, injection methods, characteristics of obstruction, vascular reaction, and toxicity. The level and quality of obstruction obtained depend on many factors which are discussed.

Interventional radiologists use many different agents for vascular occlusion and many opinions are offered regarding the characteristics of obstruction obtained with the various agents. The choice of specific agent to be used in a given case depends on the lesion to be treated, the characteristics of the obstruction (e.g., distal or proximal, permanent or temporary), and the catheter to be used. For example, microcatheters permit use of only fluid materials. This explains the number of agents available. A comprehensive compilation of the characteristics of the various agents is desirable.

This work is an organized summary of the experimental literature on natural and synthetic particulate materials and certain fluid agents. We intentionally excluded the mechanical devices for proximal obliteration (balloons, metallic devices) and electrocoagulation. Each occlusive agent was studied in regard to its physical properties, injection methods, characteristics of obstruction, vascular reaction, and toxicity. The effects on the embolized tissues were not studied, since they depend on the vascularization and type of the tissue treated as well as the agent used. The characteristics of the major embolization agents are given in table 1.

Natural Particulate Emboli

Autologous Clots

Numerous experiments have been performed in vitro and in vivo (dogs, rats, pigs). Theoretically the pig makes an ideal model because its fibrinolytic system closely simulates that of man [1]. The euglobulin lysis time in dog is much shorter (40 min) than in man (2–8 hr). Different types of autologous clots have been used: unmodified fresh clot, fresh clot modified by heating or by adding substances such as aminocaproic acid, oxydized cellulose, thrombin, and aged clot.

Unmodified fresh clots [2, 3] are prepared by allowing fresh blood to clot in a sterile cup; it is then cut to obtain various size emboli. Heated fresh clots [3] are prepared in the same manner in a water bath at 56°–66° C. The denaturation of the euglobulin proteins by heating might significantly retard clot lysis. Clots with aminocaproic acid [3–5] are prepared by mixing 10 ml of fresh blood with 1 ml of 0.5 M aminocaproic acid. In vitro, aminocaproic acid reacts with plasmin to form a fibrin more resistant to fibrinolysis. This clot can be used 30 min later.

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TABLE 1: **Characteristics of the Major Embolization Agents**

Agents	Resorbtion	Occlusion Characteristics	Vascular Reaction	Toxicity
Particulate:				
Clots	Resorbable	Lysis, fragmentation, distal migration	No	No
Tissue	Theoretically unresorbable	Fragmentation, distal migration		No
Gelfoam	Resorbable	Fragmentation, distal migration	Acute necrotizing arteritis	No
Oxycel	Resorbable			
Ivalon	Nonresorbable	Distal migration	Inflammatory reaction Fibrosis	No
Fluids:				
Silicone	Nonresorbable	Viscosity dependent	No	No
Cyanoacrylates	Slowly resorbable	Variable	Inflammatory reaction	?

Clots with oxydized cellulose [2–5] are prepared by mixing oxycel fibers with blood. Aminocaproic acid can also be added. Clots with thrombin [6] are made by adding 1000 U of thrombin to 10 ml of fresh blood.

Aged clots are prepared by placing blood in polyethylene tubes (3 mm ID); 1–3 days later, the cloted blood is cut into 2–3 cm emboli. Tantalum powder (particle diameter 5 μ) can be sprayed on their surfaces to make them radiopaque. Various size emboli are manually injected through catheters with a syringe.

In most experiments [2, 3, 7] the duration of the obliteration was the same with the different types of clot. The volume of oxycel and thrombin clots increases after their injection. This could be due to induction of additional thrombosis on the surface of the clot [6]. Fragmentation and early lysis of all types of clot lead to distal migration [5, 6, 8]. This migration can be observed as soon as the 15th minute, and up to the 21st day [8]. Migration of aged clot seems to be less important, probably due to a less prominent lysis [9]. Clots are not completely resorbable and histologic traces can be found after 6 months [9].

Neovascularization with fibroblastic reaction is observed in the clot 4 days after embolization [8]. At the 14th day [3] the thrombus is adherent to the arterial wall and is lined by endothelium. If tantalum has been used, it is always found associated with the clot; no tantalum is found free within the lumen of the embolized vessel. However Barth et al. [10] found tantalum particles within the vessel wall at 4 months.

Comments. Modification of fresh clot for emboli does not seem useful since the same results are obtained. Early lysis and fragmentation appear responsible for distal migration of emboli. This phenomenon explains the modifications in distribution and site of the obstruction after embolization. Thus smaller vessels may be occluded after larger emboli are injected.

Autologous Tissues

Muscle [11–12] and subcutaneous tissue [13–14] have been used as autologous clots. These autologous tissues are taken from the patient just before the embolization. Almgard and Ljungquist [11] cut the muscle into small pieces to form a "meatball" which is then suspended in 2–5 ml isotonic saline; 14–18 days after embolization, partial revascularization was observed. Histologically the large and small arteries contain fibrinous thrombi with fragments of muscle tissue. Theoretically the tissue is unresorbable, so the embolization should be permanent. The level of obstruction is related to the embolus size but also to its compressibility and possible fragmentation.

We found no reported experimental work on nonautologous lyophilized dura mater. However this material is extensively used in therapeutic angiography in France [15]. Easy to use, it is thought to be unresorbable and without toxicity.

Synthetic Particulate Emboli

Gelatin Sponge (Gelfoam)

Experimental work has been performed in pigs, rats, dogs, and monkeys [4, 5, 10, 16–19]. Gelfoam is available as a powder or as a sheet of sponge. The sponge can be cut into emboli of various sizes and resterilized for later use [20]. These particles can be opacified with tantalum powder, or injected with contrast medium. Picard et al. [21] use an iodine-131-labeled Gelfoam allowing postembolization controls. Gelfoam powder is mixed with contrast medium [17]. The final product is an opaque viscous material that can be injected through small catheters. J. H. Anderson (personal communication) mixes 200 mg of powder with 10 ml of 38% iodine contrast medium.

No experimental work has been published yet concerning Gelfoam powder. With Gelfoam sponge, a distal migration is observed as soon as 2 hr after embolization [5–8]. The gelfoam induces clot formation in which Gelfoam is found. Clots can be found until the 4th month [10], but at this time the Gelfoam is completely resorbed. Gelfoam resorption occurs within 7–21 days [10–18]. Bracken et al. [22] and Goldstein et al. [23] found histologic sections of arteries occluded with Gelfoam to show an acute necrotizing arteritis of the entire thickness of the arterial wall.

Comment. Gelfoam is a resorbable material that is easy to use and can be opacified. Vessel obstruction is caused by the emboli and the thrombus that forms within and around

it. The emboli migrate distally and distal obstructions may persist up to 4 months [10].

Oxydized Cellulose (Oxycel), Cellulose Acetate (Surgicel)

These materials have been studied in pigs and rats [10–24]. The cellulose gauze or fibers can be opacified with tantalum. It is reabsorbed in vivo within 6–8 weeks [10]. An early revascularization is observed and only residual thrombi are found 4 months later [10].

Polyvinyl Alcohol Foam (Ivalon)

Ivalon is available as a compressible sponge. The compressed dry sponge expands 10 times its original volume when soaked in saline. It can be opacified by barium-sulfate addition during its manufacture. Since it is fixed with formalin during manufacture, it must be rinsed thoroughly before use.

Tavadarthy et al. [25] cut 0.5–1-mm-diam plugs from the compressed dried material with a hole punch. These plugs are a few millimeters long and are preloaded in small plastic tubings. These tubings are gas-sterilized. At the time of embolization the preloaded tubes are connected to the catheter and the plugs are flushed into the cathether and blood vessels by manual saline injection. Kaufman [26] cuts Ivalon into 1 × 1 × 10 mm strips. Immediately before use, these strips are soaked in flushing solution and loaded into an extension tube filled with contrast material. For embolization, the tube is then connected to the angiographic catheter. Kerber et al. [27] cut the wet sponge into 2 × 2 × 2 cm cubes. These cubes are blended with water in a high-shear blender. A series of graded sieves separates the particles into batches varying in size from 0.5 to 2 mm. These emboli are then placed into bottles with saline and steam sterilized. Immediately before the embolization, it is necessary to break up the aggregates formed during sterilization.

Dogs and pigs have been the animals used in those experiments [1, 25, 28]. Three days after embolization [28], the vessels are completely occluded by the Ivalon and fresh clot; 5 months later a dense fibrous tissue within and around the Ivalon is found [1]. An adherent, organized, partially calcified thrombus containing Ivalon is found at 9 months [28]. However, after experimental embolization of gastrosplenic and renal arteries in three pigs [1], Ivalon was historically found in only one case. Distal migration of the emboli is the explanation given.

Three days after embolization the arterial wall is normal. At 2 weeks the wall of the artery is infiltrated with polymorphonuclear leukocytes. The intima disappears [28]. At 3 months little inflammation and rare giant cells are found in or around the area of thrombosis [1]. At 9 months, the arterial wall is fibrosed and seems to be in continuity with the thrombus.

Ivalon, extensively used in thoracic and digestive surgery, is considered to be a nontoxic material [25]. Residual formalin from inadequately rinsed emboli could cause untoward reactions.

Comment. Ivalon is a nonresorbable material. Although it can be opacified with barium, it is difficult to visualize in vivo. The preparation used by Kerber et al. [27] reduces the time of the procedure and provides large numbers of emboli of known and uniform size. Migration occurs as with clot emboli. This material is nontoxic but induces a mild inflammatory reaction.

Beads

To our knowledge there is no experimental study about these emboli. Lead [12], stainless steel [29], and silicone [30, 31] beads have been used in man.

Microspheres

Carbon microsphere (25–50 μ) embolization has been performed in pigs [32]. An arteriolocapillary obliteration was obtained, but the arterial trunk was impossible to obliterate. The high risk of reflux makes this technique hazardous. Iron microspheres can be used to occlude large vessels using an electromagnet [33]. Polystyrene microspheres (150 μ) [34] are hard to control because of their light weight and difficulties of injection. Dried Sephadex microspheres (50–150 μ) are cross-linked polysaccharide macromolecules [34]. They have the capacity to swell up to five times after 3 hr contact with water. The complication rate is high due to reflux into nontarget arteries.

Fluid Emboli

Silicone

Silicone (dimethyl polysiloxane) is a low surface tension, nonwettable, polymerizable liquid. Its viscosity can be controlled by dilution with silicone fluid 360. Polymerization time is directly related to the amount of catalyst (stannous octoate). This reaction occurs at room temperature, without volume modification [35, 36], and is not exothermic.

The preparation differs with each author (table 2). Monomer viscosity is too high to be injected in arteriographic catheters. It is necessary to add a diluent which increases the polymerization time in such a way that it may be necessary to add a cross-linker (tetraethylsilicate). However, manual injection may remain difficult and a pump is used by some authors [40]. With this technique, it is possible to inject 0.25–0.5 ml/min through 2 French catheters. Tantalum opacification allows fluoroscopic control [38]. Picard et al. [39] gave up this technique because of clump formation obstructing the fine catheters.

The obstruction level depends on silicone viscosity [36]. Sobin et al. [36], injecting a 30 centipoises silicone in the aorta of rabbits, showed that this agent can pass through the capillary bed. On the other hand, other authors [37, 38, 40] with their own preparation (table 2) obtain an occlusion that stops at the capillary level. The obstruction of larger vessels is then obtained by retrograde filling from the capillary bed. The polymerized silicone does not adhere to the vessel wall. This nonadherence allows a "collateral" flux

TABLE 2: **Silicone Preparation**

Author	Silastic 382 (%)	Silicone Fluid 360 (%)	Stannousoctoate	Crosslinker Tetraethyl Silicate	Working Time (min)	Opacification	Miscellaneous
Doppman et al. [29]	50	50	1%	0	1	Tantalum	...
Hilal and Michelson [30]	20	80	+	5%	5	Tantalum	...
Miller et al. [32]	17	83	15 drops for 6 ml	4 drops	3	0.25–0.50 g tantalum	...
Mosso and Rand [37]	50	50	2 drops	0	15	...	1 g iron for 15 ml
Snyder and Rand [38]	50	50	2 drops for 15 ml	0	...	...	1 g iron + 1 g barium sulfate for 15 ml
Picard et al. [39]	14	86	3 drops for 4 ml	0	15	Telebrix 30, 50%	

TABLE 3: **Chemical Structure of Alkyl-alpha-cyanoacrylates**

Cyanoacrylates Formula	Radical	Name
$CH_2=C(CN)-COOR$	$-CH_3$	Methyl-alpha-cyanoacrylate
	$-CH_2-CH3$	Ethyl-alpha-cyanoacrylate
	$-CH_2-CH_2-CH_2-CH_3$	Isobutyl-alpha-cyanoacrylate
	CH_3	
	$(CH_2)_5-CH_3$	Hexyl-alpha-cyanoacrylate
	$(CH_2)_9-CH_3$	Decyl-alpha-cyanoacrylate

between the silastic cast and the vessel wall [32–41]. In some cases an organized thrombus is found between the vessel wall and the cast [32]. In one clinical case, migration of the cast out of the embolized artery occurred 24 hr after the embolization [42].

Silicone does not induce any vascular reaction, even with tantalum or iron added. Silicone has been used for many years as a biomedical material, and is known not to have any toxicity.

Comment. Silicone has a viscosity controlable by addition of various amounts of diluent. Since the level of obstruction is related to the viscosity, it is mandatory that this be controlled. We are currently studying the relation between the level of obstruction and the viscosity in our laboratory. This material must be made radiopaque to control the injection. There is no adhesion to the vessel wall. This material is nontoxic.

Cyanoacrylates

Alkyl-alpha-cyanoacrylate monomers are low viscosity liquids. Changes in the length and isomeric configuration of the alkyl side chain modify the physical and chemical properties of cyanoacrylate molecules (table 3). The polymerization is induced by ionic media. Its speed is inversely related to the alkyl chain length. When sprayed on tissues, the n. butyl and isobutyl monomers (four carbons chain) require 4–15 sec for polymerization, and the methyl homolog (one carbon chain) 30–55 sec [43]. This reaction is exothermic. A 2°–12°C temperature rise can be observed [43]. Isobutyl 2-cyanoacrylate polymerization is instantaneous in blood, requires 15–40 sec in saline, and does not occur in 5% dextrose [44]. Mixing 50% dextrose with cyanoacrylate yields an unstable emulsion with a longer polymerization time, but no consistent results are obtained [45, 46]. Mixing iophendylate and isobutyl cyanoacrylate half and half makes the emboli radiopaque and increases the polymerization time (5 sec in blood at 22°C), but slightly increases the viscosity [45].

The biodegradation speed of cyanoacrylates is related to the chain length; 6% of methyl-cyanoacrylates and 92% n. butyl form are still present at the implantation site at 5 months [47]. Degradation products of methyl cyanoacrylates are formaldehyde, thyocyanate [47], and cyanoacetate [48]. No conclusive information has been published regarding intravascular degradation. Histologic staining is obtained with Nile blue and Oil red O.

Butyl cyanoacrylates can be made radiopaque by adding tantalum [44] just before the injection. Because of their low viscosity, they can be injected through small catheters. Flushing catheters with 5% dextrose just before and after cyanoacrylate injection is necessary to avoid polymerization within the catheter. A coaxial system can be used for the same purpose.

Three factors influence the level of obstruction, polymerization time, injection rate, and blood flow. Methyl cyanoacrylate, because of its long polymerization time, can pass through the capillary filter [24]. A slow injection of isobutyl cyanoacrylate (0.3 ml/2 sec) obliterates the vessel just distal to the injection site. The same amount injected in 0.5 sec produces fragmented emboli which are found in small arteries (30 μ) and in one case in veins (200 μ) [49]. Without blood flow reduction, the embolization is both proximal and distal. With blood flow reduction (with a balloon or a manual compression), a more proximal embolization can be achieved [50].

Histologic controls 1 month [32–48] and 3 months [1–50] after embolization show that the vessels are still occluded

by a thrombus formed by isobutyl cyanoacrylate and organized clot with giant cell reaction [1].

According to Zanetti and Sherman [50], only 15% of the vessel wall is in direct contact with isobutyl cyanoacrylate. A disappearance of the intima was observed as soon as the 3rd hour, but only where the material was in direct contact with the vessel wall. These modifications remained unchanged after 24 hr and 3 months. Other authors made the same observations at 1 month, with a chronic inflammatory reaction of the vessel wall [1, 32, 49–51].

No general toxicity has been observed in animals [43–47]. Local histotoxicity decreases as the chain length increases. Methyl cyanoacrylate subcutaneous implants give a caseous necrosis, with no granulation tissue, which can be observed up to the 19th month [48]. This toxicity might be due to the cyanil radical [52], or to the formaldehyde which is released during the biodegradation. Fibrosarcoma have been observed at 14 months in rats [48]. However, no carcinoma has been observed in dogs within a period of 2 years.

Ethyl 2-cyanoacrylate applications on the cat femoral neurovascular bundle gives at 2 days a necrosis of the vascular wall in contact with the polymer. The unexposed wall remains normal. After local application of isobutyl 2-cyanoacrylate or n. butyl 2-cyanoacrylate, an early inflammatory reaction with granulation tissue and giant cells is observed [47]. At 40 days a fibroblastic reaction is demonstrated [53]. The acute stimulus might be related to impurities: hydroquinone [47] and formic acid [53]. The later fibroblastic reaction might be an immunologic process [53]. No carcinoma has been detected after 22 months in dogs, 1 year in first- and second-generation rats, and 1 year in mice [43].

Comment. N. butyl and isobutyl cyanoacrylates are the only cyanoacrylates used in man. Their low viscosity permits injection through very small catheters. The level of obstruction depends on polymerization time, injection rate, and blood flow. It is incorrect to state that they give only a proximal occlusion. A proximal obstruction will be obtained with a slow rate of injection and/or if the blood flow is reduced or stopped.

Cyanoacrylates are not resorbable. Histologically, disappearance of the intima is observed where it was in direct contact with the polymer. Neither general toxicity nor carcinogenesis has been observed with n. butyl and isobutyl cyanoacrylates. However there are no studies with a long enough follow-up to indicate that this material is not carcinogenic. This material should not be used, except for life-threatening situations in which no other form of therapy is available.

Barium

The diameter of the $BaSo_4$ particles is of the order of 1 μ. Goldin et al. [54, 55] embolize the renal artery of pigs by short burst injections. A total of 2.5–3.5 ml of barium sus pension is used; 3 weeks [5] and 1 month [54, 55] after the embolization, the vessels are still occluded and no revascularization is observed. The barium is found as far as the glomeruli [4–58] but also in some venules [5]. However, no lung embolization was observed [4]. The barium is incorporated into the fibroblastic reaction within the vessel. Giant-cell reaction is also seen.

Discussion

Analysis of the experimental literature on embolic materials reveals that the initial occlusion characteristics depend on many factors. Among these the most important are the size and physical properties of the emboli, the method of injection (selectivity, catheter size, blood flow control), and the hemodynamic characteristics of the lesion to be treated.

Very little is known about embolization dynamics: the status of the embolized vascular bed keeps changing after the patient leaves the laboratory. Many factors are involved. Among these some are well known: fragmentation of the emboli, the vasomotor response of the embolized vessel, and the subsequent spontaneous thrombosis that develops in the occluded vessels. Some others probably play an important role: the histologic reaction of the vessel wall and possible adhesion of the material to the wall. On the other hand, the tissue response to the embolization is totally unknown. It obviously depends on whether the lesion is traumatic or dysplastic, benign or malignant.

Thus, given the complexity and the incompleteness of the present knowledge, it is impossible to formulate precise instructions for the choice of the embolization material. Each case must be considered individually. Future research is required in this area in particular as well as in that of tumour response to vascular occlusion in general.

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