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An Arteriovenous Malformation Model for Testing Liquid Embolic Materials

Sangsoo Park, Hisook Yoon, Dae Chul Suh, and Ho-Young Song

Summary: An arteriovenous malformation model with a transparent nidus was constructed to investigate the embolization behavior of polyvinyl acetate (PVAc) solution relative to flow velocity in the feeding artery and injection speed. It was found that the liquid embolic material flowed distally when injected too fast or when the flow velocity was too low. In addition, we found that solution consisting of PVAc plus metrizamide was a better embolic material than solution containing only PVAc.

Index terms: Arteriovenous malformations, embolization; Interventional neuroradiology, models

For embolization of cerebral arteriovenous malformations (AVMs), cyanoacrylate glues, (such as isobutyl cyanoacrylate [IBCA] and *N*-butyl cyanoacrylate [NBCA]) and particulate embolic material (such as Ivalon) have long been used clinically.

Ivalon is made of polyvinyl alcohol, and various sizes are commercially available to match the variety of vessel diameters in the AVM nidus. Among the liquid embolic materials, IBCA has been used since the 1970s (1, 2) and NBCA since the middle of the 1980s (3).

Both NBCA and IBCA, however, have the disadvantage of being adhesive to the catheter, requiring the catheter to be removed as quickly as possible after injection. Moreover, these materials are known to be angiotoxic (4), and thus have been barred from clinical use by the Food and Drug Administration. The search for new liquid embolic materials other than the cyanoacrylate glues has produced several new embolic agents, including polyvinyl acetate (PVAc), ethylene vinyl alcohol copolymer, cellulose acetate, and Ethibloc (5–14). These relatively new liquid embolic materials are fundamentally different from the cyanoacrylate glues in that they are polymers dissolved in an organic solvent, such as ethanol or dimethyl sulfoxide, or in a mixture with water, whereas the cyanoacrylate glues are monomers that polymerize on contact with blood.

To understand further the embolization mechanism of these precipitating liquid embolic materials, we developed an AVM flow model to study the precipitation behavior of PVAc with regard to flow velocity through the AVM nidus.

Materials and Methods

AVM Model

The nidus of the AVM model is shown in Figure 1. The external case of the nidus was made of a Tygon tube with a ⅜-inch inner diameter (Nalgene, Rochester, NY) as follows. The Tygon tube was cut into a 15-cm piece and straightened by placing it in an 80°C oven with a glass rod fitted inside the tube for 10 minutes, after which the tube was cooled in tap water. When the tube was cooled, the glass rod inside was removed. The middle portion of the tube was then heated locally with steam and tapered by pulling both ends of the tube outward. The tube was then cut to about 7 cm from the tapered neck.

Five stainless-steel springs, 4-mm in diameter and 2.5-cm in length, were forced into a U-shape and pushed, from the nontapered end, into the tube successively to fill the tube, as shown in Figure 1. The total length of the coils inside the tube was about 5 cm.

Fluid Circuit

The schematics of the AVM flow model are shown in Figure 2. A water bath with a thermoregulator (model NTT-1100, Tokyo [Japan] Rikakikai Co) was used for controlling the temperature of the flowing water and a peristaltic pump (Manostat, New York, NY) was used for circulating water through the model. The incoming water

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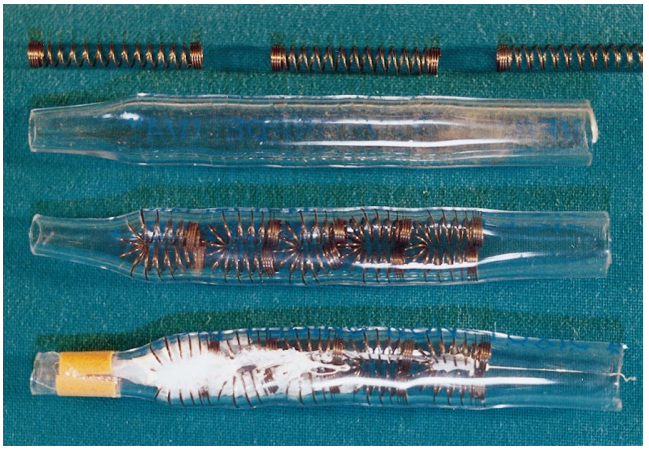

Fig 1. Model AVM nidus. The springs were forced into a U shape and pushed inside the Tygon tube successively. The bottom tube shows the PVAc precipitated inside the nidus. The white lines in the distal part of the tubes are artifacts of reflected light.

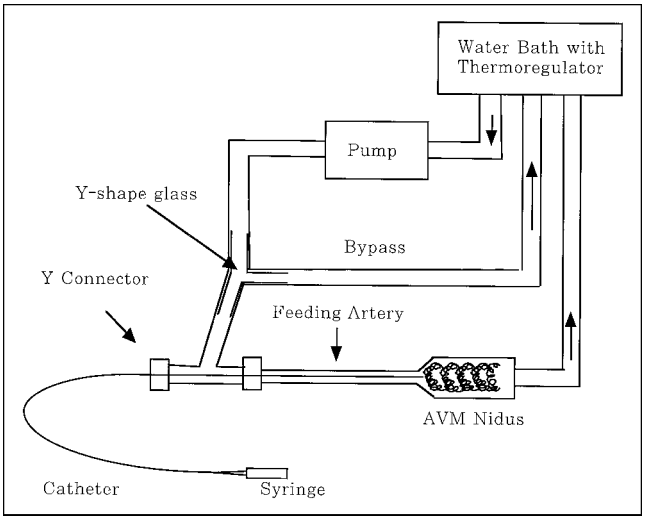

Fig 2. Schematic diagram of the AVM flow model.

was supplied through a plastic tube with a ⅝-inch inner diameter, which was connected through a Y-shaped glass to a Y connector (Target Therapeutics, Fremont, Calif), through which the catheter and a bypass were introduced. For connection of the AVM nidus to the Y connector, we used a straight polyethylene tube with 0.4-cm inner diameter. The polyethylene tube was fitted to both the Y connector and the narrowed neck of the AVM nidus. Another polyethylene tube was inserted in the bypass to even the flow. The polyethylene tube connecting the AVM nidus and Y connector served as a feeding artery. The ratio of the lumen of the feeding artery to the AVM nidus was 1:5.7, and thus it was assumed that the flow in the AVM nidus would be slower than that in the feeding artery by a factor of 5.7.

The maximum flow rate of the peristaltic pump was 3000 mL/min, and an adjustable knob with a scale of 1 to 9 was used to change the flow rate. The flow rate through the AVM model was determined at each increment of the scale by measuring the amount of flow through the AVM nidus for 10 seconds with a graduated cylinder. The flow rate through the model varied from 1.5 mL/s with the knob positioned at 1 to 21 mL/s at 9. The flow velocity in the feeding artery (polyethylene tube) was obtained by dividing the flow rate by the lumen of the feeding artery, approximately 0.125 cm^2. The flow velocity at each knob position is shown in Tables 1 and 2.

TABLE 1: Arteriovenous malformation model of polyvinyl acetate solution at different flow rates and injection speeds

Knob Position on Peristaltic Pump	Flow Velocity in Feeding Artery, cm/s	Injection Time, s	Length of Precipitated Polymer, cm
5	40	100	8.3
4	56	79	3.5
5	72	53	3
6	100	42	6 (+ threads)
4’	56	33	7.5
5’	72	48	3.5

Note.—Embolic solution in a 1-mL syringe was injected through a Tracker 18 catheter to the AVM nidus.

TABLE 2: Arteriovenous malformation model of polyvinyl acetate plus metrizamide solution at different flow rates and injection speeds

Knob Position on Peristaltic Pump	Flow Velocity in Feeding Artery, cm/s	Injection time, s	Length of Precipitated Polymer, cm
5	72	28	3
6	100	41	6.5
7	120	32	5
8	144	41	7
9	168	30	3.5

Note.—Embolic solution in a 1-mL syringe was injected through a Tracker 18 catheter to the AVM nidus.

Polymer Solution Preparation

The polymer solutions were prepared similarly to the one described by Su et al (5). Ethanol was first mixed with distilled water at a ratio of 56 to 44 by volume, and 1.4 g of PVAc was then dissolved in 10 mL of the mixed solvent by stirring and heating the mixture on a hot plate. After the polymer was completely dissolved, the solution was cooled to room temperature. To make the PVAc plus metrizamide solution, 1.0 g metrizamide was added to 5 mL PVAc in a vial. The concentration of metrizamide was about the same as that used in the study by Su et al (5).

Embolization Study with the AVM Model

The thermoregulator was turned on 30 minutes before the experiment at 37°C, and the peristaltic pump was

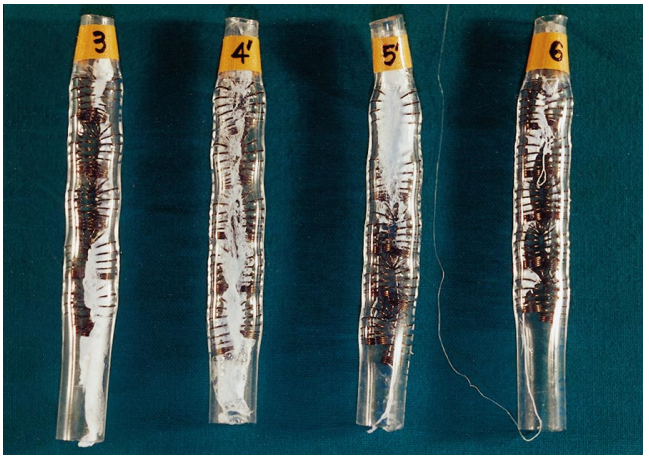

Fig 3. PVAc precipitated inside the model AVM nidus at different flow velocities. The numbers indicate the knob position on the peristaltic pump. PVAc precipitated outside the spring-filled region when the flow was slow (*3* and *4′*), but precipitated proximally when the flow velocity was increased (*5′*). With further increase in flow velocity, the polymer formed threads that passed the nidus (*6*).

turned on just before the experiment. The catheter, a Tracker 18 (Target Therapeutics), was irrigated with 0.5 mL of 30% (volume in volume) ethanol to prevent premature precipitation of PVAc inside the catheter. A 1-mL Luer-Lok syringe was loaded with the polymer solution and connected to the catheter. While the water was circulating, the polymer solution was injected slowly through the catheter into the AVM nidus with the tip of the catheter always inside the nidus. After injection of the PVAc solution, the time required for delivery of the solution was recorded, along with the length of the precipitated polymer. The experiment was then repeated at different knob positions on the peristaltic pump.

Results

Embolization with PVAc

The results of the AVM model study with PVAc are summarized in Table 1, and illustrated in Figure 3. When the flow in the feeding artery was slow, at 40 cm/s, the polymer precipitated distally a distance of 0 to 8.3 cm. The injection was done very slowly because we learned that the polymer flows out of the nidus tube when injected faster. With an increase in flow velocity to 56 cm/s, the polymer flowed a distance of just 3.5 cm. The proximal precipitation continued up to 72 cm/s, at which the precipitated polymer flowed a distance of 0 to 3 cm. When the flow velocity was increased to 100 cm/s, however, the trend reversed: not only did the polymer precipitate more distally but long, thin threads formed, which passed the AVM nidus. A thread still attached to the precipitated polymer is clearly seen in Figure 3.

To ascertain the effect of injection speed, we injected PVAc faster than before, with the knob positioned at 4; at this flow rate, the polymer precipitated more distally (compare rows 4 and 4′ in Table 1). When we evaluated reproducibility, we found the precipitation distance was about the same at similar injection speeds (compare rows 5 and 5′).

Polymer that precipitated past the spring-filled region can be clearly seen in the AVM nidus structures labeled 3 and 4′ in Figure 3. In these tubes, the polymer was still clear, transparent, and gellike while it flowed through the spring-filled region before solidifying and turning white when it reached the end of the nidus. Because the Tygon tube is transparent, the precipitation in the nidus was visible without the help of fluoroscopy. Thus, we could deliberately adjust the injection speed so that the polymer did not pass the tube itself.

The Effect of Adding Metrizamide to PVAc Solution

The results of the model AVM study with the PVAc plus metrizamide solution are collected in Table 2, and illustrated in Figure 4. Compared with the precipitation of PVAc-only solution, the most striking difference was that solution containing PVAc plus metrizamide did not pass the nidus when the flow velocity was greater than

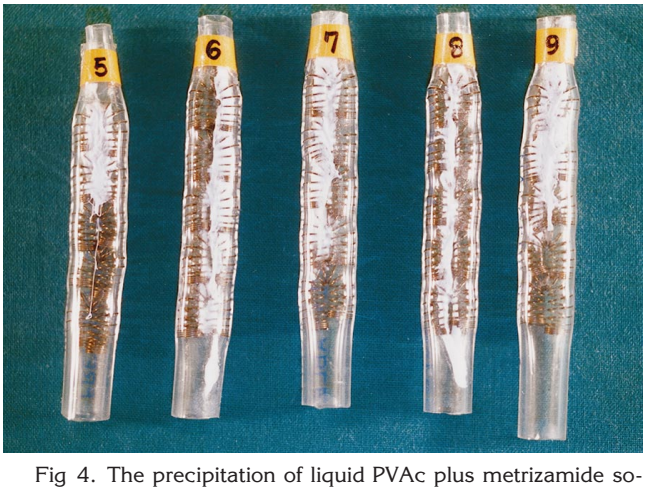

Fig 4. The precipitation of liquid PVAc plus metrizamide solution in the model AVM nidus at different flow velocities. Note that polymers remained inside the nidus at all flow velocities. No passage of threads was observed for this PVAc plus metrizamide solution. Precipitation behavior with the knob positioned at 3 and 4 was basically the same as that in Figure 3.

100 cm/s. As can be seen in Figure 4, the PVAc remained inside the AVM nidus at most flow velocities up to 168 cm/s. Moreover, with the PVAc plus metrizamide solution, threads did not form. The precipitation behavior of PVAc plus metrizamide at knob positions of 3 and 4 was basically the same as that of the PVAc-only solution.

Discussion

Unlike the cyanoacrylate glues, PVAc is an already polymerized chain that precipitates in a water environment, such as blood. To bring the water-insoluble PVAc onto the embolization site, the polymer is dissolved in the ethanol/water mixture with ethanol greater than 56% by volume. When the polymer solution is injected into water, a wall is formed around the interface of the PVAc solution and water, and the polymer solution inside the wall gradually turns solid in a few minutes as ethanol inside and water outside exchange (6). In our study, the polymer precipitated more proximally with the increase in flow velocity, as seen with the PVAc-only solution, in which the flow velocity increased from 40 cm/s to 72 cm/s. We believe this happened because the solvent exchange becomes more effective with increased flow velocity as ethanol around the polymer wall is washed away more quickly at higher flow velocities. However, there appears to be an optimum flow velocity for PVAc precipitation, because the polymer solution formed threads that passed the AVM model when the velocity became greater than 100 cm/s. We think that the PVAc wall encasing the solution was too elastic and stretchable to resist the pressure from the increased flow velocity.

PVAc precipitated more distally at higher injection speeds, a phenomenon that is opposite to the behavior of cyanoacrylate glue: glue needs to be injected fast to arrest blood flow in a fistulous, high-flow vessel. This behavior of PVAc precipitation may be explained by the same argument as above that is, the wall encasing the polymer solution expands more quickly when the injection speed is high, and the polymer solution inside the wall breaks out while the solution inside flows together with the stream before resolidification, resulting in a more elongated shape of the precipitate.

The addition of radiopaque contrast material, metrizamide, clearly enhanced PVAc quality as an embolic material, because the PVAc with metrizamide did not flow distally at high flow velocities whereas the PVAc-only solution formed threads that flowed past the AVM model. We think that the membrane wall encasing the PVAc solution becomes stronger, probably through hydrogen-bonding with the metrizamide molecules, and less elastic when metrizamide is added to the solution. The decreased precipitation distance was also observed when PVAc was mixed with Ultravist (iopromide). The contrast molecules in both metrizamide and iopromide have chemical function groups for a hydrogen-bonding donor, and the acetate group in PVAc is a good H-bonding acceptor.

A model for AVM was constructed by Kerber and Flaherty (15), who used a disposable blood filter as the nidus, which was good only for particulate embolization. Later, Kerber et al (16) and Debrun et al (17) developed plastic AVM models for liquid polymers, but they were more similar to arteriovenous fistulas than to AVMs, as the models lacked a nidus structure. Recently, Bartinsky et al (18) developed an AVM model in which the nidus was made of a mesh pad packed inside a sandwich bag. The nidus had four openings connected to two feeding arteries and two draining veins. These investigators were able to simulate the embolization of a nidus with both Ivalon and NBCA under fluoroscopic guidance. One advantage of our model relative to theirs is that our model nidus is completely visible and thus does not require the use of angiography. Another advantage of our model is that it is more reproducible than others. The meshes made of springs are always the same size, whereas the pore size of the nidus made of scouring pads is dependent on packing density; thus, our model allows a quantitative study of precipitation distance.

Our AVM model is far from a real clinical AVM in that the vessel structure of clinical AVMs is much more tortuous. In a sense, this model is more similar to an arteriovenous fistula that has been filled with coils, yet the blood flow has not diminished. Also, the nidus in our model was made not spherically but cylindrically. These simplifications, however, were done deliberately, since our goal was to study the quantitative dependence of precipitation distance on flow velocity and speed of injection. Thus, while the model is not like a clinical AVM, it proved good enough to furnish valuable information about the behavior of a precipitating liquid embolic material. We believe that this model is

quite useful for feasibility testing of new liquid embolic materials.

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