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Technical Note

Simulation Model of Arteriovenous Malformation Embolization Using Onyx

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Objective: Although Onyx has made effective embolization possible in the endovascular treatment of arteriovenous malformation (AVM), its infusion requires a high level of skill and experience. The purpose of this study is to create a simulation model that will help to solve this technical issue.
Model Presentation: Using data of 3D DSA images of a clinical case, an acrylonitrile–butadiene–styrene (ABS) resin model of the AVM was created with a 3D printer. Then, a hollow elastic model was created by applying silicone and eluting the ABS resin, which was finally connected to the human vascular model. Simulation of angiography and Onyx embolization using the model showed similar angiographic features and flow dynamics of contrast media and Onyx. During Onyx embolization, the plug and push technique could be performed as in a clinical case.
Conclusion: 3D AVM model created with 3D printer enabled us to stimulate Onyx embolization of AVM.

Keywords ▶ arteriovenous malformation, Onyx, simulation model

Introduction

The objective of endovascular treatment for brain arteriovenous malformation (AVM) is to lessen the difficulty of surgery by reducing the amount of bleeding in resection. It may also be performed for curative embolization and palliative embolization such as intranidal aneurysm embolization and nidus size reduction before stereotactic radiation therapy. In 2008, Onyx (Medtronic, Minneapolis, MN, USA) which is a precipitation type non-adhesive liquid embolic agent, obtained pharmaceutical approval in Japan, and effective embolization has become possible by its appropriate selective use with n-butyl cyanoacrylate (NBCA), which is a cyanoacrylate adhesive used before the advent of Onyx. In embolization using NBCA, split-second decisions and a high technical level are required for the adjustment of the infusion rate and reflux and determination of the timing of catheter withdrawal. It is used by adjusting the concentration by mixing it with lipiodol, but experience is also needed for the judgment of an appropriate concentration. In addition, Onyx, with which embolization can be performed by continuous injection using the plug and push technique, permits some more time than NBCA for the judgment, but its behavior is often unpredictable, and attention is needed for catheter trapping. Since catheter trapping increases the risk of vascular damage and hemorrhage at the time of catheter withdrawal, the technical difficulty poses cause a problem in treating AVM.

Since the results of the ARUBA trial[1)] were released, indications of AVM treatment are being reevaluated, but safe and effective preoperative embolization is essential for future improvements in the therapeutic results, for which advancement in skill is important. In the previous studies, AVM nidus models, such as the one using the swine carotid rete mirabile, have been reported for checking biological responses to the embolic material.[2)] However, it is extremely difficult to perform experiments and preoperative simulation at facilities that provide routine

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clinical services, and training of young surgeons is also not easy. The objective of this study was to develop a simulation model that can solve ethical problems of the use of animals and is useful for technical training of young surgeons by preparing a hollow AVM model where Onyx could be injected.

Model Presentation

Preparation of 3D AVM model

A model was prepared by applying actual cerebral angiography data of an AVM patient to the 3D/4D visualization and analysis software Avizo (Thermo Fisher Scientific, Weltham, MA, USA). Since adjacent blood vessels appear as a mass and are recognized as one vessel in 3D images of real cases, using this model as a reference, a simple AVM model that approximately mimics the vascular arrangement was prepared newly by reproducing the feeding arteries, draining veins, and nidus using the 3D workstation 123D Design (Autodesk, San Rafael, CA, USA) (**Fig. 1A** and **1B**). On the 3D workstation, the nidus was prepared with a vascular diameter of 1–3 mm by changing the curvature of the blood vessels. In this study, a model with two feeding arteries (**Fig. 1A**, arrows) and one draining vein (**Fig. 1A**, arrowhead) was prepared. The diameters of the feeding arteries and draining vein were made larger than that of the nidus to create fast flows in the nidus. By combining loops with different shapes, a model with morphology close to a real nidus was prepared. Also, to make a hollow model by applying silicone to the printed nidus in later processes, the model was prepared with temporary outlets for complete lysis of the printed nidus (**Fig. 1B**, arrows).

Preparation of 3D printer acrylonitrile–butadiene–styrene (ABS) resin model and silicone AVM model

The AVM model prepared on the 3D workstation was printed with the 3D printer Mojo (Stratasys, Eden Prairie, MN, USA) (**Fig. 1C**). With this 3D printer, the vascular parts are printed with ABS resin, and the base that supports the vascular part is printed with SR30 (Stratasys), which dissolve in an alkaline solution. In this way, the intended vascular model alone could be extracted by immersing the printout in an alkaline solution for 24 hours (**Fig. 1D**). Silicone tubes were attached to the feeding arteries, draining vein, and outlet ports in the printed AVM model, and transparent silicone for casting (Zoukei-mura, Kyoto, Japan) was repeatedly applied to the AVM model from three to about six times as necessary with drying each time (**Fig. 1E**). After applying silicone, the ABS resin inside alone was eluted without lysing the silicone by immersing the model in eSolve 21PR-22 (KANEKO CHEMICAL, Saitama, Japan), which is an organic solvent. A hollow model was prepared by immersing the model in this organic solvent for 24 hours, carefully taking it out, and finally removing fine ABS resin remaining in the silicone AVM model by washing with water (**Fig. 1F**).

Pulsatile flow model mimicking the human vasculature

A pulsatile flow model mimicking the human vasculature was prepared. Our original silicone model of the inguinal region to the aortic arch was prepared by connecting various parts with silicone tubes. As the parts distal to the common carotid artery, the common carotid artery and internal carotid artery were prepared by the same method as above. All these parts were designed to be connected with silicon tubes of the same diameter so that water could be flowed through them from the ascending aorta. The perfusion system could continuously flow water in the model as pulsatile flow using the tube pump WP1000-P6.4M2-W6-CP (WELCO, Tokyo, Japan). The specifications of this perfusion pump were as follows: rated voltage, DC24V; number of pump rollers, 2 (150 rpm); internal diameter of the tubes in the pump, 6.4 mm; flow rate, 450 mL/min; and flow velocity, 0.23 m/s. Simulation was performed by connecting the prepared silicone AVM model to the above pulsatile flow model mimicking the human vasculature. The completed AVM model had two feeding arteries, which were connected to the middle cerebral artery (**Fig. 1G** and **1H**). The tube connected to the draining vein was not closed but drained into a tray set at a low place. By this, the venous pressure was lowered, the resistance distal to the nidus was reduced, and the flow velocity was increased to make the model similar to a real AVM. Under X-ray fluoroscopy, the guiding catheter was advanced from the inguinal region to the internal carotid artery, and angiography was performed (**Fig. 2A**).

Infusion of Onyx

When simulation was performed by connecting the pulsatile flow model and silicone AVM model, the contrast medium flowed into the silicone AVM model and drained smoothly via the feeding arteries (**Fig. 2A**, arrow) and nidus into the draining vein (**Fig. 2A**, arrowhead). By angiographic roadmapping, the microcatheter Marathon (Medtronic plc, Dublin, Ireland) was advanced into one of

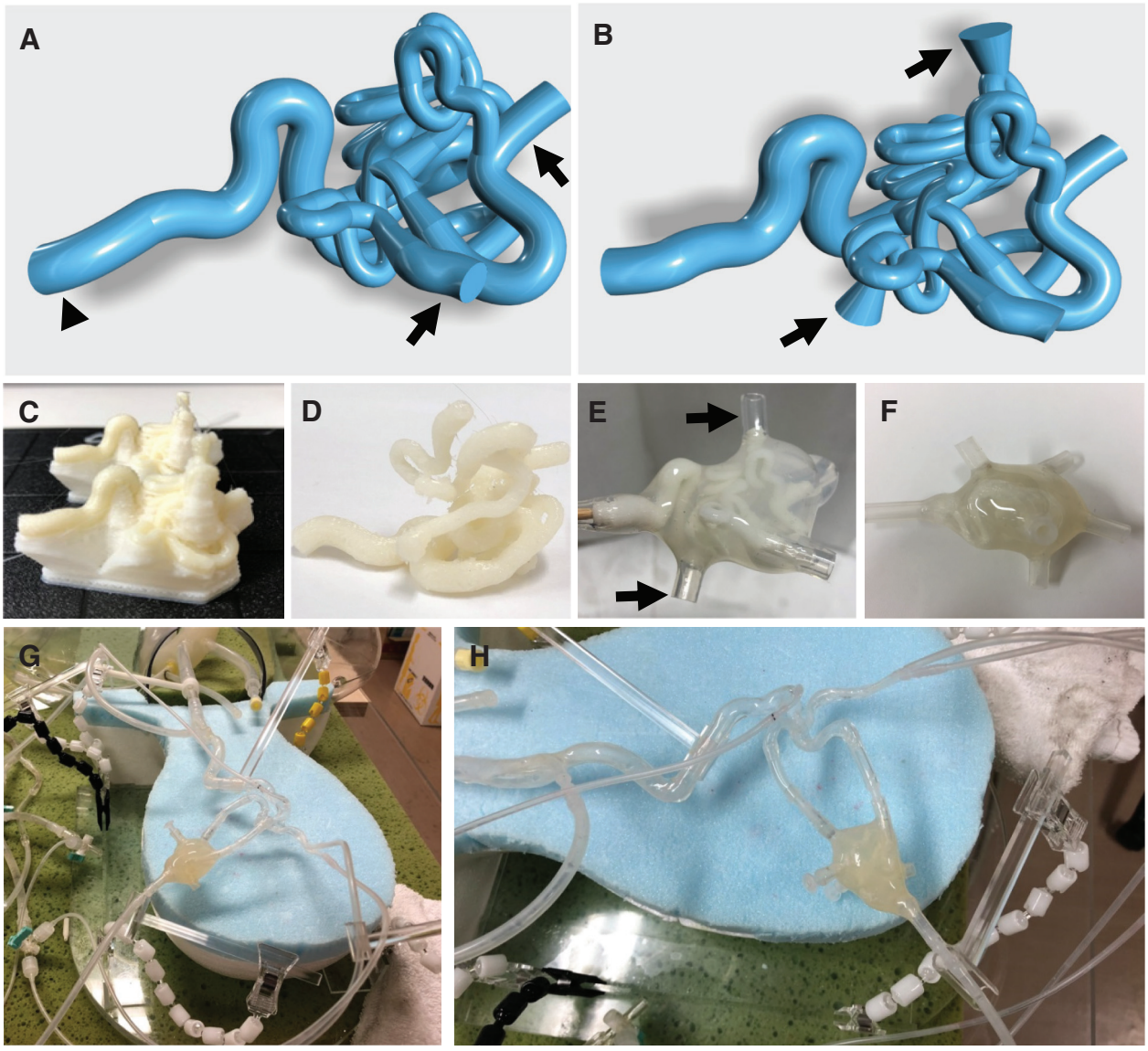

Fig. 1 **(A)** Nidus model created by CAD. Arrows show feeders and arrowhead shows drainer. (**B**) Two outlets (arrows) attached to the nidus model because of dissolution of ABS resin.(**C**) 3D printer models of nidus made from ABS resin with the supporting material. (**D**) 3D printer model after dissolving the supporting material. (**E**) The process of applying the 3D printer model of ABS resin with silicone and drying was repeated three times. Arrows show drains for dissolution of ABS resin. (**F**) Silicone model of nidus after dissolving ABS resin. (**G** and **H**) Silicone model of nidus was connected to our simulation model for endovascular surgeons, which was produced at our institute. ABS: acrylonitrile–butadiene–styrene; CAD: computer-aided design

the feeding arteries. When the tip of the Marathon arrived at the proximal side of the nidus, infusion of Onyx 18 (Medtronic plc) was initiated. When Onyx 18 was injected slowly from the Marathon, reflux was observed at a site slightly inside the nidus. Therefore, the plug and push technique was performed by stopping the injection for about 30 seconds (**Fig. 2B**, arrow) and resuming it. By performing the plug and push technique, Onyx 18 exhibited behavior similar to that in actual patients such as the arrest of the flow of Onyx 18 to distal parts and its advance to other vessels (**Fig. 2C** and **2D**). With caution not to cause reflux at the end of the catheter, Onyx 18 was injected into the nidus. The catheter was extracted after about half of the nidus was embolized. Little reflux of Onyx 18 was noted, and little resistance was felt in extraction. Thereafter, when angiography was performed via the guiding catheter, since the contrast medium flowed via the other feeding artery (**Fig. 2E**, arrow) to the draining vein, embolization was performed after inserting a new Marathon into the other feeding artery and changing the working angle. When Onyx 18 was injected into the nidus after first forming a plug by the plug and push tech-

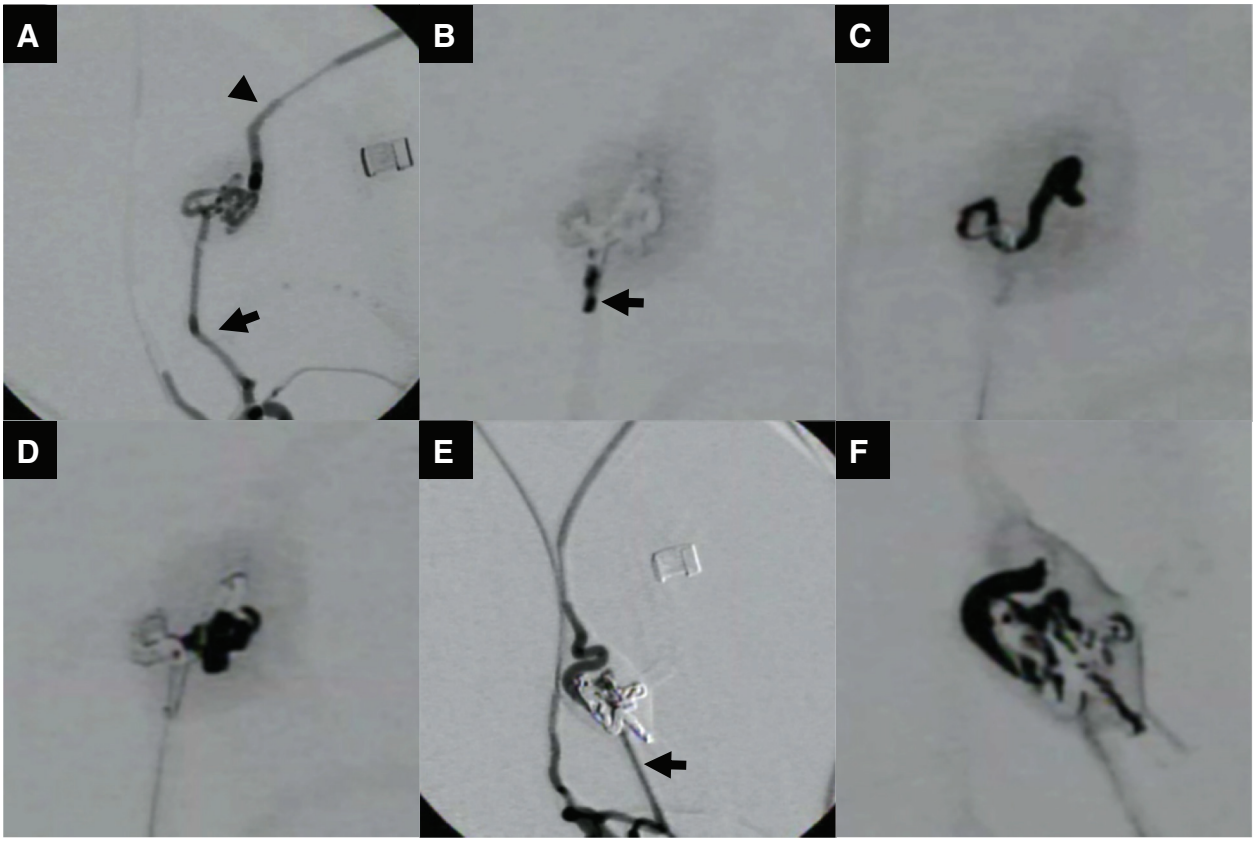

Fig. 2 (**A**) Radiograph before embolization of nidus model. Arrow shows one of the feeders and arrowhead shows drainer. (**B**) Injection of Onyx from Marathon. Plug was made at the tip of the catheter (arrow). (**C**) Onyx filled in the nidus model using the plug and push method. (**D**) After pausing the injection of Onyx, Onyx filled in another vessel of the nidus model. (**E**) Radiograph injected from another feeder (arrow). (**F**) Injection of Onyx from another feeder. The remain of the nidus was occluded and Onyx reached the drainer.

nique similarly to the first vessel, Onyx 18 reached the draining vein after passing small vessels in the nidus, so the injection was ended at that point (**Fig. 2F**).

When the AVM model was examined under X-ray fluoroscopy, Onyx 18 was confirmed to have reached the draining vein through the feeding artery and small vessels in the nidus (**Fig. 3A**, arrows: feeding arteries, arrowhead: draining vein). During and at the end of simulation, the condition of Onyx embolization could be monitored visually while the injection was paused (**Fig. 3B**). After simulation, the AVM model was removed, and Onyx was confirmed to have filled the entire nidus (**Fig. 3C**).

Discussion

Training in Onyx embolization of AVM has been made in animal models using swine or sheep vessels. By assuming the carotid rete mirabile specific to lower mammals as the nidus, a false model of AVM has been prepared by artificially anastomosing the internal carotid artery and internal jugular vein in many reports.[2–4] Conditions required for qualification of a physician capable of Onyx embolization include practical training in Onyx injection, and swine models are used for this training. However, such animal models are difficult to prepare and maintain and are not suited for mass production from the viewpoint of the cost, and the development of a new alternative model that can be produced in large numbers at a low cost is expected. Although such animal models are considered to immensely contribute to the understanding of biological phenomena and development of surgical techniques at the precious sacrifice of animals, standards concerning the care and management of experimental animals and mitigation of their pain announced by the Japanese Ministry of Environment include the maximum adoption of alternative methods that can save the use of animals and maximum reduction of animals subjected to experiments. The development of alternative methods for learning surgical techniques is very important for reducing the use of experimental animals.

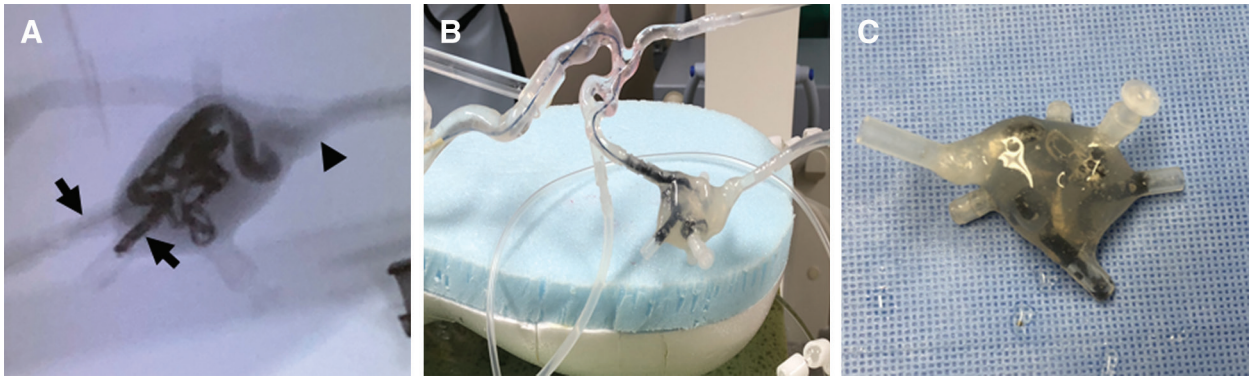

Fig. 3 (**A**) Radiograph after embolization of the nidus model using Onyx. Arrows show two different feeders, and arrowhead shows the drainer. (**B**) Visually checking the status of the nidus while pausing Onyx injection. (**C**) Silicon model of the nidus after the final injection of Onyx.

Recently, there have been sporadic reports of preparation methods and the usefulness of hollow silicone models for training in the treatment for cerebral aneurysms.[5] Such hollow models are prepared by outputting the patient's digital imaging and communications in medicine (DICOM) data of cerebral angiography with a 3D printer using ABS resin, applying silicone, and lysing the ABS resin after hardening of the silicone. We also attempted to develop an AVM training model based on such techniques. While the cost of purchase of a 3D printer is necessary, a model could be prepared relatively reasonably at about 500 yen. Although the processes needed for the preparation of a model take about 3 days including the time of drying, the time required in each process is short, being about 1 hour. However, the following problems have arisen in preparing such hollow AVM models. There are a large number of very small blood vessels in a real nidus. In preparing this model, we attempted to reproduce the feeding arteries, draining veins, and nidus using DICOM data obtained by preoperative 3D rotation angiography, but it was difficult to reproduce the fine vasculature because the 3D/4D visualization and analysis software used recognized closely adjacent blood vessels as a single mass. Particularly, in angiograms, the arrangement of blood vessels in the central part of the nidus is complicated and could not be reproduced from computer-aided design (CAD) data as an aggregate of separate vessels. We tried to separate the mass into individual vessels by elevating the processing threshold but encountered great difficulties such as the disappearance of some of the fine vessels with increases in the threshold. We, therefore, designed a sham nidus that can be output with a 3D printer from angiographic data using CAD software. Another problem was that this hollow AVM model is prepared by applying silicone over a 3D printout and then lysing the ABS resin inside but that it was difficult to completely lyse and washed out the ABS resin from minute parts despite prolonged immersion in an organic solvent. Therefore, in designing the nidus using CAD software, we set a few outlets for drainage of the resin at sites where the resin is difficult to lyse. Because of these drains, complete lysis of the resin became possible. Since complete reproduction of clinical data was difficult, the model prepared in this study turned out to be a sham model derived from clinical data. However, the behavior of Onyx after its actual infusion sufficiently allowed replication of clinically important manipulations, such as the plug and push technique, and this model is considered to be applicable to training, particularly, of young surgeons. Presently, the modeling technology using 3D printers is one of the fields that are developing most primarily in the manufacturing domain, and the shaping precision has reached the micrometer level. Such development of engineering technology may make preparation of even more detailed AVM models possible. For the future, reproduction of blood vessels ranging from several to tens of micrometers, which are pathologically evaluated in clinical settings, may become possible,[6] and models that faithfully reproduce the patients' real niduses are expected to become available in time.

In addition to animal models, studies using in vitro AVM models using a tube or a syringe and beads[7,8] and those using a silicone in vitro AVM model with a honeycomb 3D structure[9,10] have been reported. However, many of these in vitro AVM models do not permit sufficient simulation of the plug and push technique at the time of Onyx injection in AVM with irregular shapes in real patients. An advantage of our model compared with these models is that, despite room for improvement as mentioned above, it replicates the complex vasculature in the nidus and allows the user to experience the plug and push technique and Onyx reflux.

A limitation of this study, in addition to the insufficiency of detailed reproduction of the fine vasculature in real patients, is that we have as yet evaluated only one type of AVM model. We consider that our model can be developed into a more useful simulation model by comparing multiple types of AVM models and performing more detailed evaluation with comparison of the embolization rate and infusion volume in models after embolization.

Conclusion

In this study, a hollow AVM model could be prepared by a relatively inexpensive and simple method compared with conventional animal models. In this model, the behavior of Onyx in the plug and push technique could be reproduced in vitro by actually infusing it. This model is considered to be useful as an AVM simulation model applicable to the training of young surgeons without using animals.

Disclosure Statement

The authors declare no conflicts of interest.

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