In Vitro Analysis of the Efficacy of Endovascular Thrombectomy Techniques according to the Vascular Tortuosity Using 3D Printed Models

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ABSTRACT

BACKGROUND AND PURPOSE: Achieving complete recanalization with the front-line endovascular thrombectomy device improves the outcome of acute stroke. The aim of this study was to evaluate whether various thrombectomy techniques including contact aspiration, stent retriever thrombectomy, and combination therapy differ in first-pass effect and distal emboli in acute large-vessel occlusion simulated using 3D printed nontortuous and tortuous cerebrovascular anatomy models.

MATERIALS AND METHODS: 3D printed flow models were manufactured using angiographic data of nontortuous and acutely angulated tortuous vascular anatomy from real patients. Three thrombectomy techniques, contact aspiration, stent retriever, and combined methods, were tested under proximal protection with the balloon-guiding catheter. The first-pass effect and distal emboli rates were analyzed in addition to the thrombectomy-failure mechanisms of the respective techniques.

RESULTS: A total of 30 thrombectomy experiments were performed. The overall incidence of first-pass effect in the nontortuous and tortuous anatomy was 80.0% versus 46.7%. The overall incidence of distal emboli in the nontortuous and tortuous anatomy was 26.7% versus 46.7%. The contact aspiration technique showed better first-pass effect (80.0%) and distal emboli rates (20%) in the tortuous model compared with other techniques. The combined technique did not show remarkable superiority of the first-pass effect and distal emboli in either the nontortuous or tortuous anatomy. Shearing off of the thrombus was the main mechanism of thrombectomy failure in the combined group.

CONCLUSIONS: The tortuous vascular anatomy may worsen the first-pass effect and distal emboli rates. The combined techniques failed to show improvement in outcome due to the shearing-off phenomenon of the thrombus during retrieval.

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and may be one of the major causes of recanalization failure. However, the exact mechanism of how the tortuous anatomy affects the efficacy of EVT is not well-known. Fortunately, with the recent development of 3D printing and modeling techniques, it has become possible to replicate this difficult anatomy with a flow model matching the real patient that can be tested in vitro. Therefore, the aim of this study was to compare the efficacy of various thrombectomy techniques including CA, SR thrombectomy, and combination therapy in terms of FPE and DE and to elucidate the mechanisms of thrombectomy failure in acute large-vessel occlusion simulated using 3D printed nontortuous and tortuous cerebrovascular anatomy flow models obtained from real patient data.

MATERIALS AND METHODS

Model Anatomy
3D DSA data were obtained from 2 patients who had been treated by EVT for acute ischemic stroke at our stroke center. Data were obtained from a patient with nontortuous cerebrovascular anatomy who achieved FPE and a patient with very tortuous anatomy who achieved recanalization only after multiple retrieval attempts. The collection and use of the patient’s angiographic data were approved by the institutional review board. Blood vessel data were extracted from the distal cervical segment of the ICA, through the carotid bifurcation, to include the M1 segment of the MCA and the A2 segment of the anterior cerebral artery (ACA). The tortuosity of the vessel was visually verified and also numerically confirmed (arc-to-chord ratio) by comparing the distance between the 2 points on a straight line between the distal M1 and the distal cervical ICA in each model and the total length of blood vessels between the 2 points (arc-to-chord ratio: 1.77 for the tortuous model and 1.49 for the nontortuous model).

Flow Model
The angiographic DICOM data were extracted in Virtual Reality Modeling Language (Matlab; MathWorks) format using the 3D Workstation (IntelliSpace Portal; Philips Healthcare). These were converted into a stereolithography file using CAD software (MeshLab; Cignoni et al). Using these files, we produced semitranslucent vascular models with photopolymerization resin (standard Clear Resin, Version 4; Formlabs) with a 3D printer (Form2; Formlabs). After printing, we applied multiple silicone coatings to the surface of the models, and removed the inner mold to produce a flexible, hollow, and transparent vascular model (Fig 1). The manufactured model was placed in a water-filled tank made of acryl and connected to a water-circulation system at the proximal ICA, MCA, and ACA. The system was connected to a transparent silicone tube and was connected to a peristaltic pump (EMP-100; EMS technologies), which maintains a pulse rate of 80 beats per minute to simulate blood circulation. A separate water tank was connected to collect the distally migrated embolus. The entire model was filled with a mixture of normal saline fluid and glycerin (60/40 volume saline/glycerin) to mimic the characteristics of blood. A route through which a guiding catheter and thrombectomy devices can be inserted was separately connected to the proximal ICA of the circulation system (Fig 2). Experimental procedures were recorded with video and photographs using a high-resolution digital camera.
Table 1: Incidence of FPE and DE in nontortuous and tortuous models according to the EVT technique

<table>
<thead>
<tr>
<th></th>
<th>FPE Nontortuous</th>
<th>FPE Tortuous</th>
<th>DE Nontortuous</th>
<th>DE Tortuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>12/15 (80.0%)</td>
<td>7/15 (46.7%)</td>
<td>4/15 (26.7%)</td>
<td>7/15 (46.7%)</td>
</tr>
<tr>
<td>CA</td>
<td>5/5 (100.0%)</td>
<td>4/5 (80.0%)</td>
<td>0/5 (0%)</td>
<td>1/5 (20.0%)</td>
</tr>
<tr>
<td>SR</td>
<td>4/5 (80.0%)</td>
<td>2/5 (40.0%)</td>
<td>1/5 (20.0%)</td>
<td>3/5 (60.0%)</td>
</tr>
<tr>
<td>Combined</td>
<td>3/5 (60.0%)</td>
<td>1/5 (20.0%)</td>
<td>3/5 (60.0%)</td>
<td>3/5 (60.0%)</td>
</tr>
</tbody>
</table>

Table 2: Incidence of failure of complete recanalization in nontortuous and tortuous models according to the EVT technique

<table>
<thead>
<tr>
<th>Failure of Complete Recanalization</th>
<th>Nontortuous</th>
<th>Tortuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5/15 (33.3%)</td>
<td>9/15 (60.0%)</td>
</tr>
<tr>
<td>CA</td>
<td>0/5 (0%)</td>
<td>1/5 (20.0%)</td>
</tr>
<tr>
<td>SR</td>
<td>2/5 (40.0%)</td>
<td>4/5 (80.0%)</td>
</tr>
<tr>
<td>Combined</td>
<td>3/5 (60.0%)</td>
<td>4/5 (80.0%)</td>
</tr>
</tbody>
</table>

Thrombus Analog
The method of producing a fresh thrombus analog is well-documented and has been used in many prior studies.12,13 Per 4 mL of fresh swine blood, 32 mg of fibrinogen from bovine plasma (Sigma-Aldrich) and 1 U of thrombin from bovine plasma were mixed, put in a plastic cage, and incubated at room temperature for 60 minutes. The prepared clot was cut into 10-mm lengths and inserted into the flow system using an 8F guiding catheter.

Endovascular Thrombectomy Techniques
After connecting the 8F sheath to the flow model through a silicone tube, an 8F BGC (Flowgate2; Stryker) was inserted and placed in the distal cervical ICA portion of the model. The thrombus was placed in the MCA M1 portion through the guiding catheter. EVT in the SR group was performed using a Solitaire FR 4/20 (Medtronic) or Trevo 4/20 (Stryker) stent after passing the thrombus with a 0.021-inch microcatheter and a 0.014-inch microwire. The active push deployment technique was performed when deploying the SR. In the CA group, manual aspiration thrombectomy was performed using an AXS Catalyst 6 aspiration catheter (Stryker) and a 20-mL syringe after direct catheter tip contact with the thrombus. In the combined group, a microwire and a microcatheter were navigated across the occlusion site followed by coaxial advancement of the aspiration catheter (Catalyst 6) close to the occlusion site. After the deployment of the SR through the occlusion site, the aspiration catheter was advanced just proximal to the portion of the SR-engaged thrombus. Then, with simultaneous suction via the aspiration catheter, the entire system was cautiously retrieved as a unit. In all groups, proximal flow arrest was achieved using the BGC.

FPE was defined as complete flow restoration without any remaining thrombus in the MCA, ACA, or ICA segments after a single thrombectomy attempt. DE was defined as identification of a visible, migrated embolus that reached the reservoir tank through the MCA, ACA, or ICA segment regardless of the size of the embolus. FPE and DE were evaluated at the end of the procedure after BGC deflation mimicking the real-world procedure. Successful first-pass recanalization with a DE small enough to migrate distally and enter the reservoir tank system was considered as both FPE and DE. If the thrombus was fragmented but large enough to remain in the MCA or ICA segment without distal migration, it was considered as an FPE failure and not classified as DE. Moreover, we defined failure of complete recanalization by combining all cases of failure to achieve FPE and cases of DE. Analyses of the video recordings were performed to identify the mechanisms of thrombectomy failure.

RESULTS
A total of 30 thrombectomy experiments were performed for the CA (n = 10), SR (n = 10), and combined groups (n = 10), respectively. Of these, half in each group (n = 5) were tested in the nontortuous anatomy model, and the remaining half (n = 5) were tested in the tortuous anatomy model.

EVT Results according to the Vascular Tortuosity
In terms of the tortuosity of the vessel, the FPE rate of the nontortuous anatomy model was higher than that of the tortuous anatomy model (80.0%, 12/15, versus 46.7%, 7/15). The incidence of DE was lower in the nontortuous anatomy model (26.7%, 4/15, versus 46.7%, 7/15) (Table 1). The failure of the complete recanalization rate in the nontortuous anatomy model was lower than that in the tortuous anatomy model (33.3%, 5/15, versus 60.0%, 9/15) (Table 2).

Comparison of Various Thrombectomy Techniques
CA showed the best FPE and DE rates in both the nontortuous and the tortuous models compared with the SR or combined techniques. In the nontortuous model, FPE/DE rates were 100%/0% versus 80%/20% versus 60%/60% for the CA, SR, and combined techniques, respectively. In the tortuous model, the FPE/DE rates worsened for all devices compared with the nontortuous model; however, CA maintained a relatively favorable outcome compared with the SR or combined techniques (80%/20% versus 40%/60% versus 20%/60%) (Table 1). The combined technique failed to show superior results compared with the other techniques in all aspects, with notably poor FPE outcome in the tortuous anatomy model (80% versus 40% versus 20%).

Mechanism of Thrombectomy Failure
The analysis of the video recordings revealed the mechanisms of thrombectomy failure for the respective techniques. In the CA technique, FPE and no DE were observed when the thrombus was completely ingested at the site of occlusion. However, when the clot was not completely ingested, deflection and straightening of the tip of the aspiration catheter occurred when passing through the curved angle of the vessel, resulting in an increase in the angle between the axis of the aspiration catheter tip and the axis of the captured thrombus, causing fragmentation and detachment of the thrombus (Fig 3A, -D). In the SR technique, the stent was elongated, resulting in partial collapse of its lumen when passing through the curved segments such as the carotid siphon. These

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collapsed segments caused rolling, detachment, and fragmentation of the captured thrombus (Fig 3B, -E). In the case of the combined technique, shearing of the thrombus occurred when the thrombus-engaged SR was pulled into the aspiration catheter tip and during retrieval of the devices. This shearing phenomenon was more pronounced in the tortuous vessels (Fig 3C, -F).

**DISCUSSION**

The current in vitro study shows that the tortuosities of the cerebral vessels may impact the outcome of EVT techniques. The efficacy of EVT was inferior in the tortuous anatomy compared with the nontortuous anatomy irrespective of the techniques used. We found that both CA and SR techniques with proximal flow arrest showed acceptable FPE and DE results in the nontortuous anatomy. On the other hand, in the tortuous anatomy model showing severe angulations, the application of the CA technique was more effective in achieving better FPE and DE results than other techniques. The combined technique failed to show its effectiveness in terms of the FPE and DE in both the nontortuous and tortuous anatomy models.

In our experiment, CA showed the best FPE achievement with no DE in the nontortuous anatomy. It also showed relatively favorable FPE and DE results (FPE, 80%; DE, 20%) in the tortuous model. Many studies have reported that the CA technique shows angiographic and clinical outcomes comparable with those of conventional SR. However, in a real-world patient, whether to pursue CA in the face of a tortuous anatomy or switch early to another technique may be a dilemma. Our in vitro study suggests that CA may be preferred in terms of improving the FPE and preventing DE in the tortuous anatomy scenario. Our analysis showed that complete ingestion of the thrombus was the main reason for the better results of CA in the tortuous anatomy. When the thrombus was completely ingested into the catheter lumen, DE did not occur. Arslanian et al also reported the positive effects of CA on FPE and DE when the clot was completely ingested into the catheter lumen. On the other hand, Madjidyar et al showed, with a flow model study, that the likelihood of DE increased when the thrombus was clogged without being completely ingested into the catheter tip.

Our results also showed that the thrombus fragmentation could occur when the catheter tip was clogged with a long segment of the thrombus outside the catheter tip. The catheter-clogged thrombus remaining outside the catheter failed to remain intact due to the friction with the vessel wall, especially when deflection and straightening of the catheter tip occurred while passing through the angled curvature. According to Alverne et al, the retraction force of the thrombectomy devices can be physically reduced as it disperses through the different vectors in the tortuous vessels. Bernava et al showed that the angle of interaction between the aspiration catheter tip and the thrombus also influences the thrombectomy efficacy at MCA branches in an in vitro study. In this regard, larger inner-diameter aspiration catheters capable of complete ingestion of the clot may be the best solution for patients with severely tortuous vascular anatomy. However, despite the in vitro advantages of CA clot retrieval in the tortuous anatomy shown in this experiment, the tortuous anatomy may preclude fast and safe navigation of the aspiration catheter to the occlusion site in real-world patients. Development of more flexible and soft-tipped aspiration catheters with larger inner diameters is warranted.
The FPE and DE rates were 80.0% and 20.0%, respectively, in the nontortuous anatomy model when the SR technique was used with a BGC. In the tortuous anatomy model, the FPE rate decreased (40.0%) and DE was observed with a higher incidence (60.0%). The mechanisms of thrombectomy failure with the SR has been reported in several studies. Insufficient thrombus integration into the stent strut and thrombus rolling between the vessel wall and the strut are known to be common mechanisms and were observed in our analysis as well. Elongation and collapse of the device was observed in several cases of our tortuous anatomy model. The integrated thrombus was dislodged from the stent lumen at these collapsed segments. It has been reported that the elongation and collapse of the SR mesh may occur in curved and angulated segments. Also, the longer retrieval length of the SR due to the tortuous anatomy is thought to be associated with failure of thrombus retrieval. The physical elongation and collapse of the stent together with the increased length of the retrieval from the M1 to the cervical ICA in the severely angulated vessel may be the cause of the poor performance of SR in these cases. Considering these mechanisms of thrombectomy failure shown in this study, SR may be a suboptimal technique, especially in patients with a tortuous vascular anatomy. A longer length of the SR may be an alternative option. Recent introduction of many new SRs with modified structures such as segmented/hybrid design, dual-layer, and closed-end structures of the device may show improvement in the outcome.

Although a synergistic effect of the combined method may have been expected, our results show that there was no obvious advantage in achieving FPE and reducing DE compared with other techniques (Table 1). Rather, the FPE rate was quite low, especially in the tortuous anatomy (20%). Several SR-aspiration catheter combination thrombectomy techniques have been studied. Prior reports have reported that these combination techniques may be effective in improving the recanalization rate and reducing the distal embolization compared with single-device techniques. However, Yoo et al reported that when the SR was retrieved inside the aspiration catheter, there could be a risk of shearing off the thrombus between the aspiration catheter tip and thrombus-engaged SR. McTaggart et al emphasized the importance of appropriate tension adjustments to prevent shearing of the clot from the length mismatch of the SR and the aspiration catheter during retrieval. This shearing-off phenomenon may be difficult to visualize during the real-world patient treatment. However, the analysis of our study revealed that as the SR is retrieved into the tip of aspiration catheter, shearing off or squeezing out of the noningested thrombus occurs followed by fragmentation. This phenomenon was more pronounced in cases of tortuous curves where control of the length and tension mismatch between the stent and the aspiration catheter may be more difficult during retrieval.

Also, the stent struts may actually pin the clot to the vessel wall and interfere in the ingestion process of the thrombus by the CA catheter. Recently, Koge et al reported that the combined method showed more superior FPE results than in the SR and CA groups in the nontortuous ICA curve group, but the superiority was lost in the tortuous curve group. This finding seems to partly contradict our experimental results, which showed no superiority of the combined method in both the nontortuous and the tortuous models. Our analysis suggests that the shearing-off phenomenon is associated with not only vascular tortuosity but also multiple other factors. Our experiment included only M1 occlusions, but Okuda et al showed that the efficacy of the combined method may be influenced by the location of the occlusion, ie, it is more effective in ICA and M2 occlusions. Another concern of the combined method in the tortuous anatomy may be the safety of the procedure. Although the tensile force for retrieval of the devices was not analyzed in our study, more force was often necessary to retrieve the aspiration catheter and stent retriever together, probably due to the higher friction related to the combined use of the devices.

This study has some limitations inherently related to the in vitro nature of the experiment. Although the main arterial flow and its arrest with the BGC were simulated, the effects of the collateral flow on the thrombus could not be completely replicated. Other limitations include the endothelium and the coagulation factors and their effects on the friction and tension of the actual vessel wall. Also, only 1 type of red blood cell–rich thrombus analog and single models of the nontortuous and tortuous vascular anatomy were used. Another limitation is that although video recordings were used, the thrombectomy failure mechanisms could not be identified in some of the experiments; thus, quantitative analysis was not performed. The angle of the video recording was not optimal to visualize and identify the exact mechanism in some of the cases.

On the other hand, the major strength of this study is the anatomic simulation of the real human vasculature. Various model studies have attempted to simulate the real human cerebrovascular anatomy. Animal experiments may simulate relatively angulated vascular anatomy, but the anatomy and blood vessel size are different from those of actual human arteries. Fabrications of silicone or glass tubes may allow angulated and tortuous curvature models. However, this procedure also has limitations in simulating the actual curvature of human blood vessels. Flow-model production using 3D printing has the advantage of being able to accurately depict the cerebrovascular structure of a real patient. Furthermore, with a transparent material, the mechanisms of the device-thrombus-anatomic interaction can be directly observed. More diverse experiments such as the impact of the different histologic clot components and the efficacy of various devices/techniques in various models should be the subject of future studies.

CONCLUSIONS

We observed that the tortuous vascular anatomy may worsen the FPE and DE rates. Deflection and straightening of the aspiration catheter, elongation of the SR, and the shearing-off phenomenon during combined techniques were the main mechanisms of thrombectomy failure. CA was effective despite the tortuous anatomy when complete ingestion of the thrombus was achieved.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES


