In-vitro analysis of the efficacy of endovascular thrombectomy techniques according to the vascular tortuosity using 3d printed models

Junhwee Kim

Department of Medicine

The Graduate School, Yonsei University

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This certifies that the Doctoral Dissertation of
Junhwee Kim is approved.

Thesis Supervisor : Dong Joon Kim

Thesis Committee Member#1 : Young Dae Kim

Thesis Committee Member#2 : Yong Bae Kim

Thesis Committee Member#3: Hyun Seok Choi

Thesis Committee Member#4: Changho Yu

The Graduate School
Yonsei University

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We hope that this study will lead to further advances in neurointervention techniques and endovascular treatment for acute stoke patients in the future.

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ABSTRACT

In-vitro analysis of the efficacy of endovascular thrombectomy techniques according to the vascular tortuosity using 3d printed models

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Objectives: Achieving complete recanalization with the front-line endovascular thrombectomy device improve the outcome of acute stroke. The aim of this study is to compare whether various thrombectomy techniques including contact aspiration (CA), stent retriever (SR) thrombectomy and combination therapy differ in first pass effect (FPE) and distal emboli (DE) in acute large vessel occlusion simulated using 3D printed non-tortuous and tortuous cerebrovascular anatomy models.

Methods: 3D printed flow models were manufactured using angiographic data of non-tortuous and tortuous anatomy from real patients. Three thrombectomy techniques; CA, SR and combined methods were tested under proximal protection with the balloon guiding catheter. The FPE and DE 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 FPE in the non-tortuous and tortuous anatomy were 80.0% vs 46.7%. The overall incidence of DE in the non-tortuous and tortuous anatomy were 26.7% vs 46.7%. The CA technique showed better FPE (80.0%) and DE rates (20%) in the tortuous model compared to other techniques. The combined technique did not show significant superiority of FPE and DE in neither the non-tortuous and 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 FPE and DE rates. CA with proximal flow control may be preferred over other techniques in the tortuous anatomy. Combined techniques failed to show improvements in outcome.

Key words: acute stroke, endovascular treatment, mechanical thrombectomy, first pass effect, distal emboli

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I. INTRODUCTION

Endovascular thrombectomy (EVT) has become the treatment of choice for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) through several randomized controlled studies.[1 2] The use of a stent retriever (SR) shows an effective recanalization rate and acceptable safety.[3 4] With the introduction of new large bore aspiration catheters, direct contact aspiration (CA) shows comparable results to SR thrombectomy.[5] Additional use of a balloon guided catheter (BGC) for proximal flow control is recommended for the prevention of distal emboli (DE) during thrombectomy and improved outcome.[6 7] Recently, techniques using a combination of these devices have gained interest in terms of the potential improvement in the successful recanalization rates and clinical outcome.[8]

With the development of the techniques and devices, recent emphasis has moved on from successful recanalization to effectively achieving fast and complete recanalization. Clinical indices such as the FPE, which achieves complete recanalization with the first thrombectomy attempt, has shown to improve the clinical outcome of EVT and lower the mortality rate.[9] Thrombus fragmentation and DE migration occurs in 12~22% of cases, which may affect the prognosis of the patients after treatment.[10] Optimization of the efficacy of EVT by improving these indices (FPE, DE) may be achieved by tailoring to the occlusion characteristics of the individual patient.

Tortuous vessel anatomy is one of the most common challenges that neurointerventionists encounter in clinical practice 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 the difficult anatomy with a flow model matching the real patient that can be tested in vitro.

Therefore, the aim of this study is 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 LVO simulated using 3D printed non-tortuous and tortuous cerebrovascular anatomy flow models obtained from real patient data.

II. MATERIALS AND METHODS

1. Model anatomy

We obtained two 3D digital subtraction angiography data from patients who had been treated by EVT for acute ischemic stroke at our stroke center. Data were obtained from a patient with non-tortuous cerebrovascular anatomy that achieved FPE, and a patient with very tortuous anatomy that achieved recanalization only after multiple retrieval attempts. The collection and utilization of the patient's angiographic data was approved by the Institutional Review Board. Blood vessel data were extracted from the distal cervical segment of the internal carotid artery (ICA), through carotid bifurcation, to include the M1 segment of the middle cerebral artery (MCA) and the A2 segment of the anterior cerebral artery (ACA). The tortuosity of the vessel was visually verified and also numerically confirmed (Arc chord ratio) by comparing the distances between the two points in a straight line for each arterial segment and the total length of the vessel between them.[11] (Arc chord ratio; 1.77 for tortuous model, 1.49 for non-tortuous model)

2. Flow Model

The angiographic DICOM data was extracted in VRML (Virtual Reality Modeling Language) format using the 3D Workstation (ISP, Philips Healthcare, Best, Netherlands).

These were converted into an STL (STereo Lithography) file using a CAD software (MeshLab, Cignoni et al). Using these files, the semi-translucent vascular models with photo-polymerization resin (Standard Clear Resin v4, FormLabs, Cambridge, MA) were produced with a 3D printer (Form2, FormLabs, Cambridge, MA). After printing, multiple silicone coatings were applied to the surface of the models, and the inner mold was removed 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 with a transparent silicone tube, and was connected to a peristaltic pump (EMP-100, EMS tech, Korea) that maintains a pulse rate of 80 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.

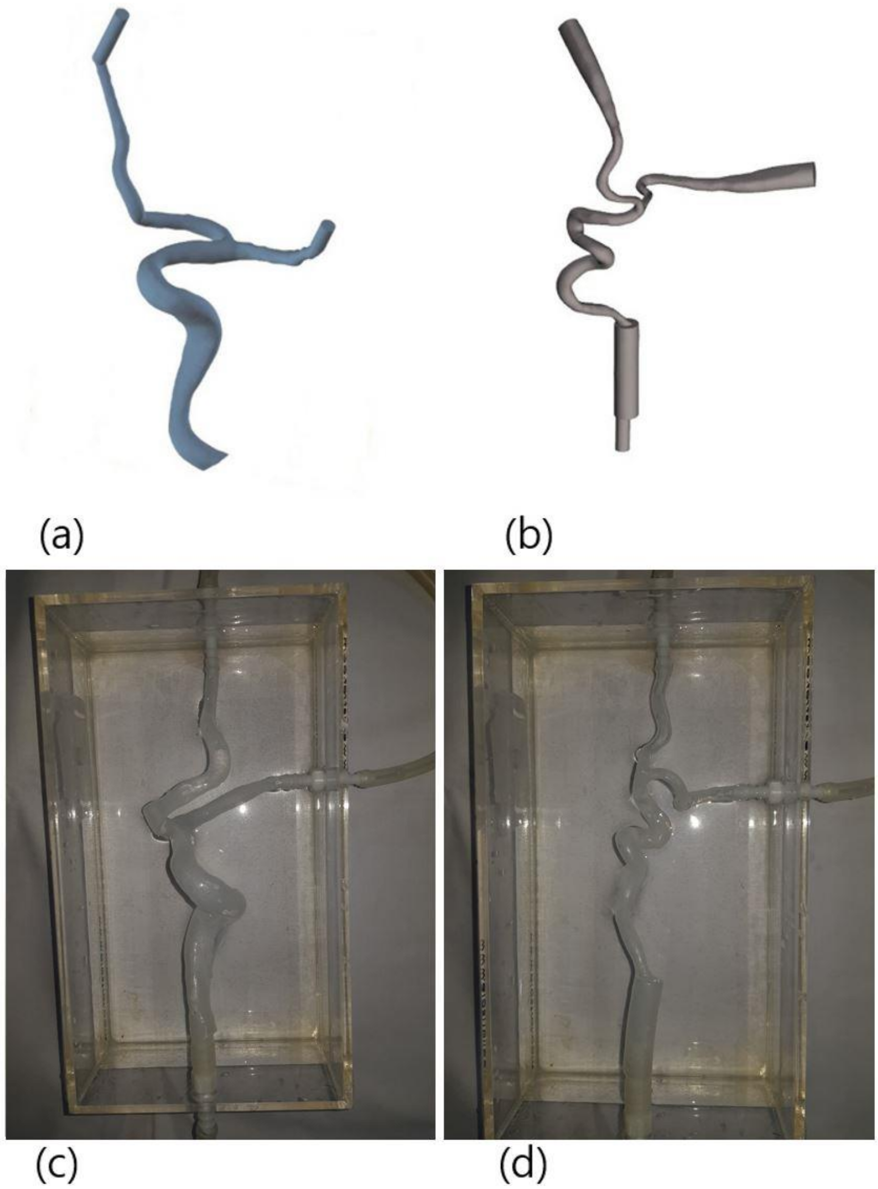

Fig 1. CAD processed 3D images of the non-tortuous (a) and tortuous (b) cerebrovascular angiographic data. Silicone vascular models of the non-tortuous (c) and tortuous (d) anatomy manufactured from the 3D printing models.

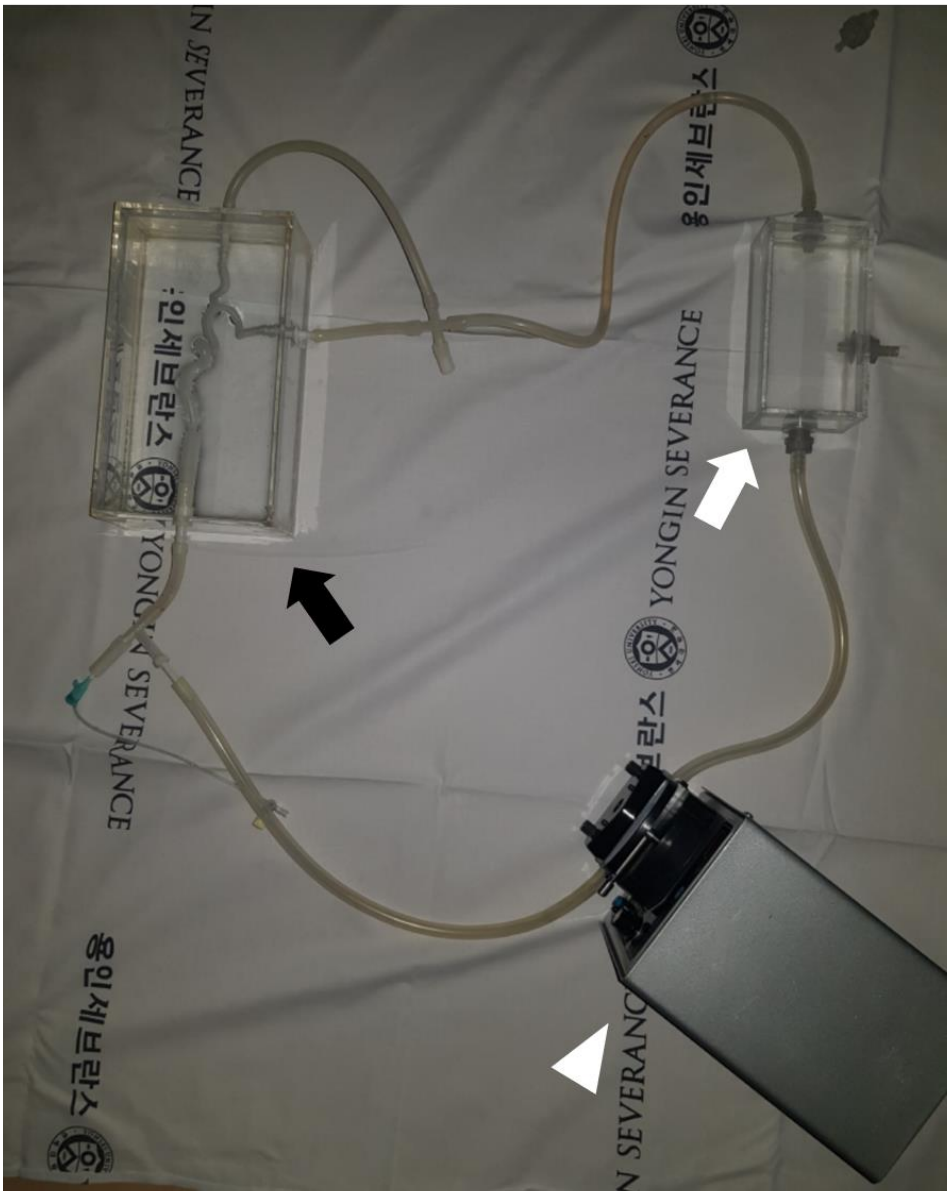

Fig 2. Vascular model placed in the acrylic tank and connected to the closed circuit. Black arrow : Flow model in water filled tank. White arrow : Separate tank for collecting distal embolus. White arrowhead : Peristaltic pump

3. Thrombus analog

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

4. Endovascular thrombectomy techniques

After connecting the 8F sheath to the flow model through a silicone tube, an 8F BGC (Flowgate2, Stryker, Fremont, CA, USA) was inserted and placed in the 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, Minneapolis, MN, USA) or Trevo 4/20 (Stryker, Fremont, CA, USA) stents after passing the thrombus with a 0.021 inch microcatheter and a 0.014 inch microwire. 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, Fremont, CA, USA) and 20cc 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 and ACA segments after a single thrombectomy attempt. DE was defined as identification of a visible, migrated embolus that reached the reservoir tank through the MCA or ACA 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 FPE and DE at the same time. If the thrombus was fragmented, but large enough to remain in the MCA segment without distal migration, it was considered as an FPE failure and not classified as DE. Failure of complete recanalization was defined as either FPE failure or DE. Analysis of the video recordings were performed to identify the mechanisms of thrombectomy failure.

III. RESULTS

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

1. EVT results according to the vascular tortuosity

In terms of the tortuosity of the vessel, the FPE rate of the non-tortuous anatomy model was higher than the tortuous anatomy model (80.0% (12/15) vs 46.7% (7/15)). The incidence of DE was lower in the non-tortuous anatomy model (26.7% (4/15) vs 46.7% (7/15)) (Table 1). The failure of complete recanalization rate of the non-tortuous anatomy model was lower than tortuous anatomy model (33.3% (5/15) vs 60.0% (9/15)) (Table 2).

Table 1. Incidence of FPE and DE in non-tortuous and tortuous models according to the EVT technique

	FPE		DE	
	Non-tortuous	Tortuous	Non-tortuous	Tortuous
Total	12/15 (80.0%)	7/15 (46.7%)	4/15 (26.7%)	7/15 (46.7%)

CA	5/5 (100.0%)	4/5 (80.0%)	0/5 (0%)	1/5 (20.0%)
SR	4/5 (80.0%)	2/5 (40.0%)	1/5 (20.0%)	3/5 (60%)
Combined	3/5 (60.0%)	1/5 (20.0%)	3/5 (60.0%)	3/5 (60.0%)

Table 2. Incidence of failure of complete recanalization in non-tortuous and tortuous models according to the EVT technique

	Failure of complete recanalization	
	Non-tortuous	Tortuous
Total	5/15 (33.3%)	9/15 (60.0%)
CA	0/5 (0%)	1/5 (20.0%)
SR	2/5 (40.0%)	4/5 (80.0%)
Combined	3/5 (60.0%)	4/5 (80.0%)

2. Comparison of various thrombectomy techniques

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

3.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) 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 collapsed segments caused rolling, detachment and fragmentation of the captured thrombus. (Fig 3b) 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)

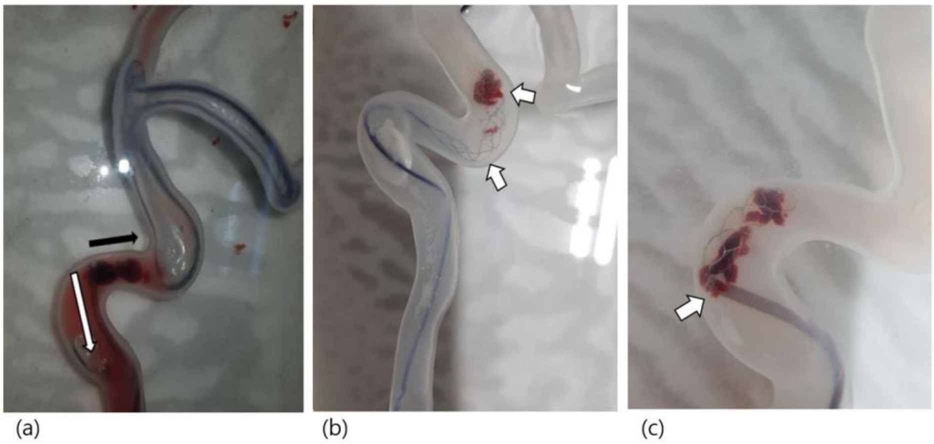

Figure 3. Mechanisms of thrombectomy failure in the tortuous anatomy model. (a) In the CA experiment, the thrombus is clogged at the tip of the aspiration catheter. The thrombus brushes against the tortuous vessel wall during retrieval and fragments when the aspiration catheter tip deflects perpendicular to the axis of the lumen at the angulated curve (white arrow: catheter tip alignment, black arrow: axis of the lumen and thrombus alignment). (b) In the SR experiment elongation and segmental collapse of the stent is noted (white arrows) when retrieving across the curved segment of the vessel causing fragmentation of the thrombus. (c) In the combined experiment, shearing of the thrombus occurred (white arrow) while crossing the curved segment when the SR was inadvertently pulled into the aspiration catheter during retrieval of the SR-CA unit due to aggravation of the length mismatch.

IV. DISCUSSION

The current in-vitro study shows that the tortuosity of the cerebral vessels may impact the outcome of the EVT techniques. The efficacy of EVT was inferior in the tortuous anatomy compared to the non-tortuous 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 non-tortuous 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 non-tortuous and tortuous anatomy models.

EVT using CA and SR are currently the standard treatment methods in acute ischemic stroke patients with successful recanalization rates reaching up to about 90% in some studies.[3 4] However, the achievement of FPE, which is associated with better clinical outcome and decreased mortality is reported to be relatively low ranging from 25-30% with either SR or CA.[9 14] On the other hand, DE is another major factor affecting the clinical prognosis with the incidence of 12 to 22% when the SR is used alone, although some report a lower incidence when using the DA technique is used.[10 15] With advances in the knowledge and technology regarding EVT of acute ischemic stroke, increasing emphasis is placed on the selection of the optimal first-line thrombectomy technique for achieving fast and complete recanalization and ultimately improved clinical outcome. Various factors including the device types and techniques, clot composition and vessel wall-thrombus interaction, occlusion site, and the use of thrombolytic agents and medications may be associated with FPE and DE. The tortuous vascular anatomy may also be an important factor.[16]

In our experiment, CA showed the best FPE achievement with no DE in the non-tortuous anatomy. It also showed relatively favorable FPE and DE results (FPE : 80%, DE : 20%) in the tortuous model. Many studies report that the CA technique shows comparable angiographic and clinical outcomes to the conventional SR.[5 17] In the scenario of a tortuous vascular anatomy, our in-vitro study shows that CA may be preferred in terms of improving the FPE and preventing DE. 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.[18] 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.[19] 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.[20] 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.[21] One of the clinical implications from our study is that CA may be the preferred method in patients with the 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 diameter are warranted.

The FPE and DE rates were 80.0% and 20.0%, respectively in the non-tortuous anatomy model when the SR technique was used with a BGC. In the tortuous anatomy model, 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.[22 23] Insufficient thrombus integration into the stent strut and thrombus rolling between the vessel wall and the strut are known to be common mechanisms and was observed in our analysis as well.[22] Elongation and collapse of the device was observed in 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.[23], [24] Also, the longer retrieval length of the SR due to the tortuous anatomy is thought to be associated with thrombus retrieval failure. 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 SR may be an alternative option.

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, FPE rate was quite low especially in the tortuous anatomy (20%). Several SR-aspiration catheter combination thrombectomy techniques have been studied.[8 25] Prior report claiming that these combination techniques were effective in improving recanalization rate and reducing distal embolization compared to single device techniques.[26] However, Yoo et al described that when the SR was retrieved inside the aspiration catheter, there can be a risk of shearing off the thrombus between the aspiration catheter tip and thrombus engaged SR.[27] McTaggart et al. emphasized the importance of appropriate tension adjustments to prevent the shearing of clot from the length mismatch of the SR and the aspiration catheter during retrieval.[28] 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 non-ingested 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. 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.

Our study used the proximal flow control with BGC in all the experiments. Proximal flow arrest using BGC and its effects have already been demonstrated in many in vitro and in vivo studies.[6 7] Specifically, the reduction of DE when using BGC has been reported in several studies.[6 29] Recently, Teleb et al. demonstrated that the use of BGC is also helpful in increasing the probability of FPE.[30] The BGC was used in all our experiments and we assumed that it had a positive treatment effect on both the non-tortuous and tortuous anatomy models.

This study has some limitations inherently related to the in-vitro nature of the experiment. The endothelium and coagulation factors cannot be implemented. The silicone model cannot perfectly simulate the effects of friction and tension of the actual vessel wall. Also, only single models of the non-tortuous and tortuous vascular anatomy were used in a small number of experiments. 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 hands, 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 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 should be the subject of future studies.

V. CONCLUSION

In conclusion, we observed that the tortuosity of the cerebral arteries has an impact on the EVT procedure and that the choice of the EVT technique may influence the outcome. A decrease in the FPE rate and an increase in the DE rate may occur in patients with tortuous vascular anatomy. In the tortuous anatomy, CA may be preferred showing an improved FPE and decreased incidence of DE compared to other techniques. Combined techniques failed to show improvements in outcome due to the shearing off phenomenon of the thrombus.

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ABSTRACT(IN KOREAN)

혈관모형을 사용한 급성 허혈성 뇌졸중 모델에서 혈관의 해부학적 구조의 차이에 따른 기계적 혈전제거술의 효과성 분석

<지도교수 김동준>

연세대학교 대학원 의학과

김 준 휘

목적: 이 연구의 목적은 3D printing을 이용해 해부학적으로 굴곡이 심한 뇌혈관의 모델과 굴곡이 심하지 않은 뇌혈관 모델을 제작하여 각 모델에서 contact aspiration (CA), Stent retriever (SR), combined method의 3가지 급성 뇌졸중시 혈전제거술 방법별로 first pass effect (FPE)와 distal emboli (DE)의 발생 차이를 비교하는 것이다.

방법: 실제 급성 뇌졸중으로 혈전제거술을 시행 받은 환자의 혈관촬영술 영상을 바탕으로 굴곡이 심한 뇌혈관과 심하지 않은 뇌혈관의 3D printing 모델을 제작하였다. 각 혈관모델에 인공혈전을 삽입한 후, CA, SR, combined method의 3가지 혈전제거술 방법을 각 혈관모델에서 수행하였다. FPE와 DE의 발생률을 모델별, 혈전제거술 방법별로 비교하였고 혈관 모델의 투명성을 이용하여 실제 내부에서 일어나는 혈전제거술의 기전을 관찰하여 기술하였다.

결과: 각 혈관모델에서 15번씩 총 30번의 혈전제거술 실험을 수행하였다. 굴곡이 심한 혈관과 심하지 않은 혈관에서 FPE의 전체 발생률은 80.0% 대 46.7%였으며 DE의 발생률은 26.7% 대 46.7%였다. CA기법은 다른 기법에 비해 굴곡이 심한 혈관에서 더 좋은 FPE(80.0%) 및 DE 비율(20%)을 보였다. Combined method는 굴곡이 심한 혈관과 심하지 않은 혈관 모두에서 FPE와 DE 모두 유의한 우월성을 보이지 않았다. 혈전의 shearing off는 combined method에서 혈전제거술 실패의

주요 기전이었다

결론: 해부학적으로 굴곡이 심한 혈관에서는 혈전제거술시 FPE와 DE의 비율이 악화된다. CA 기법은 굴곡이 심한 혈관에서 가장 효과가 좋은 혈전제거술의 기법일 수 있다. Combined method는 혈관의 해부학과 상관없이 혈전제거술의 효과 향상에 기여하지 못하였다.

핵심되는 말: 급성 뇌졸중, 뇌혈관내 치료, 기계적 혈전제거술, 초회통과효과, 원위부 색전.