



The Evolution of the Neurosurgical Treatment of Ischemic Stroke

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The neurosurgical approach to the management of ischemic stroke has evolved dramatically over the past century with the bulk of these changes occurring over the past 25 years. With recent advances in technology and continued refinements in neurosurgical techniques there has been significant improvement to the safety and efficacy of our treatment options. The focus of this article will be to review the historical and recent reports in the literature related to revascularization techniques.

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INTRODUCTION

The neurosurgical approach to the management of ischemic stroke has evolved dramatically over the past century with the bulk of these changes occurring over the past 25 years. While it is true that ischemic strokes continue to have devastating consequences, the modern neurosurgeon has become better equipped than-ever to make a significant impact on the lives of those affected. With recent advances in our fund of knowledge and with new tools in an updated armamentarium, neurosurgeons can now much more frequently not only prevent stroke, but restore blood flow and sometimes even completely restore neurological function to patients in the early stages of a stroke. The use of modern neurosurgical interventions in the management of stroke can be an extremely profound and rewarding experience. To continue to move forward and to fully appreciate the evolution of

the newer neurosurgical approaches to the management of ischemic stroke it is important to review some of the historical events which have led to this point. It is also important to point out that a comprehensive review of the scientific and clinical contributions to the management of ischemic stroke would be very vast and would fill many chapters of many textbooks. With that notion in mind, the focus of this article will be specifically on reviewing both historical and current reports in the literature related to revascularization techniques, which are of interest to the field of neurosurgery.

EARLY CAROTID SURGERY

Chiari firmly tied the association between occlusive disease of the carotid arteries and the symptoms of ischemic stroke in 1905 leading to further investigations of potential treatments.⁵⁾²⁴⁾ Chao at the Medical

College of Peking performed the first successful surgery aimed at treating carotid occlusion on two people with carotid artery disease and anxiety and depression-like symptoms in 1938.⁴⁾ The procedure he described was a carotid artery excision without restoring blood flow.⁴⁾ Following the procedure both patient's mental conditions reportedly resolved leading to carotid excision becoming the neurosurgical treatment of choice for occlusion of the carotid artery.⁴⁾ Very few subsequent patients improved and it is hypothesized that the improvement reported in successful cases came from prevention of repeat embolization. Although this procedure was infrequently performed it remained the treatment of choice throughout the 1940's.¹⁸⁾²⁴⁾ The first well-documented procedure that successfully restored blood flow to the internal carotid artery was done in Buenos Aires by Carrea, Molina, and Murphy.²⁵⁾ Angiography revealed severe narrowing of the internal carotid artery above the bifurcation in a patient with symptoms of ischemic stroke.²⁵⁾ The internal carotid and external carotid artery were cut 5 mm above the lesion. The proximal external carotid artery and distal internal carotid artery were anastomosed and patency was confirmed by angiography.²⁵⁾ This was the first reported internal-external carotid artery bypass.²⁵⁾ The patient recovered from hemiparesis and aphasia.²⁵⁾ This was the first demonstration that returning blood flow to the brain following ischemic stroke could return motor function. While this particular procedure was successful, carotid endarterectomy would soon surpass it to become the technique of choice in the coming years for the management of carotid stenosis.²⁴⁾

CAROTID ENDARTERECTOMY

DeBakey at Baylor University successfully performed the first carotid endarterectomy in 1953.⁸⁾⁹⁾ Interestingly, DeBakey did not localize the lesion with angiography and performed his first endarterectomy based on reports that lesions were frequently localized to the carotid bifurcation.⁸⁾⁹⁾ DeBakey described removing a partially occluded clot from the common carotid bi-

furcation and closing the vessel.⁸⁾⁹⁾ This initial successful operation led to a rapid increase in attempts to restore flow to occluded carotid artery segments. While DeBakey was the first to perform the procedure, Cooley became the first to publish on successful endarterectomy in 1956.⁷⁾ He created a temporary polyvinyl shunt to be placed within the internal carotid bypassing the lesion until he could remove the plaque and became the first to successfully use this technique.⁷⁾ Various techniques for this surgery developed over the ensuing years using varying degrees of temporary arterial bypass. Some surgeons choose not to use a bypass if the procedure will be quick and there is enough blood flow from the contralateral circulation. Over the next 40 years, surgical technique moderately improved although the indications for this procedure became less clear as negative reports on the procedure emerged.

The first of the randomized clinical trials regarding ischemic stroke and the effectiveness of carotid endarterectomy had negative results when compared to medical management leading to a relative decrease in procedural volume in the late 80's.¹¹⁾²⁸⁾ The North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial and the European Carotid Surgery Trial were large randomized controlled trials published in the 90's that both showed substantial benefit of carotid endarterectomy in symptomatic patients who had carotid stenosis of 70-99%.¹⁰⁾²³⁾ The NASCET trial demonstrated a 9% rate of ipsilateral stroke at two years in surgical patients with high-grade stenosis compared to a 26% rate in the medically managed patients with high-grade stenosis (absolute risk reduction [ARR] 17% \pm 3.5%, $p < 0.001$).²³⁾ Medical management in this trial involved management of comorbid conditions plus aspirin at 1300 mg per day. The medically managed group of patients with high grade stenosis had a significantly higher rate of strokes that caused permanent disability or death compared to the surgically managed patients (13.1% vs. 2.5%; ARR 10.6% \pm 2.6 ($p < 0.001$)).²³⁾ While the perioperative mortality rate was slightly higher in the surgical group, this risk was negated by the significant reduction in mortality measures after a two year follow

up.²³⁾ The European Carotid Surgery Trial was structured very similarly and showed that after 3 years there was a 12.3% rate of death from surgical complication, or stroke in the high grade stenosis group treated surgically compared to 21.9% percent in the medically managed group (ARR 9.6%, standard deviation 3.32, $p < 0.01$).¹⁰⁾ While these studies left a large number of questions unanswered in particular, what to do with asymptomatic patients and with patients with moderate stenosis, this therapy was the first neurosurgical procedure that was proven with a randomized controlled trial to have a mortality benefit.

Intravenous tissue plasminogen activator (IV t-PA)

Similar to carotid endarterectomy, the initial trials regarding thrombolytic agents failed to demonstrate benefit and were associated with a marked increased risk of intracranial hemorrhage.¹²⁾²⁰⁾ However unlike other thrombolytics, early studies evaluating t-PA were promising and ultimately lead to the NINDS double blinded randomized controlled trial evaluating the efficacy of intravenous (IV) t-PA administration within 3 hours of the onset of a stroke.³⁰⁾ The study showed significant improvement in the median National Institute of Health stroke scale (NIHSS) score in patients treated with t-PA (NIHSS, 8) compared to patients treated with placebo (NIHSS, 12). The second leg of the study demonstrated that a higher percentage of patients treated with t-PA had a 'good neurologic outcome' at 90 days, which was defined as the ability to return to an independent lifestyle (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.2 to 2.6, $p = 0.008$).³⁰⁾ By using the modified Rankin score (mRS) as an outcome measure of the ability of patients to function independently they reported that 39% of the patients treated with IV t-PA had a mRS of < 2 at 90 days compared to 26% of patients treated with placebo (OR 1.7, 95% CI 1.1 to 2.6). However, there was a 7% rate of intracranial hemorrhage in the t-PA group compared to a 1% rate in the placebo group. The benefits of improved outcomes at three months outweighed the risk of intracranial hemorrhage in this study. The authors of this study attributed a large

part of the differences seen in this study compared to previous studies to the strict limitation of administration of IV t-PA to 3 hours from the time of onset of stroke symptoms.³⁰⁾ The results of the NINDS study ultimately lead to establishment of the gold standard for the treatment of ischemic stroke being IV t-PA administration for patients presenting within three hours of the onset of symptoms.

Extension of the window

The next major trial that markedly changed the recommendations of stroke management was the ECASS III trial, which specifically looked at extending the window of t-PA.¹⁶⁾ This study compared the outcomes of patients given t-PA during a 3-4.5 hour window to patients given a placebo. Using the mRS with a favorable outcome being defined as a score of 0 or 1, the study showed a relative risk reduction of 1.16 in adverse outcomes (95% CI 1.01 to 1.34, $p = 0.04$).¹⁶⁾ Further analysis of the of the probability of returning to an independent life style with same variables assessed in the NINDS study (NIHSS, Barthel index, modified Rankin scale, and Glasgow outcome scale) at 3 months showed a 28% higher chance of returning to an independent lifestyle in the t-PA group compared to placebo (OR 1.28, 95% CI 1.00 to 1.65, $p < 0.05$).

Intraarterial thrombolytics

A huge hurdle in treatment of ischemic stroke remained what to do with patients with extended times from the onset of symptoms to presentation. It had been demonstrated that after 4.5 hours the harm outweighs the risk of IV tPA.¹⁷⁾ Intraarterial thrombolytics were proposed to improve outcomes in patients who presented too late for IV tPA. The PROACT II trial was a randomized controlled double-blinded trial that was designed to evaluate the efficacy of intraarterial recombinant prourokinase (r-proUK) compared to heparin alone in patients presenting before 6 hours.¹³⁾ The study showed a 60% increase in patients with slight or no neurologic disability at 90 days (40% r-proUK vs. 25% heparin, $p = 0.04$).¹³⁾ This was first study to show a benefit of treating patients outside of the 4.5 hour window, extending the window of possible intervention

all the way to 6 hours. While this study showed benefits in improving the quality of life of people who survived, it failed to show any mortality benefit (25% r-proUK vs. 27% heparin) and partially due to a greatly increased rate of symptomatic intracranial hemorrhage rate in the r-proUK group (10% vs. 2%, $p = 0.06$).¹³⁾

Mechanical Thrombectomy

Initial development and the first generation device: the Merci® retrieval system (Concentric Medical, Mountain View, CA, USA)

Following the PROACT II trial in 1999 the problem still remained of what to do for people who had strokes and presented greater than 6 hours after the onset of symptoms. Additionally, a large number of patients are excluded as candidates for thrombolytic therapy secondary to an increased risk of hemorrhage, such as those with a history of a recent trauma or surgical procedure. In 2005 the initial trial using the Merci® retrieval system (Concentric Medical) was published and established efficacy and safety of the first mechanical thrombectomy device.²⁹⁾ Additionally, this treatment modality demonstrated an improvement in neurologic outcomes in patients with acute onset stroke up to 8 hours after their initial presentation. The trial showed that the Merci® device achieved recanalization of large vessels in 48% percent of patients treated with the device, which was lower than the 66% achieved with intra-arterial r-proUK. However, this procedure was associated with a lower intracranial hemorrhage rate of 5% compared to 10% in the PROACT-II intra-arterial r-proUK trial.¹³⁾²⁹⁾ Using the first generation device 46% of patients with successful recanalization had mRS of < 2 at 90 days and a mortality rate of 32% compared to only 10% mRS < 2 and a 52% mortality rate in which recanalization was unsuccessful.²⁹⁾ This procedure had similar intracranial hemorrhage rates as compared to thrombolytics and showed additional improvement in both mortality and neurologic outcomes at 90 days in patients that the procedure achieved revascularization. These findings established mechanical thrombectomy as the new treatment of choice for patients who were ineligible for thrombolytics and led to further development of

different mechanical thrombectomy devices.

Mechanism

The first generation Merci® device functions as a clot retriever. A guide wire is advanced through the arterial circulation at which point a catheter is advanced over it. The guide wire is then advanced distal to the clot. A large catheter is advanced over the guidewire and stopped proximal to the clot. A microcatheter is then advanced within the larger catheter over the guide wire and the guide wire is withdrawn leaving the microcatheter distal to the clot. The Merci® device is then inserted through the microcatheter and deployed, which then forms a corkscrew like structure distal to the clot. The large catheter is inflated to occlude flow through the vessels. Suction is provided through the large catheter while the microcatheter along with the Merci® device are withdrawn attempting to capture and pull the clot back through the large catheter, and out of the vessel.

Second generation: the Penumbra® System (Penumbra Inc., Alameda, CA, USA)

The next clot retriever to come out was The Penumbra® System (Penumbra Inc.) in 2008. The Penumbra® device was able to obtain revascularization of large cerebral vessels in 81.6% of people, which was significantly higher than the 48% of patients in the 2005 with Merci®.²⁹⁾³¹⁾ Although it was more effective at revascularization the rate of symptomatic hemorrhage was also higher with the Penumbra® device (11.2% vs. 7.8% with the Merci® retriever). Despite the increase in hemorrhage, the 90 day mortality was less in the Penumbra® trial compared to the Merci® retriever.³¹⁾ The percentage of patients with 90-day mRS of < 2 were very similar (25% Penumbra® vs. 27.7% Merci® trial).²⁹⁾³¹⁾ One potential reason for this failure to achieve better neurologic outcomes is the increased rate of fragmentation of the clot forming distal emboli with the Penumbra® device compared to the Merci® clot retriever.

Mechanism

The Penumbra® system acts differently than the Merci® retriever in that the device is inserted just proximal

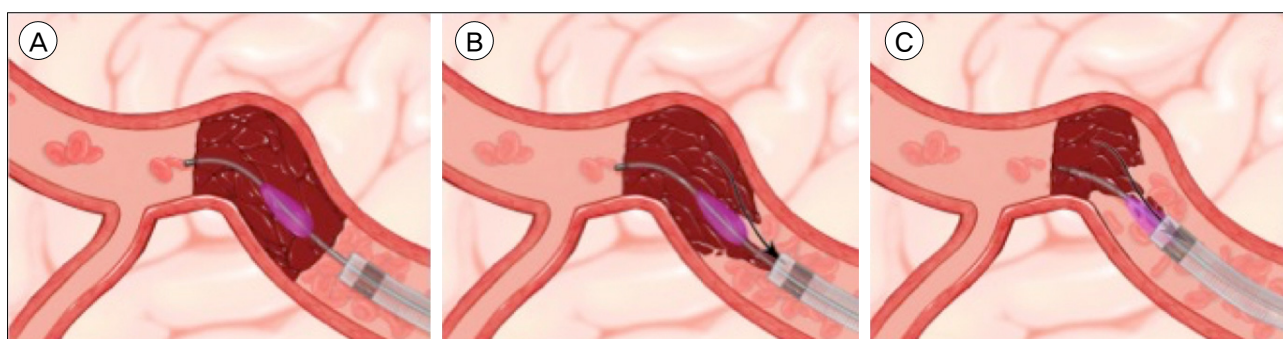


Fig. 1. (A) shows the initial deployment of the Penumbra device proximal to the clot. (B, C) show the separator disrupting the clot and suctioning of the fragments through the microcatheter.

clot instead of all the way through it (Fig. 1A). Suction is then applied to the Penumbra® device using a vacuum system. A small separator extends from the tip of the device, which can be deployed back and fourth to break up the clot into smaller pieces to facilitate removal by suction (Fig. 1B, C). A proposed problem with this system has been distal embolization of fragments of the clot.

Stent retrievers

Both Solitaire® (Solitaire MEDTRONIC, Minneapolis, MN, USA) and Trevo® (Trevo-STRYKER, Fremont, CA, USA) are third generation thrombectomy devices which function as stent retrievers. The first data published in 2012 created a revolution in mechanical thrombectomy.^{22,27} These devices were the first to show both improved recanalization rates and improved outcomes since the Merci® trials. The Solitaire® stent retriever device had a recanalization rate of 61% compared to the Merci® Clot retriever, which only had a 24% rate of recanalization. Additionally the Solitaire® device had improved rates of 'good neurologic outcome' at 90-days (58% vs. 33%) and a significantly lower 90-day mortality rate (17% vs. 38%) compared to the Merci® clot retriever.²⁷

The Trevo® stent retriever had superior canalization rates (86% vs. 60%) and neurologic outcomes at 90 days (< 2 mRS, 40% vs. 22%) compared to the Merci® device.²² Additionally, the safety of this device was similar to the Merci® device with an immediate complication rate of 15% compared to 23% in the Merci®

device. These two facts taken together indicate Trevo® has significantly improved efficacy compared to the Merci® device and raises the question of whether the efficacy of these retrievers may ultimately be superior to that of IV t-PA. However, to date no study has had had enough power in the group of patients not treated with t-PA to evaluate this idea.²²

Mechanism

Stent retrievers operate most similarly to the first generation Merci® device. The microcatheter is inserted through the clot over a guidewire similar to the Merci® device. Using fluoroscopy the distal most part of the stent is visualized at the end of the microcatheter. Following appropriate placement of the stent at the end of microcatheter, the microcatheter is withdrawn and in doing so the stent device is deployed both distal to the clot and within the clot (Fig. 2A, B). The device expands radially distal to the clot, within the clot, and proximal to the clot embedding itself completely within the clot. The most significant advantage the stent retrievers have over other devices is that the stents provide a radial traction force, which decreases the likelihood of clot fragmentation and allows for more consistent removal of the entire clot. While the stent is deployed reperfusion is also being re-established. After 3 to 5 minutes of deployment the stent device can be closed by withdrawing it into the microcatheter and subsequently removing the entire unit containing the clot, stent and microcatheter out of the patient (Fig. 2C).

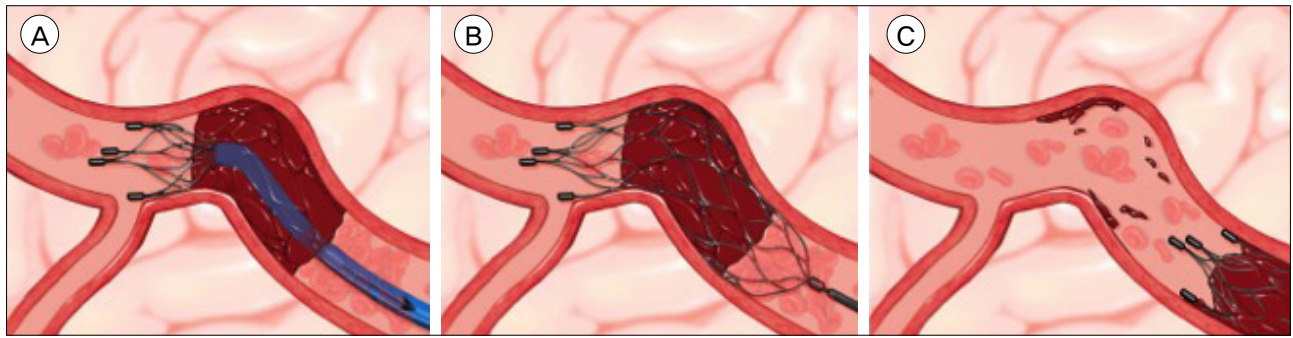


Fig. 2. (A, B) show the deployment of a stent retriever. The device and microcatheter are inserted distal to the clot and the microcatheter is withdrawn proximally leaving the stent retriever embedded throughout the clot. (C) shows the stent retriever being withdrawn into the microcatheter carrying the clot after the 3-5 minute waiting period for the clot retriever to stabilize within the clot.

CURRENT ROLE OF MECHANICAL THROMBECTOMY

The early data regarding the efficacy and safety of mechanical thrombectomy supported its usage in patients in which t-PA could not be used. There were three studies done early in the development of mechanical thrombectomy that primarily looked at the benefit of endovascular treatment with the first and second generation mechanical thrombectomy devices instead of IV t-PA and as a follow up treatment for people who failed t-PA therapy which all failed to show any benefit to endovascular treatment.²⁾⁽⁶⁾⁽¹⁹⁾ The Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS Expansion) study compared intraarterial t-PA and mechanical thrombectomy as a substitute for initial treatment with IV t-PA and failed to show a benefit.⁶⁾ Two later studies, Interventional Management of Stroke (IMS) III and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), examined the benefit of these treatments as follow up interventions in patients who continued to have large artery occlusion following the administration of t-PA.²⁾⁽¹⁹⁾ MR RESCUE and IMS III both failed to show any benefit using these interventions as follow up treatment for people who failed initial treatment.²⁾⁽¹⁹⁾ These studies achieved a rate of recanalization of 27-41%.²⁾⁽¹⁹⁾ As mechanical thrombectomy technology improved and became

more widespread there has been renewed interest in research utilizing these therapies both as follow up therapies and as a primary therapy in lieu of IV t-PA.

From January 1, 2010 to December 23, 2015 there have been five significant positive trials that looked at utilizing stent retrievers in conjunction with t-PA, which have established mechanical thrombectomy and endovascular stroke therapy as the standard of care for proximal anterior occlusions.¹⁵⁾ These five trials demonstrated a significant improvement of adequate recanalization (Thrombolysis in cerebral infarction grade 2b/3) in 59-88% of patients treated with t-PA in conjunction with stent retrievers compared to the 27-41% that was shown in the previous trials as well as a significantly reduced chance of disability at 90 days (Table 1). All 5 studies randomly assigned patients to receive thrombectomy plus medical care or medical care alone. Before randomization all patients were treated with a standard dose of IV t-PA if eligible. A recent Meta-analysis of patient data from 570 patients from all five trials and showed a significantly higher the National Institutes of Health Stroke Scale (NIHSS) score after 24 hours as well a greater improvement from baseline to 24 hours NIHSS among all patients assigned to thrombectomy.¹⁵⁾ The Meta-analysis also reported that the 90-day mortality and risk of intraparenchymal hematoma and symptomatic intracranial hemorrhage did not differ between populations.¹⁵⁾ Additionally, a subgroup analysis showed improved outcomes in several subgroups of special interest and

Table 1. Brief Summary of recent studies reporting positive results utilizing stent retrievers in conjunction with t-PA

Trial	Study design	Device	Revascularization rate	% of mRS 0-2 at 90 days
MR CLEAN ¹⁾	Standard of care (IV t-PA for eligible people) vs. Standard of care plus mechanical thrombectomy		59%	32.6% vs. 19.1% Absolute difference 13.5% (95% CI, 5.9-21.2%)
ESCAPE ¹⁴⁾	Standard of care (IV t-PA for eligible people) vs. Standard of care + stent retriever		72%	53% vs. 29.3% $p < 0.001$ Mortality at 90 days 10.4% vs. 19% Adjusted rate ratio: 0.5; 95% CI, 0.3-0.8
SWIFT PRIME ²⁶⁾	Standard of care (IV t-PA eligibility required) vs. Standard of care (IV t-PA eligibility required) + stent retriever	Solitaire	88%	60% vs. 35% OR, 1.70; 95% CI, 1.23 to -2.33
EXTEND-IA ³⁾	Standard of care (IV t-PA eligibility required) vs. standard of care (IV t-PA eligibility required) plus stent retriever	Solitaire	86%	71% vs. 40%; $p = 0.01$
REVASCAT ²¹⁾	Standard of care (IV t-PA for eligible people) plus standard of care plus stent retriever	Solitaire	66%	43.7% vs. 28.2% Adjusted odds ratio, 2.1; 95% CI, 1.1 to -4.0

mRS = modified Rankin Scale; CI = confidence interval; OR = odds ratio.

typically excluded including patients older than 80 years, patients randomized more than 6 hours after symptom onset, and patients not receiving IV t-PA.¹⁵⁾

Prospects

Mechanical thrombectomy using stent retrievers are the first new therapeutics to significantly alter outcomes in patients with ischemic stroke since the incorporation of IV t-PA in the early 90's. Endovascular thrombectomy has been shown to reduce disability in a wide range of patients especially in large vessel anterior circulation infarcts. Benefits have been shown a wide range of age, stroke severity, as well as in absence of t-PA administration. Theoretically, with a lower rate of intracranial hemorrhage and improved rate of recanalization this therapy has the potential to improve outcomes in patients treated with a stent retriever device in lieu of t-PA in settings where the technology is readily available and the 'time to the groin interval' is not significantly increased compared to the time to t-PA administration. However, to date no trial has had enough power to evaluate the outcomes of mechanical thrombectomy without t-PA. Further work needs to be done evaluating the efficacy of thrombectomy with stent retrievers in patients presenting beyond 6 hours, with poor initial NIHSS, with early radiographic changes, and strokes involving the posterior circulation.

Technical note

Currently at our institution we use a modified technique for acute stroke intervention that includes the

use of both a stent retriever in conjunction with an aspiration device. We use a 6 French shuttle sheath, which acts as both a sheath and a guide catheter to gain access to the vessel of interest. Once in position, we pass a microcatheter coaxially through an intermediate catheter to the level of occlusion. A stent retriever is then deployed in the thrombus and allowed to stay in position 3-5 minutes. The intermediate catheter is then connected to continuous suction once the stent is retrieved. The future of mechanical thrombectomy is boundless as new technology propels the field forward. The next generation of stent retrievers such as the Revive[®] device are on the horizon and may continue to improve current intervention techniques.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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